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American Society of Clinical Oncology
55th Annual Meeting

Descriptions of Scientific Sessions

**Plenary Session**
The Plenary Session includes abstracts selected by the Scientific Program Committee as having practice-changing findings of the highest scientific merit.

**Highlights of the Day Sessions**
Highlights of the Day Sessions invite expert discussants to provide an overview of the previous day's Oral Abstract presentations, focusing on key findings and putting abstracts into clinical context.

**Oral Abstract Sessions**
Oral Abstract Sessions include didactic presentations of abstracts of the highest scientific merit, as determined by the Scientific Program Committee. Experts in the field serve as discussants and provide comprehensive themed discussions of the findings from the abstracts.

**Clinical Science Symposia**
Clinical Science Symposia provide a forum for science in oncology, combining didactic lectures on a specific topic with abstract presentations. Experts in the field serve as discussants, placing studies in the appropriate context and critically discussing the applicability of the conclusions in clinical practice. Three special Clinical Science Symposia will be designated around specific topics that cut across cancer types.

**Poster Discussion Sessions**
Select posters from the Poster Sessions will be discussed by expert discussants, with the abstract authors participating in a question and answer period as panel members. These sessions will be followed by networking with the discussants and authors.

**Poster Sessions**
Poster Sessions include selected abstracts of clinical research in poster format. Trials in Progress (TPS) abstracts are presented within a track's Poster Session.

**Publication-Only Abstracts**
Publication-only abstracts were selected to be published online in conjunction with the Annual Meeting, but will not be presented at the Meeting.

*All presented and publication-only abstracts are citable to this Journal of Clinical Oncology supplement. For citation examples, please see the Letter From the Editor.*

This publication contains abstracts selected by the ASCO Scientific Program Committee for presentation at the 2019 Annual Meeting. Abstracts selected for electronic publication only are available in full-text versions online through ASCO.org and JCO.org. The type of session, the day, and the session start/end times are located to the right of the abstract number for scheduled presentations. To determine the location of the abstract session, refer to the Annual Meeting Program or the iPlanner, the online version of the Annual Meeting Program, available at am.asco.org.

*Dates and times are subject to change. All modifications will be posted on am.asco.org.*
The 2019 ASCO Annual Meeting Proceedings (a supplement to Journal of Clinical Oncology) is an enduring record of the more than 2,400 abstracts selected by the ASCO Scientific Program Committee for presentation at the 55th ASCO Annual Meeting. Accepted abstracts not presented at the meeting are included in the online supplement to the May 20 issue of Journal of Clinical Oncology at JCO.org.

The majority of abstracts selected for presentation are included here in full and are categorized by scientific track. Abstracts can be also accessed online through the ASCO Meeting Library (meetinglibrary.asco.org). Online abstracts include the full list of abstract authors and their disclosure information.

Late-Breaking Abstracts are represented here by abstract title and first author only. The full-text versions of these abstracts will be publicly released during the Annual Meeting. Print versions of these abstracts will be available onsite at the Annual Meeting in the ASCO Daily News.

All abstracts carry Journal of Clinical Oncology citations. The following are citation examples for print and electronic abstracts:

J Clin Oncol 37:5s, 2019 (suppl; abstr LBA1)
J Clin Oncol 37, 2019 (suppl; abstr e12000)

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

Michael A. Carducci, MD
Editor, ASCO Annual Meeting Proceedings
Important Tiers and Pricing Notes
Additional rates along with tier descriptions are available online at http://ascopubs.org/pb-assets/pdfs/ASCO-institutional-catalog-1536072550257.pdf

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ASCO Abstracts Policy

Public Release of Abstracts
The abstracts published in the 2019 ASCO Annual Meeting Proceedings, including those abstracts published but not presented at the Meeting, were publicly released by ASCO at 5:00 PM (EDT) on Wednesday, May 15, 2019. These abstracts are publicly available online through ASCO.org, the official website of the Society. Late-Breaking Abstracts, which include all Plenary Abstracts, will be publicly released according to the following schedule:

- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Saturday, June 1, will be publicly released Saturday, June 1, through ASCO.org at 7:30 AM (EDT).
- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Sunday, June 2, will be publicly released Sunday, June 2, through ASCO.org at 7:30 AM (EDT).
- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Monday, June 3, or Tuesday, June 4, will be publicly released Monday, June 3, through ASCO.org at 7:30 AM (EDT).

Late-Breaking Abstracts will be available in ASCO Daily News on the day of their scientific presentation, with the exception of abstracts presented on Friday (these will appear in the Saturday issue) and those presented on Tuesday (these will appear in the Monday issue).

In the unlikely event that ASCO publicly releases an abstract in advance of the scheduled time, the release will be publicly announced on ASCO.org.
Conflict of Interest Disclosure

As the CE provider for the Meeting, ASCO is committed to balance, objectivity, and scientific rigor in the management of financial interactions with for-profit health care companies that could create real or perceived conflicts of interest. Participants in the Meeting have disclosed their financial relationships in accordance with ASCO's Policy for Relationships with Companies; review the policy at asco.org/rwc.

ASCO offers a comprehensive disclosure management system, using one disclosure for all ASCO activities. Members and participants in activities use coi.asco.org to disclose all interactions with companies. Their disclosure is kept on file and can be confirmed or updated with each new activity.

Please email coi@asco.org with specific questions or concerns.
ABSTRACTS
American Society of Clinical Oncology
55th Annual Meeting
May 31-June 4, 2019
McCormick Place
Chicago, IL

SPECIAL AWARD LECTURE ABSTRACTS

David A. Karnofsky Memorial Award and Lecture
Breast cancer: 40 years of research and progress.
Gabriel N. Hortobagyi, MD, FACP, FASCO; University of Texas MD Anderson Cancer Center

More progress was made in breast cancer management over the past 40 years than ever before. Surgical management transitioned from radical procedures to breast-conserving surgery with sentinel lymph node biopsy, resulting in reduced morbidity. Progress in radiation therapy included well-defined indications for postoperative radiotherapy, hypofractionated schedules, and partial breast irradiation. Effective systemic therapy (chemotherapy, endocrine therapy, and targeted treatments) led to improvements in control of metastatic breast cancer and reductions in breast cancer mortality for patients with primary breast cancer. My group contributed to the development of anthracyclines, taxanes, bisphosphonates, and multiple endocrine agents. Adjuvant and neoadjuvant systemic therapies became an integral part of combined modality management, today's standard of care. Having pioneered neoadjuvant chemotherapy, our group led to enhancing the application of limited surgical excisions resulting in the adoption of an outstanding research tool. Improvements in supportive care significantly reduced toxicity of treatments, enhanced quality of life, and improved treatment adherence. The incorporation of bisphosphonates and later, denosumab, into the management and prevention of bone metastases had a major impact on complications of advanced cancer, reduced morbidity, and later contributed to improved recurrence-free survival in primary breast cancer. Genetic and genomic studies improved our understanding of the biology of breast cancer, defined various subtypes, and opened the door to focused interventions, the initial steps toward personalized therapy. Our group contributed to the definition of familial breast cancer syndromes, empowering other investigators to identify germline mutations in several genes associated with increased risk of developing breast (and other) cancers. Our early work in gene expression profiling led to the development of prognostic and predictive gene panels, today an integral part of the standard of care. These changes brought a >40% reduction in breast cancer mortality and significantly improved quality of life to women with breast cancer.

ASCO–American Cancer Society Award and Lecture
Progress and challenges in clinical cancer genetics.
Judy Garber, MD, MPH, FASCO; Dana-Farber Cancer Institute

Cancer genetics has become an intrinsic component of much of cancer care. ASCO has been a leader in the incorporation of germline cancer genetics into oncology care, recognizing early its potential impact independent of and integrated with somatic genetics. Recognition of technical and clinical aspects of genetics in more common high-penetrance cancer predisposition syndromes began with breast/ovarian, Lynch syndrome, and a series of less common conditions (MEN1, Li Fraumeni etc). Genetic testing was expensive, focused on individual genes or conditions, and often conducted in research or in highly specialized environments. Today, with next generation sequencing and other forces, genetic testing has become multigene, across a spectrum of more than 100 syndromes, with expanding diversity of component tumors. There is increasing recognition that delivery of genetics services also requires innovation to drive inclusion of more diverse populations, as well as a broader range of individuals at risk, targeting cancer patients to enable increased efforts in Cascade testing to the relatives of carriers, and education of providers to utilize germline information most effectively in cancer surveillance and treatment. The future directions for cancer genetics remain exciting and multidimensional. For family members, there are novel approaches to the development and implementation of imaginative and accessible testing strategies, of novel early detection strategies including cfDNA, of new approaches to cancer prevention/interception in high risk populations, and deep investigation of the tumors occurring in carriers to continue to
identify mechanisms that drive therapy. It is also now recognized that the somatic/germline paired analyses of tumors provides significant information over and above tumor-only approaches. Cancer genetics research is certainly a team activity, and this work is the result of many wonderful collaborations with true leaders in the field, which will also be highlighted in this talk.

**B. J. Kennedy Award and Lecture for Scientific Excellence in Geriatric Oncology**

**Systemic treatment of elderly patients with metastatic stage IV non-small cell lung cancer: From nihilism to reasonable hope.**

Elisabeth Quiox, MD; Hopitaux Universitaires de Strasbourg

Median age at diagnosis of non-small cell lung cancer (NSCLC) is now 70 years, meaning that the management of this frequent disease, in patients age $\geq 70$ years is a daily practice concern. Nihilism, as well from patients but also doctors, was common but also false notions such as the fact that the disease progresses more slowly in elderly, justifying therapeutic abstention. Elderly patients are under-represented in clinical trials. Even if there is no more age limit, the median age of patients included did not increase significantly and very old patients remain seldom. Thus, it is difficult to generalize the results obtained and dedicated clinical trials to elderly patients are mandatory. The first one dedicated to patients age $\geq 70$ years with metastatic NSCLC was published in 1999 by the ELVIS Italian group comparing vinorelbine to best supportive care. There was a significant survival benefit in the chemotherapy arm and thus the recommendations from scholarly societies were to treat elderly patients with vinorelbine or gemcitabine. However, subgroup analyses of clinical trials showed that carboplatine-based doublets might be appropriate and thus the French intergroup IFCT conducted a trial comparing single agent therapy to carboplatine + paclitaxel showing a highly significant survival benefit in favor of the doublet, in PS 0-2 patients with age $\geq 70$ years. This finding changed the paradigm of treatment of these patients. On the other hand, maintenance therapy is not to be recommended in this setting (IFCT trial to be published). Elderly patients with EGFR mutations benefit from targeted therapies like their younger counterparts. Checkpoint inhibitors remain to be investigated specifically as the concept of immunosenescence may prevent their efficacy. As a conclusion, there is still a long way to go... but already many improvements in the management of elderly patients with metastatic NSCLC.

**Pediatric Oncology Award and Lecture**

**The molecular pathology of pediatric cancer.**

James R. Downing, MD; St. Jude Children’s Research Hospital

The treatment of pediatric cancer is one of modern medicine’s success stories. A half century of advances have led to cure rates of more than 80 percent. Recent progress has been fueled, in large part, to increased understanding of the genetic underpinnings that cause these diseases to arise, spread, and resist treatment. This information has emerged from a variety of different lines of investigation, including cytogenetics and genomic efforts to identify the underlying lesions, as well as functional studies in cellular and in vivo murine model systems to characterize the biological consequences of the identified genetic alterations. These studies serve as the foundation for individualized treatments, which offer patients the best possible chance for a cure. Individualization of therapy has resulted from improvements in the ability to diagnosis the specific tumor type, identify the genetic alterations that allow accurate risk stratification, and for some tumor types, treat using drugs that are targeted to the underlying genetic alteration. Moreover, a significantly improved understanding of pharmacogenomics allows drug doses to be individualized, giving each child the optimal treatment available. Although the scientific community has gained a better perspective of the landscape of somatic and germ-line mutations underlying pediatric cancer, questions remain. Why do some patients respond to current therapeutic approaches, while other relapse and succumb to their disease? Recent advancements in the ability to sequence pediatric cancer samples—at both a population and single cell level—are beginning to provide answers about the diverse mechanisms that can lead to refractory disease. This lecture will focus on how progress made in understanding the molecular landscape of childhood cancer can be used to benefit the pediatric and adult cancer care communities as well as to raise cure rates in countries near and far.

**Gianni Bonadonna Breast Cancer Award and Lecture**

**The contribution of NSABP clinical trials to the management of early breast cancer: A 60-year odyssey.**

Norman Wolmark, MD; Allegheny General Hospital

Since 1958, the National Surgical Adjuvant Breast and Bowel Project (NSABP) has been conducting clinical trials to determine optimal therapy in patients with early-stage breast cancer. These trials were performed in a chronologic...
sequential manner and provide a well-documented historical record of prevalent biologic hypotheses, prescient and otherwise. This endeavor has established numerous standards of care, a tribute to the 120,000 women who have participated, and is emblematic of this year’s ASCO theme, “Caring for Every Patient, Learning from Every Patient.” Two landmark studies started in the 1970s (B04, B06) initiated the retreat from radical mastectomy and established the propriety of breast-preserving operations. They convinced surgeons that treatment failures were not a consequence of inattention to operative detail but were due to the presence of micro-metastatic disease. Thus, the decline of the radical mastectomy and the ascent of adjuvant therapy are inextricably intertwined. Between 1973 and 2005, NSABP consecutive adjuvant therapy trials increased the 10-year DFS from 30% to 75% in node-positive patients. Perhaps viewed in hindsight, some of these studies might seem banal; however, the incremental gains in DFS and the number of lives saved are incontrovertible. In 1988, the initiation of preoperative chemotherapy trials (B18, B27) demonstrated that chemotherapy used in combination with tamoxifen was superior to tamoxifen alone. Both of these trials were used to validate the 21-gene RS panel (2004). This assay has significantly reduced the overall use of adjuvant chemotherapy in the United States. Perhaps the most dramatic results in the 60-year history of the group were obtained in NSABP B31 where trastuzumab was added to chemotherapy in N+ HER2+ patients. The initial joint findings were instrumental in the FDA considering accelerated approval based on pCR in 2012 and emphasizing the advantages of the non-pCR setting on the basis of the results of the Katherine (B50) study in 2019. Protocols B14 (1982-1988) and B20 (1988-1993) established the value of tamoxifen in node-negative ER-positive patients and demonstrated that chemotherapy used in combination with tamoxifen was superior to tamoxifen alone. The number of lives saved are incontrovertible. In 1988, the initiation of preoperative chemotherapy trials (B18, B27) established the association of pCR and improved survival and non-pCR as a high-risk prognostic discriminate. The trials were instrumental in the FDA considering accelerated approval based on pCR in 2012 and emphasizing the advantages of the non-pCR setting on the basis of the results of the Katherine (B50) study in 2019. Protocols B14 (1982-1988) and B20 (1988-1993) established the value of tamoxifen in node-negative ER-positive patients and demonstrated that chemotherapy used in combination with tamoxifen was superior to tamoxifen alone. Both of these trials were used to validate the 21-gene RS panel (2004). This assay has significantly reduced the overall use of adjuvant chemotherapy in the United States. Perhaps the most dramatic results in the 60-year history of the group were obtained in NSABP B31 where trastuzumab was added to chemotherapy in N+ HER2+ patients. The initial joint analysis from NSABP B31 and North Central N9831 disclosed a hazard ratio of .48 and an absolute 18% increase in DFS (2005). These results were hailed as the harbinger of a completely altered approach to the treatment of breast cancer by an enthusiastic editorialist who may yet be proven correct. Symbolically the age of therapy targeting genetic aberrations in the adjuvant setting was initiated.

The Allen S. Lichter Visionary Leader Award and Lecture

**Clinical trials and their application: Should we believe what we read?**

Ian Tannock, MD, PhD, FASCO; Princess Margaret Cancer Centre and University of Toronto

Well-designed randomized controlled trials (RCTs) prevent bias in comparing treatments and can provide a sound basis for changing practice. However, the design and reporting of many RCTs limits their relevance to clinical practice. The aim of all medical treatments is to improve survival and/or its quality. RCTs should avoid non-validated surrogate endpoints. Progression-free survival has been validated as a surrogate for overall survival only rarely and its impact on quality of life depends on balance between possible delay in new symptoms and added toxicity of a drug. Often, experimental drugs add toxicity and if patients discontinuing treatment are censored prior to disease progression, higher dropout in the experimental arm introduces bias and essentially invalidates randomization. RCTs should ask questions of clinical rather than commercial interest; clinical value is more important than the p value. Development of the ASCO Value Framework and the ESMO-Magnitude of Clinical Benefit Scales (MCBS) facilitate evaluation of clinical benefit. Many registered anticancer drugs neither satisfy MCBS thresholds for substantial benefit nor have shown improvements in survival or its quality. Entry criteria for trials have become more restrictive leading to an efficacy-effectiveness gap: lesser benefit and higher toxicity when results are extrapolated from selected patients in trials with high performance status and minimal comorbidity to routine practice. Clinical outcome studies using large databases are important to verify benefit of new treatments in the real world. Reports of RCTs should address the primary endpoint and provide complete accounting of toxicities, with updated information to capture chronic toxicity. Strict guidelines should ensure freedom from bias, with recognition that declaring potential conflict-of-interest does not prevent it. The Annual Meeting 2019 theme “Caring for every patient, learning from every patient” should obligate oncologists from every country to lobby (and, if necessary, shame) pharma, insurers, and governments to provide access to all treatments shown to convey true clinical benefit.

Ellen Stovall Award and Lecture

**The art and science of cancer survivorship.**

Ann H. Partridge, MD, MPH, FASCO; Dana-Farber Cancer Institute

As a growing number of people live for many years after their cancer diagnosis, cancer survivorship has emerged as an important part of the cancer care continuum. The life-changing consequences of cancer for patients and their loved ones pose unique medical and psychosocial challenges in the aftermath of initial treatment. There are four overarching components of survivorship care and research: (1) surveillance for recurrence and screening for second primary cancers including personalized assessment of risk; (2) identification and management of the long-term medical and psychosocial effects of cancer and cancer treatments; (3) promotion of improvements of modifiable health behaviors; and (4) coordination of care and communication among providers and with survivors to ensure that their individual needs are met. Although great strides have been
made in each of these areas, there is much work to be done. We need to continue to improve our understanding of risks faced by cancer survivors and identify how to best intervene when indicated. Ongoing research is focusing on the identification of biomarkers of risk for secondary cancers as well as complications from treatment. Integrative therapy, psychotherapeutic cognitive behavioral techniques, and energy balance interventions have demonstrated particular promise for a wide range of symptoms and have great potential for long-term risk reduction. At the same time, we need to optimize cancer survivorship care delivery so that all survivors can benefit from state-of-the-art care. Harnessing the potential of electronic health record and internet-based tools can facilitate the implementation of evidence-based guidelines to inform appropriate follow-up, while enhancing the uptake of resources to support survivors. Providers can endeavor to incorporate these tools routinely into clinical care, enabling individual patients to communicate their symptoms and concerns effectively, ensuring that the diverse needs of survivors are met.
LBA1 Plenary Session, Sun, 1:00 PM-4:00 PM
Affordable Care Act (ACA) Medicaid expansion impact on racial disparities in time to cancer treatment. First Author: Blythe J.S. Adamson, Flatiron Health, New York, NY

LBA2 Plenary Session, Sun, 1:00 PM-4:00 PM
Overall survival (OS) results of a phase III randomized trial of standard of care therapy with or without enzalutamide for metastatic hormone sensitive prostate cancer (mHSPC): ENZAMET (ANZUP 1304), an ANZUP-led international co-operative group trial. First Author: Christopher Sweeney, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA

LBA3 Plenary Session, Sun, 1:00 PM-4:00 PM
ANNOUNCE: A randomized, placebo (PBO)-controlled, double-blind, phase (Ph) III trial of doxorubicin (dox) + olaratumab versus dox + PBO in patients (pts) with advanced soft tissue sarcomas (STS). First Author: William D. Tap, Memorial Sloan Kettering Cancer Center, New York, NY

LBA4 Plenary Session, Sun, 1:00 PM-4:00 PM
Olaparib as maintenance treatment following first-line platinum-based chemotherapy (PBC) in patients (pts) with a germline BRCA mutation and metastatic pancreatic cancer (mPC): Phase III POLO trial. First Author: Hedy L. Kindler, The University of Chicago, Chicago, IL

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Sunday, June 2. Onsite at the Meeting, this abstract will be printed in the Sunday edition of ASCO Daily News.
100 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM

**Serum IL-6 and CRP as prognostic factors in melanoma patients receiving single agent and combination checkpoint inhibition.** First Author: Jeffrey S. Weiskopf, Second Author: Saec Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY

**Background:** Acute phase reactants including C-reactive protein (CRP), and chronic inflammatory proteins including IL-6, which induces production of CRP from the liver, have been associated with a poor outcome in a variety of cancers. **Methods:** Sera from the CheckMate 064, 066 and 067 studies were assessed at baseline and on treatment for levels of IL-6 and CRP by Luminex. Associations between IL-6 and CRP responded to treatment were determined. Purified endothoxin- and azide-free CRP was also tested for its immune effects in vitro using human T cells. **Results:** In patients receiving sequential nivolumab then ipilimumab in CheckMate 064 (cohort A), baseline serum IL-6 was associated with response (p = 0.03); serum IL-6 at week 12 after nivolumab alone (cohort A) or ipilimumab alone (cohort B), was also associated with response (p = 0.004 and 0.006, respectively). Baseline IL-6 above the median was associated with shorter survival in cohort A (p = 0.003) and cohort B (p = 0.0001). Serum CRP above the median was associated with shorter survival in cohort A (p = 0.001). Baseline IL-6 and CRP in cohort A were associated with one another (p = 0.131 and P < 0.0001 respectively). CRP suppressed T cell immunity and function, and levels above 10 micrograms/mL suppressed T cell proliferation (p = 0.005) and altered T cell signaling as well as calcium flux (p = 0.01), suggesting that CRP affected the earliest steps in T cell signaling and activation. **Conclusions:** High levels of CRP and IL-6 were associated with a poor response and shorter survival after nivolumab alone, and CRP with ipilimumab alone or the combination of both drugs. High levels of CRP were also associated with shorter overall survival in the randomized CheckMate 066 study of chemotherapy compared to nivolumab. IL-6 and IL-6 are prognostic factors for checkpoint inhibition.

101 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM

**Biomarker analyses from JAVELIN Renal 101: Avelumab + axitinib (A+A) versus sunitinib (S) in advanced renal cell carcinoma (ARCC).** First Author: Toshi Tsuchida, The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute and Brigham and Women’s Hospital, Boston, MA

**Background:** The phase 3 JAVELIN Renal 101 trial in previously untreated patients (pts) with ARCC demonstrated a progression-free survival (PFS) benefit and higher objective response rate with A+A vs S (Motzer, ESMO, 2018). **Methods:** We correlated efficacy with the results of molecular analyses of tissue samples from all 896 pts enrolled in JAVELIN Renal 101. Nephratomy or tumor samples were characterized by immunochemistry (CD8 and PD-L1), whole-exome sequencing (WES), and RNAseq. WES and RNAseq were used to examine somatic mutations and analyze relevant gene expression signatures (GES) in relation to clinical outcomes. GES analyses included published and de novo signatures: effector T cell (Teff), angiogenesis (angio), T cell-inflamed (Tinf), and a novel immune-related signature incorporating pathway indicators for T- and NK-cell activation and IFNγ signaling, among others. **Results:** PD-L1 expression ≥ 1% immune cells) was associated with the longest PFS in the A+A arm and the shortest in the A+Ax arm. In the low-angiogenesis subset, A+A improved PFS vs S. Pts with high TIR and TM in the A+Ax arm had longer PFS vs the S arm. In the A+Ax arm, PFS was enhanced in patients with immune-GES-positive tumors vs those in the negative group (HR, 0.63; 95% CI, 0.46, 0.86; 2-sided p = 0.004), as well as in an independent dataset (JAVELIN Renl 100, Choueiri, Lancet Oncol, 2018) (HR, 0.46; 95% CI, 0.20, 1.05; 2-sided p = 0.064). Updated efficacy, including overall survival, will be presented. **Conclusions:** These findings define molecular features that differentiate therapy-specific outcomes in first-line ARCC and may inform personalized therapy strategies for pts with ARCC. Funding: Pfizer and Merck KGaA. Clinical trial information: NCT026284005.

102 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM

**Association of STK11/LKB1 genomic alterations with lack of benefit from the addition of pembrolizumab to platinum-doublet chemotherapy in patients with squamous non-small cell lung cancer.** First Author: Fermin Madriles, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Addition of pembrolizumab (P) to platinum-doublet chemotherapy (carboplatin or cisplatin) and pemetrexed (CP) prolongs overall survival and is a standard of care (SOC) for the 1st line treatment of metastatic EGFR/ALK-astatic tumors. High levels of STK11/LKB1 (p-mut) are associated with a poor response and shorter survival after nivolumab alone, and CRP with ipilimumab alone or the combination of both drugs. High levels of CRP were also associated with shorter overall survival in the randomized CheckMate 066 study of chemotherapy compared to nivolumab. IL-6 and IL-6 are prognostic factors for checkpoint inhibition.

103 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM

**Association of polybromo-associated BAF (PBAF) complex mutations with overall survival (OS) in cancer patients (pts) treated with immune checkpoint inhibitor (ICI) therapy [carboplatin (or cisplatin) and pemetrexed (CP)].** First Author: Sarah Abou Alaiwi, Dana–Farber Cancer Institute, Boston, MA

**Background:** ICI’s have shown benefit across several metastatic carcinomas, yet predictive biomarkers are still lacking. 20% of malignancies harbor alterations in ≥1 gene that is part of PBAF complex. With recent data suggesting an association between PBRM1 mutations (mts) and outcomes in renal cell carcinoma (RCC), pts treated with ICI’s (Choueiri, Science, 2016), we examined the association between PBAF mts and OS in ICI-treated patients across several solid cancer (ca) types. **Methods:** Of 6007 pts with different ca histologies and targeted exome sequencing (Oncopanel) at Dana Farber Cancer Institute (DFCI), 138 pts had truncating mts in any PBAF gene (SMARCA4, PBRM1, and ARID2) or oncogenic missense mts in SMARCA4 and were treated with ICIs. 138 histology-matched DFCI pts had none. A publicly-available cohort (2:1 histology matched) from Memorial Sloan Kettering (MSKCC) (Samstein et al., Nature Genet, 2019) of 621 ca pts treated with ICIs included 6 pts with PBAF mts. Significant treatment arm-specific differences in PFS were observed relative to wildtype when mutations in genes such as CD1631L, PTEN, or DNMT1 were present. Tumor mutational burden did not distinguish pts with respect to PFS. High-angio GES was associated with significantly improved PFS in the S arm but did not differentiate the A+Ax arm. In the low-angio subset, A+Ax improved PFS vs S. Pts with high TIR and TM in the A+Ax arm had longer PFS vs the S arm. In the A+Ax arm, PFS was enhanced in patients with immune-GES-positive tumors vs those in the negative group (HR, 0.63; 95% CI, 0.46, 0.86; 2-sided p = 0.004), as well as in an independent dataset (JAVELIN Renl 100, Choueiri, Lancet Oncol, 2018) (HR, 0.46; 95% CI, 0.20, 1.05; 2-sided p = 0.064). Updated efficacy, including overall survival, will be presented. **Conclusions:** These findings define molecular features that differentiate therapy-specific outcomes in first-line ARCC and may inform personalized therapy strategies for pts with ARCC. Funding: Pfizer and Merck KGaA. Clinical trial information: NCT026284005.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Genetic predisposition to breast cancer among African American women. First Author: Julie R Palmer, Boston University, Boston, MA

Background: The identification of pathogenic mutations in breast cancer susceptibility genes through clinical genetic testing leads to focused screening and prevention strategies for women at increased risk of cancer. However, the frequency of mutations and the risks of cancer associated with breast cancer predisposition genes has not been established for the African American population. Methods: Germline DNA samples from African American women (5,054 breast cancer cases and 4,993 age-matched unaffected controls) from 10 U.S. studies were tested for mutations in 20 established breast cancer predisposition genes using a QIAseq multiplex amplicon panel as part of the “CAnceR Risk Estimates Related to Susceptibility” (CARRIERS) study. The frequency of mutations in each gene and associations between mutations and breast cancer risk, adjusted for study design, age, and first-degree family history of breast cancer, were evaluated. Results: The mean age at diagnosis of breast cancer cases was 54.4 years and the mean age of controls was 55.2 years. 18.2% of cases and 10.8% of controls reported a first-degree family history of breast cancer. Pathogenic mutations in any of the study. The frequency of mutations in each gene and associations between mutations and breast cancer risk, adjusted for study design, age, and first-degree family history of breast cancer, were evaluated. Results: The mean age at diagnosis of breast cancer cases was 54.4 years and the mean age of controls was 55.2 years. 18.2% of cases and 10.8% of controls reported a first-degree family history of breast cancer. Pathogenic mutations in any of the 20 breast cancer predisposition genes were identified in 7.6% of breast cancer cases and 2.4% of controls. In multivariable analyses, mutations in BRCA1, BRCA2, PALB2 were associated with high risks of breast cancer (odds ratio (OR) > 5.0). Mutations in CHEK2 were associated with moderate risks of breast cancer (OR > 2.0), whereas mutations in ATM had lower clinical relevance (OR = 1.8). Mutations in BRCA1, BRCA2, PALB2, and RAD51D, but not CHEK2 or ATM, were associated with increased risks of estrogen receptor negative breast cancer. Conclusions: Cancer predisposition genes confer similar risks of breast cancer in the African American population as in non-Hispanic Whites. These studies provide important insights into the risks of breast cancer associated with predisposition gene mutations in the African American population.

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Sunday, June 2. Onsite at the Meeting, this abstract will be printed in the Sunday edition of ASCO Daily News.
A predictive model for survival in non-small cell lung cancer (NSCLC) based on electronic health record (EHR) and tumor sequencing data at the Department of Veterans Affairs (VA).

**Background:** Machine learning tools based on EHR data hold promise to help avoid unnecessary risks associated with lung cancer and its treatment. Additionally, molecular genetic profiling is becoming an integral tool for clinicians to individualize treatment for lung cancer. However, relatively few survival models have been built that integrate this data in individualized predictive models. Here, we combine real-world EHR and tumor sequencing data from the VA Precision Oncology Data Repository (PODR) to build accurate individualized survival predictions in newly-diagnosed NSCLC patients.

**Methods:** We identified a cohort of 356 VA patients newly diagnosed with NSCLC for whom EHR, cancer registry, and targeted tumor sequencing data is available in PODR. We defined 41 features reflecting 15 baseline clinical and demographic characteristics from the EHR and registry, such as age, race, stage, histology, and therapy. We also defined features reflecting 206 clinically actionable somatic variants. We selected 5 important variants for inclusion in the model, as well as the total number of mutations. We trained a random forests algorithm to predict 1-year survival. Precision, recall, and area under the ROC curve (AUC) were assessed using 5-fold cross validation. **Results:** Mean age at diagnosis was 66 years. The majority of patients had late stage disease (15% stage I, 6% II, 15% III, 44% IV), and 59% of patients received systemic therapy, 45% died within 1 year of diagnosis, and 55% survived past 1 year. Our predictive model for 1-year survival achieves strong results. Cross-validated AUC is 0.79 (SD 0.08), precision is 0.79 (SD 0.07), recall is 0.74 (SD 0.07), suggesting that the trained model combining clinical and genomic features is effective at predicting 1-year survival. **Conclusions:** By integrating real-world EHR and sequencing data, we built a highly accurate predictive model of 1-year survival in NSCLC patients at the VA. Such a model, after ongoing validation in a larger cohort, offers the ability to make individualized predictions that could inform patient care to improve outcomes.
Her2 heterogeneity as a predictor of response to neoadjuvant T-DM1+P plus pertuzumab. Results from a prospective clinical trial. First Author: Ottom Metzger Filho, Dana-Farber Cancer Institute, Boston, MA

Background: HER2 targeted therapy without chemotherapy may be insufficient to completely eradicate a HER2+ cancer in cases of significant intratumor HER2 heterogeneity (IHT-HER2). Methods: We conducted a single-arm phase II study enrolling centrally confirmed HER2+ breast cancer. Pts received 6 cycles of T-DM1 plus Pertuzumab before surgery. Core biopsy HER2 was assessed on baseline ultrasound-guided biopsies from 2 distinct areas of each tumor (3 cores/site). IHT-HER2 was defined as at least one of the six areas demonstrating either 1) HER2 positivity by FISH in > 5% and < 50% of tumor cells (i.e., CAP guideline) or 2) an area of tumor that tested HER2 negative. The primary objective is the association between pathologic complete response (pCR) and ITH, stratified by ER status, pCR defined as residual cancer burden (RCB) 0. Results: 164 pts with centrally confirmed HER2+ tumors were enrolled from 1/2015 to 1/2018. 2 pts withdrew consent. Median tumor size by imaging was 2.8 cm (IQR 2.1-3.8cm); 111 (69%) were ER+ and 51 (32%) ER-. 8 pts discontinued tx (6 due to disease progression, 2 due to toxicity). 49% of pts had a pCR (RCB=0), 14% RCB=1, 26% RCB=11 and 11% RCB=III. Higher rates of RCB=0 were seen in ER- (65%) versus ER+ (42%). IHT-HER2 was detected in 10% (16/157) of evaluable cases. No pCR was observed among cases classified as homogeneous (RCB-I 25%, RCB-II 25%, RCB-III 50%). The study met its primary endpoint by demonstrating a significant association between ITH-HER2 and pCR stratified by ER status (p < .0001). Secondary analysis also demonstrated a significant association between ITH-HER2 and pathologic response defined as RCB 0 or I (OR = 5.6, p = 0.004). Exploratory analysis revealed higher rates of RCB=0 among tumors centrally classified as HER2+ by FISH (65%/6118) versus HER2+ 2 (27%/1037), (OR = 3.4, p = 0.002). The association of ITH-HER2 and pCR was maintained when stratifying by ER status and HER2 IHC (2+ vs. 3+), (p = 0.002). Conclusions: IHT-HER2 assessed by routine pathology evaluation is a strong predictor of pCR to a dual-HER2 targeted therapy regimen. If validated, IHT-HER2 may need to be considered in a selection of pts for HER2-targeted regimens without chemotherapy in the curative setting. Clinical trial information: NCT02326974.

Breast Cancer—Local/Regional/Adjuvant

502 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Impact of clinical risk category on prognosis and prediction of chemotherapy benefit in early breast cancer (EBC) by age and the 21-gene recurrence score (RS) in TAILORx. First Author: Joseph A. Spara, Montefiore Medical Center, Albert Einstein College of Medicine, Albert Einstein Cancer Center, Bronx, NY

Background: TAILORx established that endocrine therapy (ET) alone is non-inferior to adjuvant chemotherapy (CT) plus ET in EBC and a 21-gene RS of 16-25. (Funded by National Cancer Institute, Breast Cancer Research Foundation). Clinical trial in- formation: NCT02568839.

Methods: Clinical risk by was assessed by Adjuvant! (version 8.0) using MINDACT criteria (PMID: 27557300), defined as low clinical risk (LCR) - tumor < 3 cm and low grade, < 2 cm and intermediate grade, or ≤ 1 cm and high grade) and high clinical risk (HCR - not meeting LCR criteria).

Results: Of 9427 women with RS and clinical risk information, 70% were LCR and 30% HCR. LCR/HCR provided additional prognostic information in each RS category for IFS, including RS 0-10 (p = 0.03% vs. 0.4% overall; 0.3% vs. 0.7% overall).

Conclusions: Clinical risk stratification provides additional prognostic information to RS, a secondary trial endpoint.
Benefit from letrozole as extended adjuvant therapy after sequential endocrine therapy: A randomized, phase III study of Gruppo Italiano Mammella (GIM). First Author: Luca GD Mastro, Ospedale San Martino-Oncologia Medica, Genova, Italy

**Background:** The effect of extended adjuvant endocrine therapy (ET) with aromatase inhibitors (AI) after sequential ET with tamoxifen (Tam) followed by AIs for 5 years is still controversial. We conduct a clinical trial to assess different durations of ET of letrozole after tam.

**Methods:** The GIM4 LEAD (Gruppo Italiano Mammella 4 – Letrozoload adjuvant therapy duration study, ClinicalTrials.gov:NCT01064635) was a prospective, randomized, Italian multicentric trial. Post-menopausal patients (pts) with hormone receptor positive early breast cancer free of recurrence after 2-3 years of adjuvant tam, were randomized in a 1:1 ratio to receive 3-2 years (short arm, S) or 5 years (long arm, L) of letrozole. The primary study end point was disease-free survival (DFS).

**Results:** Between August 2005 and May 2010, 2056 pts were randomly assigned to receive 3-2 years (n=1030) or 5 years (n=1026) of letrozole. Main patients characteristics in the S and L arms were, respectively: median age 60 vs 61 years, node negative 56 vs 56%, (neo)HR+ patients (n = 29) 56.0% (43.4%, 68.0%) 59.3% (41.7%, 75.2%). p=0.031. This effect did not change in a multivariate Cox model that included nodal status, grading and age. No evidence of interaction between random assignment and nodal status, age and grading was found. Among 1963 pts evaluated for DFS, DFS was 86% (95% CI 75.7-87.2) and 85% (95% CI 82.9-87.6) in the S and L arm, respectively (hazard ratio, HR 0.82; 95% CI 0.68-0.98; p=0.031). The median DFS was 10 years (ITR 8.6-11.4). The 8-year DFS was 95% (95% CI 73.7-100). The effect of ET duration was significant on DFS, the probability of DFS at 5 years was 75% in the S arm and 81% in the L arm (chi-square=9.88; p=0.002). Bone fractures occurred in 5 (0.5%) and 9 (0.9%) pts in S and L arm, respectively (p=0.29, Fisher exact test).

**Conclusions:** After 2-3 years of adjuvant tam, extended treatment with 5 years of letrozole resulted in significant improvement in DFS compared to the standard duration of 2-3 years of letrozole. Clinical trial information: NCT01064635.

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GeparOLA: A randomized phase II trial to assess the efficacy of paclitaxel and olaparib in comparison to paclitaxel/carboplatin followed by epirubicin/carboplatin. First Author: Peter A. Fasching, University Hospital Erlangen; Comprehensive Cancer Center Erlangen-EMIN, Erlangen, Germany

**Background:** The efficacy and toxicity of olaparib in early BC pts with homologous recombination deficiency (HRD). First Author: Peter A. Fasching, University Hospital Erlangen; Comprehensive Cancer Center Erlangen-EMIN, Erlangen, Germany

**Methods:** GeparOLA (NCT02789332) randomized 102 pts to either paclitaxel 80 mg/m² weekly (PwT) or paclitaxel 100 mg twice daily for 12 weeks (PwO) with or without olaparib 80 mg/kg daily (Pt+Ol) or olaparib 100 mg twice daily (Pt) with carboplatin (C) weekly. Randomization was stratified by hormone receptor-status (HR+ vs HR-), age (‡ 40 vs ≤ 40), male vs female, and tumor-node-metastasis (TNM) stage (I vs II vs III). The primary endpoint is pathological complete response (pCR; ypT0/is ypN0). A one group χ²-test was planned to exclude the pCR rate of 5% in either arm. Secondary endpoints include DFS (® DFS). Time-to-event was used to compare patient outcome in subgroups of patients with or without HRD. GeparOLA investigates olaparib in HER2-negative early breast cancer (BC) and homologous recombination deficiency (HRD).

**Results:** Among 196 pts evaluated for DFS, 90 pts were untreated primary tumor C2—tC4a—d or tC1c with either cN+ or pN1+ or triple negative or Ki-67 > 20% were included, with either g/BRCA mutation and/or high HRD score.

**Conclusions:** The efficacy of ET duration was significant on DFS, the probability of DFS at 5 years was 75% in the S arm and 81% in the L arm (chi-square=9.88; p=0.002). Bone fractures occurred in 5 (0.5%) and 9 (0.9%) pts in S and L arm, respectively (p=0.29, Fisher exact test). These data provide further validation and establish level 1B evidence for BC as a predictive biomarker for preferential benefit from ET in HR+ breast cancer.

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TBCRC 030: A randomized phase II study of predictive cisplatin versus paclitaxel in TNBC. Evaluating the homologous recombination deficiency (HRD) biomarker. First Author: Erica L. Mayer, Dana-Farber Cancer Institute, Boston, MA

**Background:** Cisplatin (C) and paclitaxel (T) have activity in TNBC, however predictive biomarkers are lacking. The HRD assay detects impaired dsDNA break repair and may identify BRCA1/2-proficient tumors for treatment with DNA damaging therapies. TBCRC 030 was designed to determine the association between HRD and response to predictive chemotherapy (CT) in TNBC. This phase II study randomized patients (pts) with BRCA1/2-proficient/unknown stage I-III TNBC to 12 weeks (wks) of predictive C or T, followed by surgery. HRD was assessed on baseline tumor tissue with positive predictive scores >33. Non-responders at 12 wks could crossover to alternative CT. The co-primary objectives were to detect a positive association of HRD with pathologic response (RBC 0-1) vs not (RBC 2-3) to C and a negative association to T. Target accrual of 160 pts was planned to yield 140 evaluable specimens for HRD, providing 90% power for the primary objectives. Analyses used logistic models and likelihood ratio tests with one-sided Type I errors of alpha = 0.05.

**Conclusions:** At 140 pts initiated treatment, (72 Arm C, 68 Arm T; 81% T1-2, 62% node negative), 138 were evaluable for response at 12 wks. Post-enrollment testing showed 8 pts (5.8%) with germline DNA-repair pathway mutations. HRD results were available for 95 pts (68.8%, 23 inadequate tissue, 22 pending). 68 (71.6%) were HRD positive: 38 in Arm C, 30 in Arm T. In response-predictive pts, 87 (63.0%) had surgery at 12 wks, and 51 (37.0%) crossed over. Response outcomes are shown in Table. No association was seen between HRD score and RCB response to either neoadjuvant C (OR 2.78, CI 0.61, 17.74) or T (OR 0.98, CI 0.20, 5.06). There was no evidence of an interaction between HRD and CT arms. Similarly, no association was observed between HRD score and pCR to either C (OR 1.47, CI 0.40, 5.59) or T (OR 0.61, CI 0.14, 2.52). There were no new safety signals. These data provide further validation and establish level 1B evidence for BC as a predictive biomarker for preferential benefit from ET in HR+ breast cancer.

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508 Oral Abstract Session, Mon, 9:45 AM-12:45 PM
Patient-reported outcomes (PROs) in NRG oncology/NSABP B-39/RTSG 0413: A randomized phase III study of conventional whole breast irradiation (WBI) versus partial breast irradiation (PBI) in ER positive breast cancer (NCAT). First Author: Patricia A. Ganz, NRG Oncology, and The UCLA Jonsson Comprehensive Cancer Center at UCLA, Los Angeles, CA

Background: PBI is an alternative to WBI, with potentially greater therapy (tx) compliance, and better integration with chemotherapy (CTX). NSABP B-39/RTSG 0413 clinical outcome results from 2018 did not show equivalence of PBI to WBI in local tumor control; PBI was statistically inferior, but with clinically small differences. PBI may be an acceptable alternative to WBI for some women. Understanding cosmosis and quality of life (QOL) treatment outcomes is important. Methods: B-39/0413 included a prospective QOL substudy with PRO evaluation of breast cancer treatment outcomes (cosmesis, function, pain) and fatigue using BCTOS and SF-36 vitality scales. Secondary QOL parameters included treatment related symptoms, perceived convenience of care, and the BPI pain scale. The study sample was stratified by CTX or not, as CTX is given before WBI but after PBI. PRO assessments occurred before randomization, the last day of adjuvant tx (CTX or radiation), 4 wks later, and 6, 12, 24, and 36 mo later. Primary aims included comparisons of change in fatigue from baseline to end of tx and equivalency of change in cosmosis from baseline to 36 mo for PBI v WBI. Separate analyses were done for CTX and non-CTX pts, controlling for axillary dissection. Each comparison used α=0.0125. Planned sample size was 964. Results: From 2-3-05 to 5-27-09, 975 pts were enrolled in the PRO study; 950 had follow-up data. 504 did not receive CTX and were enrolled in the PRO substudy with follow-up. QOL results are shown in Table 1. Planned sample size was 964.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>WBI (n=450)</th>
<th>PBI (n=450)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosmosis</td>
<td>1-year</td>
<td>0.95</td>
<td>0.38</td>
</tr>
<tr>
<td>Function</td>
<td>1-year</td>
<td>0.94</td>
<td>0.39</td>
</tr>
<tr>
<td>Pain</td>
<td>1-year</td>
<td>0.93</td>
<td>0.50</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1-year</td>
<td>0.94</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Conclusion: In non-CTX pts, PBI had more pain at 36 mo but in CTX pts, was equivalent at 36 mo in CTX pts. Support: U10CA180868, -180822, -180823. Planned sample size was 964. Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Differential impact of endocrine therapy (ET) and chemotherapy (CT) on quality of life (QoL) of 4,262 breast cancer (BC) survivors: A prospective patient-reported outcomes (PRO) analysis. First Author: Arlindo R. Ferreira, Institut Gustave Roussy, Villejuif, France

Background: We recently witnessed a trend to de-escalate CT and escalate ET in adjuvant BC treatment (Ix). However, there has been limited prior research investigating the differential impact on QoL of CT before X (Ix) aimed to test the impact of CT and ET on QoL PROs 2 yrs after diagnosis (dx). Methods: CANTO (NCT01993498) is a multicenter prospective longitudinal study of stage I-III BC pts that characterizes long-term toxicities of BC tx. For this analysis we included 4,262 pts recruited from 2011-2012 at the University of TMC. We estimated QoL using the EORTC QLQ-C30 and BR23. Linear regression modeling was performed, adjusting for demographic and clinical factors, with use of CT and/or CT as independent variables. Analyses were stratified by menopausal status due to different tx patterns and sequence of CT. Results: Median age at dx was 65 yrs, 63% of pts were PostM (PostM) and 37% premenopausal (PreM), 80% had Charlson score 0.16 (95% 0.01-0.53). CT is associated with deterioration QoL. Reference Value: PostM vs PreM:

- Age 3.5 (0.9-5.1)
- Pain 0.4 (0.1-0.9)
- Fatigue 0.9 (0.2-3.5)
- Functional impact 0.7 (0.3-1.4)
- Psychological 1.8 (0.7-4.3)
- Social 0.8 (0.3-1.7)
- Financial 3.8 (0.6-22.5)

Conclusion: In a large prospective cohort of BC survivors, CT negatively impacts QoL up to 2 yrs after dx.

Adjusted linear coefficients (95% CI):

<table>
<thead>
<tr>
<th></th>
<th>PostM vs PreM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Role</td>
<td>0.9 (0.6-1.3)</td>
</tr>
<tr>
<td>Pain</td>
<td>2.8 (2.1-3.8)</td>
</tr>
<tr>
<td>Symptoms (positive worse)</td>
<td>4.2 (3.2-5.4)</td>
</tr>
</tbody>
</table>

Clinical validity of CTS5 for estimating risk of late recurrence in unselected, non-trial patients with early ER+ breast cancer. First Author: Juliet Richman, Royal Marsden Hospital, London, United Kingdom

Background: The Clinical Treatment Score at 5 years (CTS5) is a prognostic tool using clinicalpathological data to estimate distant recurrence (DR) risk after 5 yrs of endocrine therapy for postmenopausal women with estrogen receptor positive (ER+), non-metastatic breast cancer. It was developed and validated in the ATAC and BIG 1-98 trials. Methods: The validity of CTS5 was tested in a retrospective cohort of unselected, non-trial patients diagnosed with early ER+ breast cancer at the Royal Marsden Hospital from 2000-2007 who were alive and distant recurrence-free at 5 years. The endpoint was time to late DR (5-10 yrs). Cox regression models were used to determine the prognostic value of CTS5 and to produce Kaplan-Meier curves with associated 10-year DR risk (%). Results: A total of 2428 women were included with a median follow-up of 9.34 yrs from diagnosis. The CTS5 was significantly prognostic for late DR in post- and premenopausal women. The low risk cohort identified by the CTS5 represents a group of women whose risk of late DR is so low as to not warrant extended endocrine therapy to ten years.

<table>
<thead>
<tr>
<th>Risk level</th>
<th># patients</th>
<th>P%</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>N=576</td>
<td>68.1</td>
<td>0.83</td>
<td>0.60-1.14</td>
</tr>
<tr>
<td>Intermediate</td>
<td>N=208</td>
<td>75.6</td>
<td>69.2-80.9</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>N=644</td>
<td>76.8</td>
<td>62.7-87.9</td>
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</table>

Conclusions: CTS5 demonstrated clinical validity for predicting late DR within a large cohort of unselected, non-trial patients that included postmenopausal women. The low risk cohort identified by the CTS5 represents a group of women whose risk of late DR is so low as to not warrant extended endocrine therapy to ten years.

Event-free survival analysis of the prospectively randomized phase III ETNA study with neoadjuvant nab-paclitaxel (nab-P) versus paclitaxel (P) followed by anthracycline regimens in women with HER2-negative high-risk breast cancer. First Author: Luca Giani, IRCCS San Raffaele Hospital, Milan, Italy

Background: The ETNA study showed that substituting P with nab-P did not significantly increase the overall rate of pathological complete response (pCR) (OR 1.19, 95% CI 0.84-1.63). The nab-P arm had a higher incidence of grade 3-4 neutropenia (37% vs 27%) and grade 3-4 vomiting (23% vs 12%) compared with the P arm. Patients in the nab-P arm had a lower mean QoL compared to the P arm at 2 yrs, with a clinically meaningful change (≥10 points) from baseline in the mean scores in either arm, including on symptoms such as AEs seen with T-DM1 (eg, fatigue). While more pts in the nab-P arm reported clinically meaningful deterioration in role functioning (49% vs 41%), appetite loss (38% vs 28%), and fatigue (41% vs 32%), nausea/vomiting (39% vs 34%), and systemic treatment side effects (49% vs 36%) at ≥1 assessment, the proportion reporting clinically meaningful change in functioning was similar among arms at any given assessment. Conclusions: Mean scores showed only small deterioration from baseline in patient-reported treatment-related symptoms in both study arms. While more pts in the nab-P arm had reported deterioration in some at point in several symptoms, baseline global health status and functioning were generally maintained in both arms over the treatment course.

Clinical trial information: NCT01772472.

Event-free survival analysis of the prospectively randomized phase III ETNA study with neoadjuvant nab-paclitaxel (nab-P) versus paclitaxel (P) followed by anthracycline regimens in women with HER2-negative high-risk breast cancer. First Author: Luca Giani, IRCCS San Raffaele Hospital, Milan, Italy

Background: The ETNA study showed that substituting P with nab-P did not significantly increase the overall rate of pathological complete response (pCR) (OR 1.19, 95% CI 0.84-1.63). The nab-P arm had a higher incidence of grade 3-4 neutropenia (37% vs 27%) and grade 3-4 vomiting (23% vs 12%) compared with the P arm. Patients in the nab-P arm had a lower mean QoL compared to the P arm at 2 yrs, with a clinically meaningful change (≥10 points) from baseline in the mean scores in either arm, including on symptoms such as AEs seen with T-DM1 (eg, fatigue). While more pts in the nab-P arm reported clinically meaningful deterioration in role functioning (49% vs 41%), appetite loss (38% vs 28%), and fatigue (41% vs 32%), nausea/vomiting (39% vs 34%), and systemic treatment side effects (49% vs 36%) at ≥1 assessment, the proportion reporting clinically meaningful change in functioning was similar among arms at any given assessment. Conclusions: Mean scores showed only small deterioration from baseline in patient-reported treatment-related symptoms in both study arms. While more pts in the nab-P arm had reported deterioration in some at point in several symptoms, baseline global health status and functioning were generally maintained in both arms over the treatment course.

Clinical trial information: NCT01772472.
Results of randomized phase II trial of neoadjuvant carboplatin plus docetaxel or carboplatin plus paclitaxel followed by AC in stage I-II triple-negative breast cancer (NCT02413320). First Author: Priyanka Sharma, University of Kansas Medical Center, Kansas City, KS

Background: Addition of neoadjuvant carboplatin (Cb) to paclitaxel (T) followed by doxorubicin + cyclophosphamide (AC) improves pathologic complete response (pCR) rate compared to TAC in TNBC. An anthracycline-free regimen (CB + docetaxel (DC)) also yields high pCR rates in women with early stage breast cancer (NCT02698891). Key inclusion: age ≥ 65, ECOG PS ≤ 1, absolute neutrophil count (ANC) ≥ 1500/mm3, and no febrile neutropenia (FN) during DD-AC. Criteria to treat for T included ANC ≥ 1000/mm3 and FN ≥ 7 days. The primary endpoint was pCR (no invasive disease in the breast and axilla). The two regimens were compared for differences in pCR, residual cancer burden (RCB), treatment delivery, and toxicity. Results: Between 2015 and 2018, 100 patients were randomized; 48 to Arm A and 52 to Arm B. Median age was 52 years, median tumor size was 2.7 cm, 30% were lymph node-positive and 17% carried a BRCA1/2 mutation. Baseline demographic and tumor characteristics were balanced between the two regimens. pCR was 55% (95% CI 46-64) in Arm A vs 21% (15-30) in Arm B (p = 0.0001). The treatment completion rate was 90% (21/24) in Arm A vs 81% (20/25) in Arm B (p = 0.0001). 112 (90%) (95% CI 83-94%) pts completed DD-AC, 111 (99%) pts completed all 6 cycles of T. Omission of Peg-F was not causally related to non-completion of T in any pts. The most common reasons for dose reduction or delays were non-hematologic. One pt had FN but was able to complete T on time. Eight (6.4%) pts received Peg-F during the trial. Conclusions: Omission of routine GF use during DD-T according to a pre-specified algorithm improves the chances of achieving a significantly higher pCR rate with a reduction in use of Peg-F, relative to the current standard of care. Additional analyses including cost implications are ongoing. Clinical trial information: NCT02698891.

Association between tumor biology and occult lymph node metastases before and after primary neoadjuvant therapy (NAT) for patients with early breast cancer. First Author: Hans-Christian Kolberg, Marienhospital, Bottrop, Germany

Background: Scientific efforts aim at a reduction of axillary morbidity through reduced axillary intervention among patients with early breast cancer. However, axillary surgery is still a very common procedure and with a very high risk of axillary involvement. We analyzed the association between tumor biology and occult axillary involvement with data from arms A and B of the SENTINA trial. All patients received SLNB before NAT, in cases of negative SLNB without further axillary surgery (Arm A) and in cases of positive SLNB (Arm B) with SLNB and axillary dissection after NAT. Logistic and linear regression analyses were carried out to evaluate the association between tumor biology and axillary involvement before and after NAT. Results: Of the 1022 patients in arms A and B of the SENTINA trial 926 were evaluable for this analysis. Of these, 27.9% had triple negative (TN), 16.3% hormone receptor positive (HR) and HER2 positive (TR), 47.6% HR positive and HER2 negative (Luminal) and 8.2% HR negative and HER2 positive (HER2) tumors. 39.7% of the luminal, 28.9% of the HER2, 19% of the TN and 47% of the TP tumors had involved SLN before NAT. Subgroup comparisons showed a significant difference between luminal and TN (p < 0.0001), whereas the differences between luminal and TP (p = 0.115) and HER2 (p = 0.077) were not statistically significant. The 317 patients with involved SLN prior to NAT received SLNB and axillary dissection after completion of NAT. The analysis after NAT showed trends for lower rates of involved lymph nodes for the high-risk groups (TN 20% / TP 14.3% / HER2 8.7%) compared to luminal tumors (27.6%) without reaching statistical significance. Conclusions: Our analysis demonstrates that among patients enrolled in the SENTINA trial, patients with triple negative disease have the highest chance of occult lymph node involvement. This trend is also present after NAT. Our results do not justify more intense local intervention among patients with triple negative breast cancer.
Background: Observational studies of dietary fat intake and breast cancer have inconsistent findings. To address this issue, the Women’s Health Initiative (WHI) Dietary Modification (DM) clinical trial assessed a low-fat dietary pattern influence on breast cancer incidence and mortality. Methods: The WHI trial is a randomized, controlled clinical trial conducted at 40 US centers, where 48,835 postmenopausal women, aged 50-79 years, with no previous breast cancer and dietary fat intake ≥32% of total energy, were randomly assigned, from 1993-1998, to a usual diet comparison group (60%) or dietary intervention group (40%) with goals to reduce fat intake to 20% of energy and increase vegetables, fruit, and grain intake. This study is registered as: NCT00000611. Results: The dietary intervention significantly reduced fat intake; increased fruit, vegetable and grain intake with modest weight loss (3%)(all P < 0.001). During 8.5 years of dietary intervention, there were 8% fewer breast cancers and deaths from breast cancer were somewhat lower in the intervention group but the rates were not significantly different. However, deaths after breast cancer (breast cancer followed by death from any cause) were significantly reduced in the intervention group, both during intervention (hazard ratio [HR] 0.65 95% confidence interval [CI] 0.45-0.95) and through 16.1 years (median) follow-up, with 3,374 incident breast cancers, the significant reduction in deaths after breast cancer continued (with 1,011 deaths, HR 0.85 95% CI 0.74-0.96) and a significant reduction in deaths from breast cancer (breast cancer followed by death contributed to the breast cancer) emerged (with 383 deaths, HR 0.79 95% CI 0.64-0.97). Conclusions: Adoption of a low-fat dietary pattern associated with increased vegetable, fruit, and grain intake, demonstrably achievable by many, significantly reduced the risk of death from breast cancer in postmenopausal women. To our review, these findings provide the first randomized clinical trial evidence that a dietary change can reduce a postmenopausal woman’s risk of dying from breast cancer. Clinical trial information: NCT00000611.

Methods:

520 Poster Discussion Session; Displayed in Poster Session (Board #12), Sun, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-6:00 PM

Low-fat dietary pattern and long-term breast cancer incidence and mortality: The Women’s Health Initiative randomized clinical trial. First Author: Rowan T. Chlebowski, Los Angeles BioMedical Research Institute, Torrance, CA

521 Poster Session (Board #13), Sun, 8:00 AM-11:00 AM

Impact of the extent of resection on primary breast angiosarcoma survival. First Author: Timur Mutin, Oregon Health and Science University, Portland, OR

Background: The widely accepted standard of care in treating primary breast angiosarcoma involves surgical resection, often followed by adjuvant therapy (radiation and/or chemotherapy). The rarity of this disease has precluded large-scale analyses. The question regarding the impact of resection extent on survival has yet to be examined on a nationwide scale. Methods: The National Cancer Data Base (NCDB) from 2004-2014 identified primary breast angiosarcoma patients throughout the United States having undergone surgical resection. The extent of resection (mastectomy versus lumpectomy) was adjusted for several variables (including patient age, race, income, primary payer for care, tumor size, adjuvant therapies, and medical comorbidities) to assess its impact on breast angiosarcoma-related mortality. Results: Over this eleven-year span, 826 resected primary breast angiosarcoma patients were identified in the United States. Mastectomy was by far the most common surgical modality for primary breast angiosarcoma (86% of patients). Increasing tumor size was predictive for mastectomy over lumpectomy (p < 0.0001), and for involvement of adjuvant radiation therapy (p = 0.01). The extent of surgical resection was inversely predictive of resection. Surgical modality was not significantly predictive of breast angiosarcoma-related mortality. Conclusions: Despite the frequent preference of mastectomy for primary breast angiosarcoma treatment (more than 6 of every 7 patients), there is no survival benefit of mastectomy versus lumpectomy. This lack of benefit should be discussed with patients, given the reduced operative morbidity of lumpectomy versus mastectomy. The Class IIB evidence provided from this analysis represents the highest level of evidence to-date governing management of this disease.

Background:

522 Poster Session (Board #14), Sun, 8:00 AM-11:00 AM

Do all patients with HER2-positive breast cancer require one year of adjuvant trastuzumab? A systematic review and meta-analysis. First Author: Paul Stewart, Western University, Schulich School of Medicine and Dentistry, London, ON, Canada

Methods:

PubMed, EMBASE and The Cochrane Library were searched for eligible randomized trials. Hazard ratios (HR) for disease free survival and overall survival (DFS, OS) were weighted using generic inverse variance and pooled in a meta-analysis using random-effects models. The median of non-inferiority margins derived from each trial was calculated to set a non-inferiority margin of 1.29 for the pooled analysis. Subgroup analyses compared survival outcomes by estrogen receptor (ER) status, nodal status, length and timing of trastuzumab treatment. Results: Data of 11,376 patients from 5 trials were analyzed. A shorter duration of T was non-inferior to one year of therapy for DFS (HR 1.13, 95%CI 1.03-1.24) but worse for OS (HR 1.16, 95%CI 1.01-1.32). In addition, the non-inferiority for DFS was not met for patients with ER positive disease (HR 1.1, 95%CI 0.95-1.28) and patients treated with 6 months (HR 1.09, 95%CI 0.98-1.22) or sequential T (HR 1.26, 95%CI 1.02-1.55) and patients with node negative (HR 1.12, 95% 0.93-1.35) or positive (HR 1.16, 95%CI 0.99-1.36) disease. Conclusions: The widely accepted standard of care in treating primary breast angiosarcoma involves surgical resection, often followed by adjuvant therapy (radiation and/or chemotherapy). The rarity of this disease has precluded large-scale analyses. The question regarding the impact of resection extent on survival has yet to be examined on a nationwide scale. Methods: The National Cancer Data Base (NCDB) from 2004-2014 identified primary breast angiosarcoma patients throughout the United States having undergone surgical resection. The extent of resection (mastectomy versus lumpectomy) was adjusted for several variables (including patient age, race, income, primary payer for care, tumor size, adjuvant therapies, and medical comorbidities) to assess its impact on breast angiosarcoma-related mortality. Results: Over this eleven-year span, 826 resected primary breast angiosarcoma patients were identified in the United States. Mastectomy was by far the most common surgical modality for primary breast angiosarcoma (86% of patients). Increasing tumor size was predictive for mastectomy over lumpectomy (p < 0.0001), and for involvement of adjuvant radiation therapy (p = 0.01). The extent of surgical resection was inversely predictive of resection. Surgical modality was not significantly predictive of breast angiosarcoma-related mortality. Conclusions: Despite the frequent preference of mastectomy for primary breast angiosarcoma treatment (more than 6 of every 7 patients), there is no survival benefit of mastectomy versus lumpectomy. This lack of benefit should be discussed with patients, given the reduced operative morbidity of lumpectomy versus mastectomy. The Class IIB evidence provided from this analysis represents the highest level of evidence to-date governing management of this disease.

First Author: Paul Stewart, Western University, Schulich School of Medicine and Dentistry, London, ON, Canada

Results:

2016”的背景下，内分泌治疗的使用率已显著提高，仍需要进一步研究来评估其对乳腺癌患者生存率的影响。
524 Poster Session (Board #16), Sun, 8:00 AM-11:00 AM

De-escalating adjuvant trastuzumab in human epidermal growth factor receptor 2 (HER2)-positive early-stage breast cancer: A systemic review and meta-analysis. First Author: Hadar Goldshmit, Sheba Medical Center, Beilinson Hospital, Davidoff Center, Kryiat Ono, Israel

**Background:** One year of adjuvant trastuzumab in combination with chemotherapy is the standard of care in early-stage HER2 positive breast cancer. Existing data on shortening trastuzumab treatment show conflicting results.

**Methods:** A search of PubMed and conference databases identified randomized trials that compared abbreviated trastuzumab therapy to one year of treatment in early-stage HER2 positive breast cancer. Hazard ratios (HRs) and 95% confidence intervals (CI) were extracted for disease free survival (DFS) and overall survival (OS). Data on the number of DFS and distant relapse events were also collected as were the number of patients at risk in each group. Subgroup analyses evaluated the effect of nodal involvement, estrogen receptor (ER) expression and the duration of abbreviated trastuzumab (9-12 weeks versus 6 months). Odds ratios (ORs) and 95% CI were computed for pre-specified cardiotoxicity events including cardiac dysfunction and congestive heart failure (CHF).

**Results:** Analysis included 6 trials including 11603 patients. In most studies adjuvant chemotherapy included anthracyclines and taxanes. Shorter trastuzumab treatment was associated with worse DFS (HR = 1.14, 95% CI 1.05-1.25, p = 0.002) and OS (HR = 1.15, 95% CI 1.02-1.29, p = 0.02). The effect on DFS was not influenced by ER status (p for the subgroup difference = 0.23), nodal involvement (p = 0.44) or the different duration of trastuzumab in the experimental arm (p = 0.88). In absolute terms, after one year of trastuzumab therapy, DFS at year 2 and DFS at year 3 declined by 71% and 38% respectively in patients treated with trastuzumab was associated with an absolute increase in DFS events of 2.3%. Shorter trastuzumab treatment was associated with lower odds of cardiac dysfunction (OR = 0.67, 95% CI 0.55-0.81, p < 0.001) and CHF (OR = 0.66, 95% CI 0.50-0.86, p = 0.003).

**Conclusions:** Compared to one year, shorter duration of adjuvant trastuzumab is associated with significantly worse DFS and OS, despite favorable cardiotoxicity profile. One year of trastuzumab should remain the standard adjuvant treatment in early-stage HER2 positive breast cancer with appropriate cardiac monitoring.

525 Poster Session (Board #17), Sun, 8:00 AM-11:00 AM

Effect of tart cherry on aromatase inhibitor-induced arthralgia (AIA) in nonmetastatic hormone-positive breast cancer patients: A randomized double-blind placebo-controlled trial. First Author: Mina Shenouda, Marshall University, Huntington, WV

**Background:** Aromatase inhibitors (AI) are the standard treatment for hormone receptor-positive breast cancer in postmenopausal women. About half of patients (pts) taking AI suffer from AIA which can be severe enough to cause noncompliance. Suboptimal AI adherence is associated with decreased disease-free and overall survival, suggesting that improving adherence will lead to improved breast cancer outcomes. Effective interventions for AIA are still limited. In clinical trials, tart cherry (TC) showed beneficial effect on musculoskeletal pain associated with osteoarthritis, gout, and strenuous exercise. The flavonoids and anthocyanins in TC reportedly exert an anti-inflammatory effect that may lessen adverse effects of estrogen deficiency. This trial aimed to investigate whether TC can reduce AIA in nonmetastatic hormone positive breast cancer (NMHPBC) pts.

**Methods:** This is a randomized, placebo-controlled, double-blind trial. Eligible Pts with NMHPBC on AI for at least 4 weeks were randomized to TC concentrate (equivalent to 50 tart cherries) versus placebo (P) [syrup] in a 1:1 model. Pts were instructed to take 1 Oz of TC or P in 8 Oz water daily for 6 weeks, and to document their pain intensity at baseline, weekly and at study completion in a diary using a Visual Analog Scale (VAS), with 0 mm indicating no pain, and 100 mm indicating highest pain. Results: 60 pts were enrolled from May 2016 to August 2018. 2 pts did not complete the study due to diarrhea and non-compliance. The final results were available at the final analysis. TC group (23 pts) had 34.7% mean decrease in pain compared to 1.4% in P group (25 pts). This difference was statistically significant (Mann-Whitney U Test P = 0.034).

**Conclusions:** Tart cherry can significantly improve AIA in non-metastatic breast cancer patients.
Background: There are no well-established adjuvant chemotherapy (AC) regimens for early triple-negative breast cancer (TNBC). Our randomized phase III trial was designed to compare dose-dense paclitaxel plus carboplatin (PCdd) as adjuvant chemotherapy for early triple-negative breast cancer patients with high-recurrence risk.

Methods: Between May 2011 and November 2015, TNBC patients were randomized in 1:1 ratio to receive PCdd or ECdd-T regimen as AC for TNBC with high recurrence risk. The primary endpoint was 3-year disease free survival (DFS). The secondary endpoints included overall survival (OS) and safety. Survival analyses were also performed for different subgroups stratified by age status (<40 years vs >40 years), Ki 67 (>50% vs ≤50%), tumor size (<2cm vs ≥2cm), nodal status (N- vs N+), and treatment free survival (TFS) (<30 days vs ≥30 days). Results: In total, 132 patients with a median age of 49 years (PCdd 64 patients, ECdd-T 68 patients) were enrolled. After a median follow-up of 57.3 months, 23 events were observed (18 in ECdd-T, 6 in PCdd). Patients in the PCdd arm had significantly higher DFS rate than those in the ECdd-T arm (p = 0.0268), and the difference remained significant after controlling for baseline BMI and weight change (hazard ratio (HR) = 0.305, 95% confidence interval (CI) = 0.134-0.693). The 3-year DFS rate was 43.9% in PCdd vs 64.3% in ECdd-T, and the difference was statistically significant (p = 0.0268). Both regimens were well tolerated with acceptable hematological toxicity, and there were no significant differences in the incidence of neuropathy (Grade 3/4: 48.5% in ECdd-T vs. 21.9% in PCdd, p = 0.002) that was observed in ECdd-T arm. 3-year DFS rate for PCdd was superior in the following subgroups, age ≥40 years, clinically evaluated lymph nodes, TFS <30 days, with statistical significance (p < 0.05).

Conclusions: Our data suggested that PCdd was superior to ECdd-T as AC for TNBC patients with high recurrence risk in a 3-year DFS and OS. PCdd with lower hematological toxicity might be an appropriate regimen for early TNBC patients with high recurrence risk. Clinical trial information: NCT01378533.

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EPHA4, EPHA5, EPHA6, to cumulative systemic paclitaxel exposure. Paclitaxel dose-adjustment to

Background: Chemotherapy induced peripheral neuropathy (CIPN) is a common, debilitating paclitaxel side effect that has been primarily attributed to cumulative systemic paclitaxel exposure. Paclitaxel dose-adjustment to achieve target systemic exposure decreases but does not eliminate severe CIPN, suggesting some patients are inherently CIPN-sensitive. Ephrin (EPHA) polymorphisms have been reported to increase CIPN occurrence (Baldwin 2012, Leandro-Garcia 2013, Boora 2016) but replications has been challenging, perhaps due to the inability to isolate CIPN-sensitivity by accounting for systemic exposure differences. The study purpose was to determine if EPHA genetic variants previously associated with CIPN occurrence are associated with CIPN-sensitivity. 

Methods: PN was assessed at baseline and weekly using the 8-item sensory subscale (CIPN8) of the patient-reported EORTC CIPN20 in patients receiving paclitaxel 80 mg/m2 weekly x 12. EPHA4, EPHA5, EPHA6, and EPHA8 were sequenced in germline DNA. Associations with higher PN sensitivity were tested for three genetic models (total variants, coding variants, and rs7349683) by incorporating genotypes into previously published CIPN8 models that included measured paclitaxel exposure. Significant associations were tested for association with higher risk of PN-related treatment disruption (i.e. dose decrease, delay, or discontinuation).

Results: In the 59 included patients, carrying EPHA5 rs7349683 was associated with greater CIPN sensitivity (beta coefficient: 0.40, standard error: 0.14), indicating these patients had a greater increase in CIPN8 during treatment than would be predicted based on cumulative paclitaxel exposure. Rs7349683 was not associated with increased PN-induced treatment disruption, perhaps due to the low number of events (n = 19).

Conclusions: Using a novel approach that isolates CIPN-sensitivity by accounting for measured paclitaxel exposure, our results provide further evidence that EPHA5 rs73495683 may be a promising marker for CIPN. If additional validation studies confirm this association, genetic testing could enable personalized treatment strategies to prevent CIPN in patients with breast cancer.

Breast Cancer Index and risk stratification in luminal subtypes: A trans-ATAC study, First Author: Amina Sestak, Centre for Cancer Research and Surgical Innovation, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, United Kingdom

Background: The Breast Cancer Index (BCI) is a gene-expression based signature that provides prognostic information for overall (0-10 years) and late (5-10 years) distant recurrence (DR) and prediction of extended endocrine therapy. The current analysis aims to further characterize, correlate and compare the prognostic performance of BCI in luminal subtypes based on immunohistochemical classification. Methods: 670 postmenopausal women with HR+ or HER2- breast cancer from the TransATAC cohort were included in this analysis. Luminal A-like tumors (LumA) were identified as those with ER+ and PR+ and HER2- and Ki67 < 20% by IHC. All other tumors were classified as Luminal B-like (LumB) for this analysis. Primary endpoint was DR. Cox regression models were used to examine BCI prognostic performance according to luminal subtype, adjusting for the clinicopathological model Clinical Treatment Score (CTS).

Results: 452 (67.5%) patients were classified as LumA and 218 (32.5%) as LumB. BCI was highly prognostic in LumA cancers (adjusted HR = 1.57 (1.23-1.96), P < 0.001, \( \Delta LR^2 \chi^2 = 14.09 \), but not in LumB tumors (adjusted HR = 1.20 (0.94-1.52), P = 0.14, \( \Delta LR^2 \chi^2 = 2.23 \)). In LumA, 10-year DR risks in BCI intermediate and high risk groups were very similar (25.6% (16.4-38.6) and 25.3% (13.5-44.3), respectively) and significantly different from low risk (3.9% (2.1-7.0); HR = 7.47 (3.50-15.96) and HR = 8.13 (3.27-20.23), respectively). In LumB, 10-year DR risks in BCI low and BCI intermediate risk groups (13.8% (6.8-26.9) and 14.6% (8.3-24.9), respectively) were very similar and significantly lower than for the BCI high (29.1% (20.0-41.1)).

Conclusions: BCI subtyping was only prognostic in the BCI low risk group (LumA vs. LumB: HR = 4.27 (1.65-11.02)) but not in the other two BCI risk groups. Use of the CTS provided significant prognostic information in Lum A subtype. These results show that BCI intermediate and high risk had similar risk of DR in LumA tumors, while shared similarly low risk of DR as BCI-low in LumB tumors. Further evaluation is needed to elucidate the distinct mechanisms underlying each classification system.

Breast Cancer—Local/Regional/Adjuvant

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Adjuvant chemotherapy in small node-negative triple-negative breast cancer (TNBC). First Author: Tessa Germaine Steenbrugge, Department of Medical Oncology, Academic Cancer Institute, Amsterdam, The Netherlands.

**Background:** International guidelines differ in their recommendation for adjuvant chemotherapy in small node-negative TNBC. We evaluated associations of chemotherapy with long-term outcome in a large population-based TNBC cohort. **Methods:** All patients diagnosed with pT1N0M0 TNBC between 2005 and 2015 were identified from the Netherlands Cancer Registry. Patients, tumor, and therapy characteristics were recorded. Date and cause of death were obtained from Statistics Netherlands. We used multivariable cox regression models to evaluate associations of chemotherapy with overall survival (OS) and breast-cancer specific survival (BCSS), adjusted for baseline characteristics. Subgroup analyses were performed by tumor size and grade. **Results:** We identified 3,933 patients: 284 with T1a, 924 with T1b, and 3,185 with T1c tumors. Chemotherapy was administered in 53% of patients: 6% with T1a, 17% with T1b and 67% with T1c. Chemotherapy use increased over time and varied by geographic region. Patients receiving chemotherapy were younger, had larger tumors, higher tumor grade, and more often isolated tumor cells (ITC) in the lymph nodes. At a median follow-up of 7 years (IQR 5-10 years), 613 patients died of whom 287 due to breast cancer. Chemotherapy was associated with improved OS in the whole group (adjusted hazard ratio [aHR] 0.55; 95% CI 0.44-0.69), in the pT1 subgroup (aHR 0.53, 95% CI 0.41-0.67), and in grade 3 tumors (aHR 0.50, 95% CI 0.39-0.65). Associations were not significant for pT1a or grade 1-2 tumors (table). Findings for BCSS were in line with OS results (table). To illustrate the absolute difference we estimated 10-year OS and BCSS for a 60-year old woman with a pT1cN0(itc+) grade 3 TNBC. The predicted 10-year OS was 67% with chemotherapy and 42% with no chemotherapy. The predicted 10-year BCSS was 80% with chemotherapy and 66% with no chemotherapy.

**Conclusions:** Adjuvant chemotherapy is associated with improved OS and BCSS in small node negative TNBC. Benefit is most evident in grade 3 tumors and tumors >1 cm and not evident in tumors ≤1 cm and grade 1-2.

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Adjuvant chemotherapy in small node-negative triple-negative breast cancer (TNBC). First Author: Jose Pablo Leone, Dana-Farber Cancer Institute, Boston, MA

**Background:** Endocrine therapy resistance is a major cause of distant recurrence (DR) in HR+ breast cancer. Currently, no data exists evaluating differences in clinical behavior after DR between patients (pts) treated in the adjuvant setting with different endocrine therapy regimens. The aim of this study was to analyze post-DR survival of pts treated on BIG 1-98 compared 5 years of adjuvant treatment between 4 arms: tamoxifen (T), letrozole (L), T followed by L (TL) and L followed by T (LT). After 8.1 years median follow-up (follow-up through 2010), 911 (T = 302, L = 285, TL = 170, LT = 154) of 8,010 pts had DR as site of first recurrence. Univariate and multivariable Cox analyses were performed to determine features associated with post-DR survival. With 661 total observed deaths, statistical power was 0.8 to detect a hazard ratio (HR) >1.24 at the 2-sided 0.05 level of significance. **Results:** Median follow up time after DR was 59 months (IQR: 29-88). Among all pts with DR, 38.1% were >65 years at study enrollment, 61.9% had tumor size >2 cm, 69.7% were node positive. Neoadjuvant chemotherapy was administered to 35.6% of pts. There was no difference in post-DR survival by treatment arm (median survival: T: 20.8, L: 17.9, TL: 17.3, LT: 20.8 months; p = 0.21). In multivariable analysis, older pts (HRa 1.36, p = 0.0022), tumors ≥2 cm (HRa 1.2, p = 0.04), ≤4 positive nodes (HRa 1.32, p = 0.05) and PR-tumors (HRa 1.28, p = 0.001) had significantly worse post-DR survival. Endocrine treatment arm, type of surgery, radiotherapy and neo/adjuvant chemotherapy were not associated with post-DR survival in the multivariate model. **Conclusions:** Treatment with adjuvant T, L or their sequence were not associated with differences in survival after DR. We observed significant differences in survival by primary tumor size, nodal and PR status, which suggest that traditional high-risk features remain prognostic in the metastatic setting. Clinical trial information: NCT00004205.

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Efaluzagastim, a novel and potent long-acting GCSF for reducing chemotherapy-induced neutropenia: Integrated results from two phase III trials in breast cancer patients. First Author: Lee S. Schwartzberg, University of Tennessee Health Sciences Center, Memphis, TN

**Background:** Efaluzagastim (E) is a novel long-acting GCSF comprised of recombinant human GCSF covalently linked to human IgG4 Fc fragment via a PEG linker (MW, 72 kDa). E showed increased potency vs pegfilgrastim (P) in preclinical and Phase I and II trials. Two identically designed Phase III pivotal trials (NCT02643420, NCT02953340) were conducted globally with a fixed dose of 13.2 mg E containing 3.6 mg GCSF to evaluate E vs P (6 mg) in pts receiving chemotherapy for early-stage breast cancer. **Methods:** Each open-label trial randomized pts 1:1 to a single subcutaneous dose of E 13.2 mg/0.6 mL or P 6 mg/0.6 mL on Day 1 of each of four 21-day cycles following Day 1 adj/neoadj docetaxel 75 mg/m2 + cyclophosphamide 600mg/m2 (TO). The primary endpoint was to demonstrate E non-inferiority (NI) to P as measured by mean duration of severe neutropenia (DSN) in Cycle 1. **Results:** A total 643 intent-to-treat pts (314 E/329 P) with median age 60 yrs (24-88) were enrolled. Cycle 1 mean (SD) DSN was 0.24 (0.581) vs 0.36 (0.789) days for E and P, confirming NI (p < .0001) and suggesting clinical non-inferiority (p = 0.029). DSN NI was also shown across cycles 2-4. Among subgroups, including elderly (>65 yrs) and overweight (>75kg) pts, DSN was reduced for E vs P. In Cycle 1, E showed an absolute risk reduction for severe neutropenia of 6.5% vs P (27.1% relative risk reduction, p < .043). Neutropenic complications (hospitalization and/or anti-infective use) were 2.9% and 4.0% for E and P (p = ns). Incidence of FN was low for both E and P, 1.6% vs 1.8% in Cycle 1 and 3.2% vs 3.0% overall. ANC profiles showed sustained increased levels for E vs P in the recovery phase across all cycles. Safety profiles were similar for E and P, including primarily for expected hematologic AE and for bone pain and other musculoskeletal pain.

**Conclusions:** These integrated pivotal trial results confirm a similar safety profile and non-inferiority in reducing chemotherapy risk for E at a lower GCSF dose vs P. The data also suggests the potential for increased potency of E to deliver improved clinical benefit, a possibility that warrants further clinical trials. Clinical trial information: NCT02643420, NCT02953340.
540 Poster Session (Board #32), Sun, 8:00 AM-11:00 AM
Factors associated with twenty-year (y) risks of breast-cancer-specific mortality (BCSM) in the Surveillance, Epidemiology, and End Results (SEER) Registry. First Author: Jose Pablo Leone, Dana-Farber Cancer Institute, Boston, MA

Background: Most reports describing the risk of late relapse in breast cancer have been based on selected patients (pts) enrolled into clinical trials. The aims of this study were to report on population-based long-term risks of BCSM, and the risks of BCSM conditional on having survived 5 y. Additionally, we aimed to identify factors associated with late deaths from breast cancer.

Methods: Using SEER data, we identified women with invasive breast cancer (T1-T2, N0-N2, MO) between 1990-2005, with one primary cancer in their lifetime, and known hormone receptor (HR) status. We used Kaplan-Meier analyses to determine the effect of baseline variables on cumulative risks of BCSM, we estimated annual rate of events per 100 person-years, and performed Cox regression stratified by HR status.

Results: We included 202,080 pts (median follow-up = 12.25 y). Of all breast cancer deaths, the proportion after 5 y was 65% for HR+ vs 28% for HR- (p < 0.001). The table shows risks of BCSM by HR and N status, and annual event rates.

The cumulative risk of BCSM in y 5-20 ranged from 7.9% in HR-N0 to 38% in HR+ N1. Among HR+ pts, adjusted risks of BCSM conditional on having survived 5 y were higher for T2 vs T1a (Hazard ratio [HR] 3.3, p < 0.001) and grade III vs I (HR 2.8, p < 0.001), age at diagnosis (dx) = 64 y vs < 50 y (HR 1.4, p < 0.001), black race vs white (HR 1.3, p < 0.001) and grade III vs I (HR 2.3, p < 0.001). For HR- pts, adjusted risks of BCSM conditional on having survived 5 y were higher for T2 vs T1a (HR 2.0, p < 0.001), N2 vs N0 (HR 3.5, p < 0.001), age at dx = 64 y vs < 50 y (HR 1.6, p < 0.001).

Conclusions: For HR+ breast cancer, risks of BCSM remain high beyond 5 y and depend on T-N status and age. Our results underscore the need for better adjuvant therapies in both HR+ and HR- breast cancer.

541 Poster Session (Board #33), Sun, 8:00 AM-11:00 AM
Effects of Non-Linear or Linear Aerobic Training (AT) Dosing Regimens on Impaired Cardiovascular (CV) Function in Patients with Operable Breast Cancer: A Randomized Controlled Trial (RCT). First Author: Jessica Scott, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Breast cancer therapy causes marked impairments in CV function predisposing to elevated risk of CV morbidity. We investigated the effects of two AT dosing regimes on CV function in post-treatment patients with operable breast cancer.

Methods: In a three-arm, parallel-group RCT, 174 post-menopausal patients (2.8 years post primary adjuvant therapy) were randomized age-matched peak oxygen consumption (VO2-peak) to: (1) conventional linear AT (uniform dose-intensity / session), (2) non-linear AT (variable dose-intensity / session), or (3) stretching (attention control). AT consisted of 64 supervised treadmill walking sessions delivered four times weekly at either ~70% VO2-peak for 40 mins/session (linear) or 55% to 100% VO2-peak for 20-45 mins/session (nonlinear) for 16 consecutive weeks. Stretching was matched to AT on the basis of location, frequency, duration, and treatment length. The primary end point was change in VO2-peak.

Secondary end points were other markers of CV risk profile (biochemical CV risk profile, cardiac function, body composition), patient-reported outcomes (PROs), tolerability (e.g., relative dose intensity), and safety. All analyses followed the intention-to-treat principle.

Results: Rates of lost-to-follow were < 10% in all arms. Relative dose intensity of AT was 73% ± 27% and 80% ± 21% in linear and nonlinear arms, respectively. No serious adverse events were observed. In adjusted analysis, compared to control, VO2-peak (ml O2/kg-1.min-1) improved significantly in linear AT by 1.32 (p = 0.02) and nonlinear AT by 0.8 (± 0.4) ml O2/kg-1.min-1 (p = 0.02) in linear and nonlinear AT, respectively. Rates of VO2-peak improvement greater than the technical error of measurement (i.e., ≥ 1.32ml O2/kg-1.min-1) were 33% and 39% in linear and nonlinear AT (p = 0.03), respectively. Both AT regimens were associated with improvements in several secondary CV end points but only nonlinear AT improved PROs compared with control (all ps < 0.05).

There were no differences between the two AT regimens. Conclusion: AT significantly improves CV function and PROs in post-treatment breast cancer patients. The efficacy-tolerability ratio favors the non-linear regimen over the conventional linear prescription approach. Clinical trial information: NCT01186367.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Patterns of systemic treatment utilization in ER+PgR+/HER2-, early-stage breast cancer (BC): An analysis of the National Cancer Database. First Author: Zeina A. Nahleh, Cleveland Clinic Florida, El Paso, TX

Background: The preferences and trends of treatment utilization of adjuvant endocrine therapy (ET) versus chemotherapy (CH) for small node-negative triple positive (TP) BC are unclear. We sought to determine these preferences and assess the impact on outcome. Methods: This is a retrospective study from the National Cancer Database including patients with TP stage I BC, 2004-2011. Treatment selection was evaluated for adjuvant ET, the patient's clinical and demographic characteristics using logistic regression. Overall survival (OS) was estimated using the Kaplan-Meier method and compared among patients and treatment cohorts by log-rank test and Cox regression. Results: Of 37,777 patients analyzed, 79% were White (Non-Hispanics), 10% African Americans, and 5% Hispanic/Latinos. 57% were 50-70 years old. 86% received adjuvant endocrine therapy versus 14% CH first. Around 40% of all patients received anti-Her2 therapy. Patients younger than 70 years, with male BC, diagnosed with poorly differentiated BC, African Americans and Hispanics were more likely to be treated with chemotherapy. OS rate at 5 years was 92.3% (95% CI: 91.8-92.8). In multivariate analysis for patients with survival data, an increased rate of death was associated with: treatment in community versus academic/research centers, CH first versus ET, no treatment with anti-Her2 therapy, government versus private/no insurance, Native American ethnicity. A slight but statistically significant reduction in the risk of death at 5 years was evident for patients receiving anti-Her2 therapy plus ET, 5-year OS 93.5% (CI: 89.2-98%), when compared to patients receiving anti-Her2 therapy plus CH. 72.7% (CI: 89.4-96). Conclusions: This study provides real world data of common practices in the US. The majority of patients with node negative Stage I, ER+PgR+/HER2- BC received adjuvant ET and anti-Her2 therapy, not chemotherapy. These preferences are similar to those observed in 2011 when compared to anti-Her2 therapy plus CH, supporting the use ET plus anti-Her2 therapy in this setting. Future studies should focus on better selecting patients with hormone receptor positive and Her 2 + early stage BC who would benefit from adjuvant CH. Disparity in outcome also warrants further evaluation.

<table>
<thead>
<tr>
<th>% 5-year DFS</th>
<th>% 10-year DFS</th>
<th>% 15-year DFS</th>
<th>% 20-year DFS</th>
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<tr>
<td>Overall</td>
<td></td>
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<tr>
<td>466</td>
<td>85 (81-89)</td>
<td>70 (66-75)</td>
<td>94 (91-96)</td>
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<tr>
<td>PgR ≥ 10</td>
<td>88 (85-93)</td>
<td>83 (80-87)</td>
<td>96 (93-99)</td>
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<td>PgR &lt; 10</td>
<td>85 (82-89)</td>
<td>80 (77-84)</td>
<td>93 (90-98)</td>
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Cutoff: 10% PG

Conclusions:

- The prognostic role of progesterone receptor (PgR) in highly proliferating early breast cancer (BC) is not well established.
- We retrospectively explored this biomarker in a cohort of patients with highly proliferating tumors enrolled in a phase III trial of adjuvant therapy.
- Among 1066 patients with N- or I- 3 N + BC were randomized to receive: epirubicin followed by CMF, CMF followed by epirubicin, or CMF alone. Rapidly proliferating tumors were defined by thymidine labeling index (TLI) > 3% or histological grade 3 or S-phase > 10% or Ki67 > 20%.
- We analyze the subgroup of 466 patients with hormone receptor (HR)-positive tumors treated with sequential epirubicin/CMF regimens followed by taxomoxifen and for whom immunohistochemical assessments of estrogen receptor (ER), PgR, HER2 and Ki67 were available. Disease-free (DFS) and overall survival (OS) curves were built with the Kaplan–Meier estimator and compared by logrank test and Cox regression models.
- PgR expression was significantly associated with ER expression, HER2 status, age and menopausal status, but not with Ki67, tumor size and nodal status. PgR cutoff values of 10% and 20% were chosen based on a Receiver Operating Characteristics analysis and the literature. DFS and OS figures are set in 5 and 10 years, as well as the relative hazard ratios, according to the different PgR cutoff values, are reported in the table.

**Conclusions:** Our results confirm the prognostic relevance of PgR expression in a cohort of patients with highly proliferating HR-positive early BC treated with adjuvant ET and for whom immunohistochemical assessments of the hormone receptors were available.

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**Conclusions:** Our results confirm the prognostic relevance of PgR expression in a cohort of patients with highly proliferating HR-positive early BC treated with adjuvant ET and for whom immunohistochemical assessments of the hormone receptors were available.
548  Poster Session (Board #40), Sun, 8:00 AM-11:00 AM

Effect of prophylaxis on neratinib-associated diarrhea and tolerability in patients with HER2+ early-stage breast cancer: Phase II CONTROL trial. First Author: Carlos Hernando Barcenas, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: CONTROL (clinicaltrials.gov: NCT02400476) is an open-label, sequential-cohort, phase II study investigating the effectiveness of prophylaxis or dose escalation in preventing diarrhea and improving tolerability of neratinib, an irreversible pan-HER tyrosine kinase inhibitor. Neratinib has demonstrated benefit as an extended adjuvant therapy for early-stage HER2+ breast cancer. Various prophylactic agents are being studied in adult patients treated with oral neratinib (240 mg/day for 1 year) after trastuzumab-based adjuvant therapy. Methods: Patients (n = 485) were enrolled into cohorts investigating anti-diarrheal prophylaxis for 1–2 cycles (28 days) with the following agents: loperamide (n = 137); loperamide + budesonide (n = 64); loperamide + colestipol (n = 136); loperamide pm + colestipol (n = 104). An additional cohort assessing loperamide ppm + neratinib dose escalation with no mandatory prophylaxis (n = 44) is ongoing. Adverse events were graded according to NCI-CTCAE v4.0. The primary endpoint was incidence of Grade 3 diarrhea and drug discontinuation compared with the prior ExeNET trial (Martin et al. 2017). The median cumulative duration of Grade 3 or higher diarrhea spanned from 2.0 to 3.5 days across regimens for the entire treatment period. No Grade 4 diarrhea was reported. Results: As shown in the table, all prophylactic regimens reduce the incidence of Grade 3 diarrhea and drug discontinuation compared with the prior ExeNET trial [Martin et al. 2017]. The median cumulative duration of Grade 3 or higher diarrhea spanned from 2.0 to 3.5 days across regimens for the entire treatment period. No Grade 4 diarrhea was reported.

549  Poster Session (Board #41), Sun, 8:00 AM-11:00 AM

Oncotype DX testing in early-stage node-positive breast cancer and impact on chemotherapy use at a comprehensive cancer center. First Author: Katya Lock, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: The 21-gene Oncotype DX Recurrence Score (RS) is widely used to guide adjuvant chemotherapy decisions in hormone receptor positive (HR+), HER2-negative (HER2-), lymph node negative (LN-) breast cancer. It’s adoption in lymph node positive (LN+) disease remains controversial. In 2016, we implemented ‘relax’ RS testing for patients ≥65 years with HR+/HER2- breast cancer under including T1T2 N1 (grade 1 or 2) tumors. Providers can also order Oncotype DX outside of reflex criteria. We sought to assess RS distribution and factors associated with chemotherapy use in HR+/HER2-LN+ breast cancer patients at our center. Methods: Patients with non-metastatic HR+/HER2+LN+ breast cancer who underwent primary surgery at our center were identified from our prospective database. We examined the distribution of low (RS < 18), intermediate (RS 18-30) and high (RS > 30) RS and identified characteristics for those who did not meet reflex criteria. A multinomial logistic regression model was performed to identify factors associated with chemotherapy receipt among all LN+ patients. Results: From 1/2016-3/2018, we identified 200 consecutive patients with HR+/HER2+LN+ breast cancer. 200 (68%) patients had RS testing and 128 (64%) met reflex criteria. Reasons for not meeting RS reflex criteria included age > 65 (n = 35), grade III disease (n = 35) and N2N3 tumors (n = 10). Among the 200 patients with RS, 122 (61%) had RS < 18, 67 (34%) had RS 18-30, and 11 (6%) had RS > 30. Only 68/ 200 (34%) patients were receiving chemotherapy at the time of the study. 96 (56%) patients without RS (p = 0.0004). Compared to patients without RS testing, the odds of receiving chemotherapy were less with ≥3 positive LNs versus 1 positive LN (OR = 3.40). Conclusions: The majority of HR+/HER2+LN+ patients undergoing upfront surgery at our center fulfill our our center fulfill our criteria for RS testing, with 22 (11%) resulting in low risk RS. Patients with low risk scores (RS < 18) were less likely to receive chemotherapy. While nodal involvement remains a common driver of chemotherapy use, our study demonstrates that RS testing provides clinically useful information in this population.

550  Poster Session (Board #42), Sun, 8:00 AM-11:00 AM


Background: We have previously demonstrated that PD-L1 mRNA expression can serve as prognostic biomarker in breast cancer (BC). In ER+/HER2- BC, RS and 70-gene signature are used to predict the risk of recurrence and benefit from chemotherapy. Methods: Discovery cohort (cohort 1) included 302 patients diagnosed with primary ER+/HER2- BC (1997-2005) in Stockholm health care region. Gene expression profiling has been performed using DNA microarrays (GSE48091) while information regarding tumor characteristics, treatment and follow-up have been obtained. TCGA’s dataset including 590 ER+/HER2- patients, was used as validation cohort (cohort 2). Kaplan–Meier estimates and Cox regression univariate/multivariable analyses were performed using breast cancer-specific survival (BCSS) and progression-free interval (PFI) as endpoints in cohorts 1 and 2, respectively. Gene signature scores were calculated using the R genefu package. Likelihood ratio (LR) tests and concordance indices (c-indices) were used to assess each score’s added prognostic value. Results: PD-L1 mRNA expression (treated as a continuous variable) was independently associated with better BCSS in cohort 1 (HR = 0.72; 95% CI = 0.58-0.90; p = 0.003) and with better PFI in cohort 2 (HR = 0.67; 95% CI = 0.50-0.90; p = 0.008) in the multivariable analysis. PD-L1 provided significant additional prognostic information beyond that of both RS alone (LR-ΔX² = 9.6; p = 0.002 and LR-ΔX² = 9.7; p = 0.002, in cohorts 1 and 2, respectively), and 70-gene signature score alone (LR-ΔX² = 10.4; p = 0.001 and LR-ΔX² = 9.2; p = 0.002 in cohort 1 and 2, respectively). C-indices for PD-L1 + RS vs RS were 0.65 vs 0.60 (cohort 1) and 0.66 vs 0.60 (cohort 2), and for PD-L1 + 70-gene vs 70-gene were 0.65 vs 0.59 (cohort 1) and 0.64 vs 0.54 (cohort 2, respectively). Conclusions: PD-L1 gene expression was correlated with better outcomes and can provide added prognostic information beyond RS and 70-gene signature scores in ER+/HER2- BC.

551  Poster Session (Board #43), Sun, 8:00 AM-11:00 AM

Prediction of neo-adjuvant chemotherapy efficacy by CTC and cfDNA in patients with locally advanced breast cancer. First Author: Ge Ma, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: Neo-adjuvant chemotherapy (NCT) is the standard treatment for patients with locally advanced breast cancer (LABC). Liquid biopsy, including circulating tumor cells (CTCs) and cell free DNA (cfDNA) represent an important paradigm shift in precision medicine. The aim of this study was to estimate the value of CTCs and cfDNA in efficacy prediction of the response to NCT in patients with LABC. Methods: Patients with LABC received EC4-T4 regimen NCT. CTCs and cfDNA were obtained at time of biopsy, after first course of NCT and after the last course of NCT. All patients were divided into two groups according to pathological reactivity. A novel SE-IFISH strategy, improved for detection of CTCs, was applied. CTCs(CD45-/CD31-) with different cytogenetic abnormalities of normal breast-like chromosome 8 and small cell size CTCs (≤5 mm of WBCs) were analyzed separately in LABC patients subjected to NCT for the first time. Plasma DNA biomarkers ALU 111 and ALU 260 elements were evaluated using qRT-PCR. DNA integrity was calculated relative to the breast cancer cell line MCF-7. Clinical significance of diverse subtypes of CTCs and cfDNA was systematically investigated. Results: A total of 45 patients was enrolled in this study. According to the therapy response, 6/45 patients had high response (High-R) and 39/45 patients had low response (Low-R). There were no significant differences in CTC number and small cell size CTC number between High-R and Low-R groups in all three detections. However, the CTC number kept stable in the High-R group, but increased continually during NCT in Low-R group. In 45 patients, the percentage of CTCs with trisomy 8, which were related to cancer metastasis, increased in the Low-R group at the third detection. The concentration of cfDNA in all three detections did not indicate outcome of NCT. However, concentration of ALU 111 was significantly higher in High-R group than Low-R after first course of NCT, with 122 (61%,) resulting in low risk RS. Patients with low risk scores (RS < 18) were less likely to receive chemotherapy. While nodal involvement remains a common driver of chemotherapy use, our study demonstrates that RS testing provides clinically useful information in this population.

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Factors associated with osteonecrosis of the jaw in women with breast cancer receiving high-dose bisphosphonates to prevent breast cancer metastases as part of the SWOG S0307 trial. First Author: Darya Kizub, Everett Clinic, Everett, WA

**Background:** Bisphosphonates reduce the risk of bone metastases in post-menopausal women with early-stage breast cancer but carry the risk of osteonecrosis of the jaw (ONJ). We used the data collected in the S0307 trial to describe factors associated with provoked and unprovoked ONJ.

**Methods:** In S0307, 6097 patients with Stage I-III breast cancer who had surgery were randomized to receive zoledronic acid (ZA) 4mg IV monthly for 6 months, then every 3 months, clodronate (CL) 1600mg daily, or ibandronate (IB) 50mg daily for three years, with no difference in bone metastases or disease-free survival. Patients completed dental procedures prior to and had a dental exam at enrollment. Pearson’s Chi-squared and Student’s T-test were used to test differences in categorical and continuous variables, respectively; logistic regression was used to test independent association. **Results:** Of 5836 evaluable women, 48 developed ONJ, which was associated with bisphosphonate type (28/2124 (1.26%) for ZA, 28/1285 (2.6%) for CL and 12/1527 (0.77%) for IB) (p = 0.002). Median time to onset of ONJ was 24.9 (1.4-66.6) for ZA, 41.2 months (range 3.6-74.4) for CL, and 38.3 (3.4-76.1) for IB (p = 0.047). Infection was present in 21 (43.8%) and absent in 20. ONJ was considered unprovoked in 20 (41.7%) and provoked by dental extraction in 20 (41.7%), periodontal disease in 14 (29.2%), dentale trauma in 6 (12.5%), other dental surgery in 3 (6.3%). ONJ was associated with dental calculus (OR 2.03 (95% CI: 1.04-3.91), gingivitis (OR 1.86, 95% CI: 1.09-3.18), BC and tumor tissue available for sequencing before and after chemo+H. Whole exome sequencing (WES) was performed on each tumor and on germline DNA from blood. Tumor-normal pairs were analyzed for mutations and copy number (CN) changes. Evolutionary analysis was performed for patients with both pre- and post-treatment (tx) samples available. 22 women had successful WES samples from at least one timepoint; 13 of these had paired sequencing results both before and after chemo+H. For the majority of women, post-tx sample was following nonadjuvant chemo + H, though post-tx timepoint for other women represented locoregional or distant metastasis (Table). TP53 was the only gene that was significantly recurrently mutated in both pre- and post-tx samples. Comparison of matched pre-tx and post-tx samples demonstrated that large changes in HER2 CN over the course of tx were uncommon, only 2/13 pts had > 2-fold change in HER2 CN. Other clonal and subclonal genomic alterations were found to be acquired in the pre-tx sample compared to the pre-tx sample, and that patient acquired a clonal activating mutation in ERBB2. Another patient acquired a clonal hotspot mutation in TP53. MYC gene amplification was observed in 4 post-tx tumors. NOTCH2 alterations were found in post-tx biopsies from 2 different patients, and mutations in STL were also found in post-tx biopsies from 2 patients. Though the function of these mutations is not known. **Conclusions:** HER2+ breast tumors in young women display genomic evolution following tx with chemo+H. HER2 CN changes are uncommon, but we identified several genes that warrant exploration as potential mechanisms of resistance to therapy in this population.

Genomics of HER2+ breast cancer in young women before and after exposure to chemotherapy (chemo) plus trastuzumab (H). First Author: Adrienne Gropper Waks, Dana-Farber Cancer Institute, Boston, MA

**Background:** HER2+ breast cancer (BC) is particularly common in young women. Genomic features of HER2+ tumors before and after H-based therapy have not been described in a population of young women and may point to clinically targetable mechanisms of resistance. **Methods:** From a large prospective cohort, we included 40 women diagnosed with BC age <40 years, who received neoadjuvant chemo+H and tissue samples from both BC and tumor tissue available for sequencing before and after chemo+H. Whole exome sequencing (WES) was performed on each tumor and on germline DNA from blood. Tumor-normal pairs were analyzed for mutations and copy number (CN) changes. Evolutionary analysis was performed for patients with both pre- and post-treatment (tx) samples available. 22 women had successful WES samples from at least one timepoint; 13 of these had paired sequencing results both before and after chemo+H. For the majority of women, post-tx sample was following nonadjuvant chemo + H, though post-tx timepoint for other women represented locoregional or distant metastasis (Table). TP53 was the only gene that was significantly recurrently mutated in both pre- and post-tx samples. Comparison of matched pre-tx and post-tx samples demonstrated that large changes in HER2 CN over the course of tx were uncommon, only 2/13 pts had > 2-fold change in HER2 CN. Other clonal and subclonal genomic alterations were found to be acquired in the pre-tx sample compared to the pre-tx sample, and that patient acquired a clonal activating mutation in ERBB2. Another patient acquired a clonal hotspot mutation in TP53. MYC gene amplification was observed in 4 post-tx tumors. NOTCH2 alterations were found in post-tx biopsies from 2 different patients, and mutations in STL were also found in post-tx biopsies from 2 patients. Though the function of these mutations is not known. **Conclusions:** HER2+ breast tumors in young women display genomic evolution following tx with chemo+H. HER2 CN changes are uncommon, but we identified several genes that warrant exploration as potential mechanisms of resistance to therapy in this population.

Tailored dose-dense chemotherapy in combination with trastuzumab as adjuvant therapy for HER2-positive breast cancer: A secondary analysis of the phase III PANTER trial. First Author: Theodoros Foukakis, Karolinska Institutet and University Hospital, Stockholm, Sweden

**Background:** Dose-dense (DD) adjuvant chemotherapy improves outcomes in early breast cancer (BC). However, there is no data to inform on the combination of DD chemotherapy with trastuzumab for patients with HER2-positive disease. **Methods:** This is a protocol predefined secondary analysis of the randomized phase 3 PANTER trial. Women 65 years old or younger with node-positive or high-risk node negative BC were randomized 1:1 to either tailored according to hematologic nadirs and DD epirubicin/cyclophosphamide (4 cycles) followed by 34 cycles of docetaxel (tDD ECD) or standard 3-weekly 5-fluorouracil/E/C (3 cycles) and D (3 cycles). Patients with HER2-positive disease received 1 year of adjuvant trastuzumab. In addition, HER2-positive and an equal number of matched for age, treatment group and institution, HER2-negative patients that were enrolled in Swedish sites were included in a predefined study of cardiac safety and underwent echocardiography or MUGA and electrocardiography at baseline and at four and six years of follow-up. The primary endpoint was BC relapse-free survival (BCRFS). **Results:** There were 342 HER2-positive patients; 335 received at least one dose of trastuzumab while 29 patients discontinued trastuzumab prematurely. BCRFS was not statistically significantly in favor of tDD ECD (HR = 0.68, 95% CI 0.37 – 1.27, P = 0.231). Cardiac outcomes after four and six years of follow-up did not differ significantly between HER2-positive and HER2-negative patients, nor between tDD and standard treatment. To our knowledge, these are the only data on combining DD adjuvant chemotherapy and trastuzumab in BC. The combination decreased the risk for BC relapse by 32% compared to standard treatment, a statistically non-significant difference. Its efficacy and safety merit further evaluation as part of both escalation and de-escalation strategies. Clinical trial information: NCT00798070.

Comparative performance of Breast Cancer Index (BCIN+) and CTS5 in hormone receptor-positive (HR+) lymph node-positive (N+) breast cancer patients with one to three positive nodes (N1). First Author: Dennis Sgroi, Center for Cancer Research, Massachusetts General Hospital, Boston, MA

**Background:** Identification of N+ breast cancer patients with a limited risk of recurrence improves selection of those for which chemotherapy and/or extended endocrine therapy (EET) may be most appropriate to reduce over-treatment. BCIN+ integrates gene expression with tumor size and grade, and is highly prognostic for overall (0-10yr) and late (5-10yr) distant recurrence (DR) in N1 patients. Clinical Treatment Score post-5 years (CTS5) is a prognostic model based on clinicopathological factors (nodes, age, tumor size and grade) and significantly prognostic for late DR. The current analysis compares BCIN+ and CTS5 for risk of late DR in N1 patients. Methods: 349 women with HR+, N1 disease and recurrence-free for ≥ 5 years were included. BCIN+ results were determined blinded to clinical outcome. CTS5 was calculated as previously described (Dowsett et al, JCO 2018; 36:1941). Kaplan-Meier analysis and Cox proportional hazards regression for late DR (5-15yr) were evaluated. Results: 64% of patients were > 50 years old, 34% with tumors > 2cm, 79% received adjuvant chemotherapy and 64% received up to 5 years of ET. BCIN+ stratified 23% of patients as low-risk with a 1.3% risk for late DR vs those classified as high-risk with 16.1% (HR 12.4 (1.9-79.0), p = 0.0014). CTS5 classified patients into 3 risk groups: 29% of patients as low-risk (4.2% DR), 37% as intermediate-risk (10.6% DR), and 34% as high-risk (22.1% DR) (HR intermedium vs. low: 2.3 (0.7-7.0), p = 0.16; high vs. low: 5.3 (1.8-15.5), p = 0.002). In a subset of patients who completed 5 years of ET (N = 223), BCIN+ identified 22% of patients as low-risk with a late DR rate of 2.1%, while CTS5 identified 29% and 37% of patients as low- and intermediate-risk with late DR rates of 5.2% and 10.3%, respectively. **Conclusions:** BCIN+ classified 91 patients into binary risk groups and identified 20% patients with limited risk of late DR (< 2%) that may be advised to forego ET and its attendant toxicities/side effects. In comparison, CTS5 classified patients into 3 risk groups, with low- and intermediate-risk of late DR of 4.5% and 10%, wherein the risk-benefit profile for extension of endocrine therapy is less clear.

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556 Poster Session (#48), Sun, 8:00 AM-11:00 AM
Immunologic responses in triple-negative breast cancer patients in a randomized phase IIb trial of nelipitumumab-S plus trastuzumab versus trastuzumab alone to predict response.
First Author: Jessica Campell, San Antonio Military Medical Center, Fort Sam Houston, TX

Background: Breast cancer (BC) patients (pts) expressing low levels of HER2 by (immunohistochemistry (IHC) 1-2+) are not eligible for trastuzumab (Tz). However, in a randomized phase 2b trial, triple negative BC (TNBC) pts demonstrated a significantly better DFS with nelipitumumab-S (NPS) + Tz vs Tz alone. Here, we assess the ex vivo and in vivo immune responses (IR) in both arms.

Methods: Disease-free pts (n = 275) with HER2 1 (n = 241) and 2+ (n = 34) were randomized to Tz or NPS + Tz. The NPS+Tz group had a significant increase in CTL frequencies vs baseline: 208%, 303%, 379% at 18, 24 and 30 mo, respectively. NPS+Tz pts mean CTL frequencies increased from 0.029 ± 0.001% at baseline to 0.112 ± 0.026% at 30 mo (p = 0.01) compared to Tz pts who were 0.027 ± 0.001% at baseline and 0.057 ± 0.016% at 30 mo (p = 0.71). Only 4 NPS+Tz pts recurred as compared to 13 in the Tz arm while limiting to clinical low numbers, recurrent NPS + Tz pt did not mount an IR by ex vivo assessment (range: 0.0 - 0.026%) or by DTH (all measurements: 0 mm), while non-recurrent pts mounted both clonal CTL expansion (range: 0.000 - 0.33%) and enhanced DTH (range: 0.0 - 80.5mm).

Conclusions: NPS+Tz combination is more efficacious in generating time-dependent antigen (NPS)-specific CTL by enhanced DTH (range: 0.0 - 80.5mm). These pre-specified analyses comparing the time-dependent effect of NPS+Tz and Tz in both ex vivo and in vivo measures vs Tz. Based on these preliminary data, it appears that both ex vivo and in vivo IR to NPS were attenuated in pts with recurrent pts, while both clonal CTL expansion (range: 0.000 - 0.33%) and enhanced DTH (range: 0.0 - 80.5mm).

557 Poster Session (#49), Sun, 8:00 AM-11:00 AM
Cardiac safety of the trastuzumab biosimilar ABP 980 in women with HER2-positive early breast cancer in the LILAC study.
First Author: Hans-Christian Kolberg, Marienhospital, Bottrop, Germany

Background: Although trastuzumab is generally well-tolerated, cardiotoxicity is the main limitation in its use, leading to a severe heart failure in 2-4% of patients in adjuvant trials. In the phase 3 LILAC trial, trastuzumab biosimilar ABP 980 demonstrated similar efficacy, safety, and immunogenicity to trastuzumab reference product (RP) in women with HER2-positive early breast cancer. Here we report analyses comparing cardiac safety of ABP 980 vs RP.

Methods: In the neoadjuvant phase, all 725 patients received 4 cycles of chemotherapy with epirubicin + cyclophosphamide Q3W and were followed for recurrence. IR were evaluated ex vivo by clonal expansion of NPS-specific cytotoxic T lymphocytes (CTL) by dextramer-staining/flow cytometry at time points over 3 years. In vivo IR were assessed by delayed type hypersensitivity (DTH) reactions periodically.

Results: The trial enrolled 97 TNBC pts; 60 had 4 timepoints available for analysis (37 NPS + Tz pts; 23 Tz pts). The NPS-Tz group had increases in CTL frequencies vs baseline: 208%, 303%, 379% at 18, 24 and 30 mo, respectively. NPS+Tz pts mean CTL frequencies increased from 0.029 ± 0.001% at baseline to 0.112 ± 0.026% at 30 mo (p = 0.01) compared to Tz pts who were 0.027 ± 0.001% at baseline and 0.057 ± 0.016% at 30 mo (p = 0.71). Only 4 NPS+Tz pts recurred as compared to 13 in the Tz arm while limiting to clinical low numbers, recurrent NPS + Tz pt did not mount an IR by ex vivo assessment (range: 0.0 - 0.026%) or by DTH (all measurements: 0 mm), while non-recurrent pts mounted both clonal CTL expansion (range: 0.000 - 0.33%) and enhanced DTH (range: 0.0 - 80.5mm).

Conclusions: NPS+Tz combination is more efficacious in generating time-dependent antigen (NPS)-specific CTL by enhanced DTH (range: 0.0 - 80.5mm). These pre-specified analyses comparing the time-dependent effect of NPS+Tz and Tz in both ex vivo and in vivo measures vs Tz. Based on these preliminary data, it appears that both ex vivo and in vivo IR to NPS were attenuated in pts with recurrent pts, while both clonal CTL expansion (range: 0.000 - 0.33%) and enhanced DTH (range: 0.0 - 80.5mm).

558 Poster Session (#50), Sun, 8:00 AM-11:00 AM
Glutaminase (GLS) expression in primary breast cancer (BC): Correlations with clinical and tumor characteristics.
First Author: Neelima Vidula, Massachusetts General Hospital, San Francisco, CA

Background: Tumor cells rely on glutamine for growth. GLS is a mitochondrial enzyme that is necessary for glutamine catabolism, and is present as isoforms GLS1 and GLS2. A GLS1 inhibitor is being studied in triple-negative (TN) BC. We studied GLS1 expression in primary BC to understand associations with clinical and tumor characteristics in publically available databases.

Methods: GLS1 mRNA levels were evaluated using expression data from the TCGA (n = 817) dataset, with confirmation in METABRIC (n = 1992). Associations between GLS1 levels and tumor subtype were assessed using ANOVA, followed by the post-hoc Tukey test for pairwise comparisons. Pearson correlations were used to study associations between GLS1 and selected genes. Correlations with overall survival (OS) were studied with Cox proportional hazard model. For all analyses, p < 0.05 was considered significant.

Results: In TCGA, the expression of GLS1 and its isoform GLS2 were significantly inversely correlated (r = -0.32). GLS1 expression was highest in TN compared to hormone receptor (HR)+ and HER2+ BC (p < 0.001). In addition, GLS1 expression was higher in basal vs luminal A, luminal B, and HER2 enriched BC (p < 0.001). GLS1 expression was significantly inversely correlated with ER (r = -0.45), PR (r = -0.34), and AR (r = -0.34), and these inverse correlations remained significant when restricted to TNBC (ER: r = -0.25, PR: r = -0.25, AR: r = -0.30). Consistent with previous reports of MYC upregulation of GLS1, GLS1 expression was significantly positively correlated with MYC (r = 0.26). Similarly, in METABRIC, GLS1 was most highly expressed in basal and TNBC, significantly inversely correlated with the expression of GLS2, ER, PR, and AR, and positively correlated with MYC expression. In METABRIC, higher GLS1 expression was associated with better OS (HR 0.91, p < 0.005); this association remained significant in the TN subset (HR 0.83, p = 0.03).

Conclusions: GLS1 expression is highest in basal and TNBC, is associated with MYC expression, and may have prognostic implications. These findings support ongoing trials of GLS1 inhibition in TNBC.

559 Poster Session (#51), Sun, 8:00 AM-11:00 AM
A prospective validation cohort study of a prediction model on non-sentinel lymph node (nSLN) metastasis in early breast cancer.
First Author: Yingfei Yu, Zhejiang Cancer Hospital, Hangzhou, China

Background: Early breast cancer (cT1, cN0) with one or two sentinel lymph node (SLN) involved may avoid axillary lymph node dissection (ALND) if follow by radiotherapy supported by Z0011 and AMAROS trials. However, only less than one-third of those patients have positive non-sentinel lymph node (nSLN) and can truly benefit from radiotherapy or ALND in those two trials. It is necessary to identify the risk of nSLN metastasis before local treatment decision. We previously developed a predictive model for nSLN involvement using circulating CK19 mRNA level combined with contrast-enhanced ultrasound (CEUS) score (ASC022017 poster 239, NCT02992067) in a training set. To evaluate the predict effect of this model, we designed a further study using the model prospectively in a validation set (NCT03280134).

Methods: We identified early breast cancer cases in Zhejiang Cancer Hospital from July 2017 to June 2018. The level of circulating CK19 mRNA tested by qRT-PCR and CEUS scores were collected before surgery in each case. Patients with 1–2 SLN involved were enrolled and continued for ALND. The estimated percentage of nSLN-involved was calculated both by our model formula and the Memorial Sloan-Kettering Cancer Center (MSKCC) nomogram. The predictive accuracy and false negative rates (FNR) were evaluated and the area under curve (AUC) was compared between two predictive models.

Results: Totally, 235 patients diagnosed as early breast cancer with 1–2 SLN involved were enrolled and 35.36% of them were nSLN involved after ALND. The total accuracy and FNR by our model for nSLN-involved prediction was 94.89% and 6.02%, respectively. The AUC was 0.952 (95%CI, 0.922–0.982), significantly higher than that in MSKCC model 0.880 (95%CI, 0.833–0.927). Furthermore, only CK19 mRNA level (HR = 0.4091, 95%CI, 13.663–117.635) and CEUS score (HR = 2.009, 95%CI, 1.396–2.859) were significantly related to nSLN involvement in both univariate and multivariate analysis, adjusted by age, menopause status, tumor size, histological grade, estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 expression. Conclusions: Our model using CK19 mRNA and CEUS score showed potential predictive value of nSLN before surgery for early breast cancer patients. Further validation in larger multicenter cohort is needed before changing clinical practice.
560  Poster Session (Board #52), Sun, 8:00 AM-11:00 AM

Breast cancer treatment according to pathogenic variants in cancer susceptibility genes in a population-based cohort. First Author: Allison W. Kuran, Stanford School of Medicine, Stanford, CA

Background: Increasing use of germline genetic testing may have unintended consequences on breast cancer treatment. We do not know whether treatment deviates from guidelines for women with pathogenic variants (PV) in cancer susceptibility genes. Methods: SEER data for all women aged ≥20 years, diagnosed with breast cancer in 2014-15 and reported to Georgia and California registries (N = 77,588) by December 1, 2016 were linked to germline genetic testing results from 4 laboratories that did all available clinical testing. We examined first course of therapy (before recurrence or progression) of stage < IV patients who linked to a genetic test: bilateral mastectomy (BLM) in candidates for surgery (unilateral, stages 0-II); post-lumpectomy radiation in those with an indication (all but age ≥70, stage I, hormone receptor (HR)-positive and HER2-negative); and chemotherapy in those without a definitive indication (stage I-II, HR-positive, HER2-negative and 21-gene recurrence score < 30). We report the percent treated based on multivariable modeling, adjusted for age, race, stage, grade, insurance and socioeconomic status. Results: The table shows that 9% of patients who linked to a genetic test result had a PV (N = 1,283). Compared to women with negative results, women with BRCA1/2 PVs were more likely to receive BLM, more likely to receive chemotherapy without definitive indication, and less likely to receive indicated radiation in their first course of therapy. Lower-magnitude effects were seen with other PVs but not variants of uncertain significance (VUS). Conclusions: In a population-based setting, women with PVs in candidates for surgery (unilateral, stages 0-II) were more likely to receive chemotherapy without definitive indication, and less likely to receive indicated radiation in their first course of therapy. Lower-magnitude effects were seen with other PVs but not variants of uncertain significance (VUS).

561  Poster Session (Board #53), Sun, 8:00 AM-11:00 AM

Cognitive impairment in breast cancer patients before surgery?: Results of a subgroup of the French CANTO cohort. First Author: Marie Lange, Centre Hospitalier Universitaire, Baclesse, Caen, FR

Background: Cognitive impairment has been reported among breast cancer (BC) patients (pts) after adjuvant chemotherapy. However, very few studies focused on cognitive function at diagnosis. Here we aimed to describe cognitive impairment among recently diagnosed BC before any treatment. Methods: A predefined sub-study of the French national prospective cohort of cancer and toxicities performed extensive objective and subjective cognitive assessment before any BC treatment (surgery or neo-adjuvant treatment). This study included a group of pts with newly diagnosed invasive Stage I-III BC and a group of healthy control (HC) women matched on age and education level. Episodic and working memory, executive functions, processing speed, attention, cognitive complaints (FACT-COG), anxiety and depression (HADS) and fatigue dimensions (FA12) were assessed with neuropsychological tests and the referred self-report questionnaires. Objective and cognitive impairment were defined according to International Cognition and Cancer Task Force recommendations. Results: 264 women (median age 54±11 years) recently diagnosed (average of 37 days after initial diagnosis) with invasive BC (stage I-II, 69%) and 132 matched HC participated in this study. Impaired working memory (20% vs 4%), information processing speed (36% vs 17%), attention (16% vs 1%) and executive function (21% vs 8%) were higher among pts than in HC (p < 0.001). In addition, 24% (n = 64) of pts reported cognitive complaints versus 12% of HC (n = 16, p < 0.01). Emotional and cognitive fatigue were higher in pts than HC (24 vs 15 and 18 vs 11, p < 0.01). Similarly, higher levels of anxiety and depression were observed in patients when compared with HC (respectively in 41% and 3% of patients vs 10 and 1% for HC, p < 0.001). Objective cognitive impairment was not associated with cognitive complaints. Both objective and subjective cognitive impairment were not associated with anxiety or depression. However cognitive complaint was associated with fatigue (p < 0.001). Conclusions: In this large study, compared to HC, patients recently diagnosed with a localized BC reported more cognitive complaints and objective cognitive impairment before surgery, without link with emotional status, but with fatigue. Further understanding of the biology and correlates of cognitive dysfunction at BC diagnosis is needed (CANTO-NCT01993498).

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No relationship of axillary total tumor load (TTL) by PCR (OSNA) in early breast cancer and local and distant clinical outcomes. First Author: Jose Ales-Martinez, Complejo Asistencial de Avila, Avila, Spain

Background: The study of sentinel lymph nodes (SLN) assessed by One Step Nucleic Acid Amplification (OSNA, Sysmex, Kobe, Japan) creates a new variable, Total Tumor Load (TTL). This variable is defined as the total number of CK19 mRNA copies in all positive SLN (copies/µL). The latest edition of the Spanish Oncological Gynecology Society (SEGO) Guideline (2017) proposes a complete axillary lymph node dissection (ALND) when TTL is 15,000 copies or more in early breast cancer. In our center we are using OSNA to ascertain if there is axillary node involvement but the decision to proceed to ALND is based on Z0011 criteria. We want to determine if there is a correlation between clinical outcomes and TTL values, between TTL and pathological variables and if TTL is a useful tool to decide when to complete an ALND. Methods: Clinico-pathological and follow up data were obtained from all patients with invasive breast cancer and SLN assessed by OSNA between 2011 and 2017 at our center. Results: A total of 321 patients underwent SNB assessed by OSNA with an average follow-up of 56 months. 320 were female and 1 male. Age range 27-89 years (mean 58.9). 85% were ductal, 10% lobular and 5% other. 53.5% were luminal B, 7.78%, triple negative, 4.3%, HER2 positive and 4.3%. Luminal B-Her-2 positive. TTL was equal to 0 in 183 cases and greater than zero in 138 cases. 71 cases showed a TTL higher than 15,000 copies. Only 21 cases met Z0011 criteria and had ALND. As of now, 3 patients have had locoregional relapse and 8 metastatic disease. 10 have died, only two from metastatic breast cancer. Conclusions: Using Z0011 criteria, we have adequate clinical outcomes with a low rate of ALND. If we had basied the axillary management on TTL values we would have multiplied the number of ALND by a factor of 3.3 (from 21 to 71). We have observed a tendency to higher TTL in luminal phenotypes and to lower TTL in HER2 positive and triple negative subtypes. Work is in progress to increase our sample size.

Prediction of occult axillary metastases in treatment-naïve patients with breast cancer: A transSENTINA analysis. First Author: Marilena Kolberg-Liedtke, Charité - Universitätsmedizin Berlin, Berlin, Germany

Background: Prediction of occult axillary metastases through clinical / biological parameters may allow reduction of axillary staging. This is particularly important, as systemic therapies have become more efficient. We have conducted a systematic analysis among patients undergoing axillary sentinel lymph-node biopsy (SLNB) before initiation of primary systemic therapy as part of a clinical trial (SENTINA) with the goal to identify predictors of sentinel lymph node status in a well-defined patient cohort. Methods: Patients with a clinically negative axillary status who underwent SLNB as part of the primary TNBC (Table). Notably, there was an upregulation of anti-apoptosis and survival signaling genes (i.e. BIRC3) in the SLN metastasis. There was also an upregulation of chemotaxis genes (CCL13, CXCL19, CXCL21, CXCR5, TNFSF11, p<0.001). The most striking feature is the downregulation of genes known to regulate cell microenvironment interaction (MMP2, MMP14, COL1A1, COL1A2, COL14A1, COL5A1, COL6A6, COL11A1, COL17A1). Conclusions: TNBC, SLN metastasis has a distinct gene expression profile. Genes associated with anti-apoptosis, survival responses, and chemotaxis are upregulated, and genes associated with regulation of extracellular matrix are downregulated. Upregulated and downregulated genes with at least a 5-fold change in gene expression in lymph node metastasis compared with TNBC.

Gene Fold-Change P-Value
CYP2A6 19.71 0.002
COL17A1 14.13 0.001
FCER2 7.33< 0.001
COL6A6 -5.24 < 0.001
FGF3 -10.89< 0.001
COL17A1 -11.98< 0.001

Screening for cancer-related distress among women with newly diagnosed breast cancer. First Author: Lauren Z. Rynar, Loyola University Medical Center, Maywood, IL

Background: The Loyola University Chicago Cardinal Bernardin Cancer Center multidisciplinary Breast Oncology Center evaluates new patients (pts) for cancer-related distress using a needs-based screening tool, in accordance with Commission on Cancer (CoC) Standard 3.2. Identifying distress among newly diagnosed pre-surgical and pre-neoadjuvant pts allows for comprehensive treatment planning and establishment of a baseline for repeated assessments. Methods: Pts with newly diagnosed BC between May 2017 and June 2018 completed the “Patient Screening Questions for Supportive Care” (Coleman Supportive Oncology Collaborative, 2017), a consolidated screening tool based on validated instruments (NCCN Distress, PHQ-4, PROMIS), prior to initial provider visit. Cancer staging, demographics, and supportive oncology referrals were obtained from medical records. Descriptive statistics and chi-square were used. Results: 100 pts aged 30-94 (meanSD = 61.56(12.03) completed the screening tool; 14.9% had Stage 0, 43.6% Stage I, 34.0% Stage II, 3.2% Stage III, and 4.3% Stage IV disease. 39% of pts screened positive for anxiety on the PHQ-4, and over 20% for depression. Anxiety was associated with cancer stage (X²(df) = 7.20(4), p = 0.16). The most common practical concerns included living alone (19%), issues with work/school (16%), and paying for medical care (12%). Common physical concerns included difficulty with sleep (40%) and concentration/memory (17%), and tingling hands or feet (14%). Poor sleep was associated with depression (X²(df) = 6.50(1), p = .011) and anxiety (X²(df) = 7.17(1), p < .01). 57.7% reported at least “a little bit” of fatigue and 17.7% reported moderate to very severe pain. Nearly all pts wanted to better understand their diagnosis (87.8%), or treatment (91.8%). Conclusions: Pts with newly diagnosed, early stage BC experience high levels of physical and emotional distress at the earliest point in the treatment trajectory. This study captures BC patients at a unique time point and provides support for conducting routine screening for supportive oncology needs at initiation of care. Further studies should re-assert needs sequentially to determine changes across the care continuum.
Risk stratification in early-stage luminal breast cancer patients treated with and without RT. First Author: Charlotte Wadsten, Umeå University, Department of Surgical and Perioperative Science, Umeå, Sweden

Background: The goal was to develop and validate a biologic signature for 10-year ipsilateral invasive breast event (IBE) risk in luminal Stage 1 breast cancer (BC) patients treated surgically and either with or without radiation therapy (RT). Methods: This cohort was from Uppsala University and Västerås Hospitals diagnosed with Stage 1 BC and treated surgically between 1987 and 2004. Treatment was neither randomized nor strictly rules based, including adjuvant RT, Hormone Therapy (HT), and Chemotherapy (CT). Biomarkers (HER2, PR, Ki67, COX2, p16/INK4A, FOXA1 and SIAH2) were assessed on tissue microarrays in PreludeDx’s CLIA lab by board-certified pathologists. Risk groups were calculated using biomarkers and clinical factors age and size. A multivariate Cox proportional hazards analysis was used to determine hazard ratio for biologic signature. 10-year IBE risk was assessed using Kaplan-Meier survival analysis. Results: There were 423 luminal cases with biomarker data having 54 IBEs, and a median follow-up of 11.8 years. There were 372 patients treated with BCS and 51 with Mastectomy, and 325 received RT, 169 received HT, and 47 received CT. In a multivariate analysis, the biologic signature (HR > 1.6 , p = 0.019) and RT (HR = 0.51, p = 0.027) were associated with IBE risk adjusting for other treatments (HT and CT) and Luminal A status (p = 0.37). For patients over 50 years of age with luminal A disease and treated without CT (n = 205), an elevated biologic signature identified a subset of patients with a 15% +/- 2% 10-year IBE risk vs. RT (n = 18); 38% vs 5% IBE risk with RT (n > 72), while patients with a low biologic signature had a 10-year IBE risk of 4% +/- 4% without RT (n = 26) and 3% +/-5% IBE risk with RT (n = 69). Conclusions: With further prospective validation, the biologic signature identified herein may provide a tool enabling improved management for women diagnosed with early luminal BC.

Biomarker analysis of PALLET: A neoadjuvant trial of letrozole (L) ± palbociclib (P). First Author: Vera Martins, ICR, London, United Kingdom

Background: PALLET randomized 307 postmenopausal women with ER+ primary breast cancer to one of 4 treatment groups (2:2:2:2 ratio): A: L for 4 weeks; B: L for 2 weeks then L+P to 14 weeks; C: P for 2 weeks then L+P to 14 weeks; D: L+P for 14 weeks. This allowed a randomized 1:2 comparison of L (Group A) vs L+P (Groups B+C+D) at 14 weeks. P was given 125mg/d PO (21 days on, 7 days off). Adding P to L markedly enhanced Ki67 suppression and Complete Cell Cycle Arrest (CCCA, Ki67 < 2.7%) by 14 weeks but did not substantially increase clinical response. We now report exploratory analysis of the association of baseline expression of 6 pre-specified biomarkers involved in estrogen and CDK4/6 signaling with CCCA at 14 weeks and changes in their expression during therapy. Methods: Estrogen receptor (ER), progesterone receptor (PgR), RB and CCNE1 were measured by IHC and CCND1 by IHC and FISH (CCND1/CEP11 ratio >2.0 amplified). Baseline biomarker values were available with 14wks Ki67 values in up to 64 patients for L alone and up to 124 patients for L+P. Of these 59% and 90%, respectively, achieved CCCA, Results: With L alone CCCA was significantly less frequent (indicating relative resistance) with low baseline PgR (odds ratio (OR) 0.22, 95%CI 0.05-0.96, p = 0.04) or high CCNE1 levels (OR 10.39, 95%CI 1.90-90.48, p = 0.03). With L+P CCCA was also significantly less frequent with high CCNE1 (OR 50.34, 95%CI 5.12-495.34, p = 0.001) or with low baseline ER (OR 0.21 95%CI 0.08-0.60, p = 0.004). CCCA was not significantly different with either treatment according to CCND1 amplification status or expression overall. However, CCCA showed a tendency to being less frequent in non-amplified cases with low baseline cyclin-D1 expression when treated with L+P (p = 0.10). There were no significant changes in ER levels or CCND1 amplification over 14wks. By 14 wks PgR, RB, CCND1 and CCNE1 levels were significantly suppressed by L or L+P (geometric mean PgR = 0.6% vs -94.9%; CCND1: -79.9% vs -70.7%; CCNE1: -68.2% vs -74.7%; RB: -23.5% vs 26.1%, respectively) and there was no significant difference between the treatments. Conclusions: These data support low ER, possibly indicating limited luminal status, and high CCNE1 as markers of poor Ki67 response. RB may be a primary downstream signaling event in studies in advance of clinical trial implementation. Clinical trial information: NCT02296801

Pharmacogenomic testing impacts therapy decisions and supportive medication choices in breast cancer. First Author: Kathleen Kieran Handeen, Inova Schar Cancer Institute, Fairfax, VA

Background: Pharmacogenomics, the study of the interaction between the patient’s genome and therapeutic drug response, evaluates the associations between efficacy and toxicity through analysis of drug metabolizing enzymes. As personalized medicine advances to the forefront of cancer care, pharmacogenomics can evaluate the individual’s ability to metabolize key medications in breast cancer treatment including anti-estrogens, opioids, and taxanes. Women who do not achieve optimal levels of the active metabolites of tamoxifen are at higher risk of recurrence. Patients on chemotherapy who do not respond to anti-estemics can suffer from nausea and vomiting resulting in dehydration and hospitalization. This project evaluates the feasibility and therapeutic impact of real-time pharmacogenomics in a selection of patients at the Inova Schar Cancer Institute (ISCI). Methods: An interdisciplinary team was created through the ISCI and the Inova Translational Medicine Institute to implement cheek swab based pharmacogenomic testing in 50 new patients undergoing mastectomy or neoadjuvant chemotherapy for breast cancer. Study patients were assessed for genotypic variants of CYP2D6 and CYP3A4 and resulting impact on anti-estrogenic, perioperative pain control, and tamoxifen use. Results: Data was collected in a RedCap database. The 50 women enrolled were ages 28-83. Cheek swabs were performed in clinic and median turn around time was 7 days. 24 distinct genotypes were found in the 50 patients. 20% had abnormal CYP2D6 phenotypes and 94% normal CYP3A4 genotype. 28% of patients had results leading to changes in dose or medication choice of perioperative pain control. 6% of patients had a CYP2D6 ultra-rapid metabolizer phenotype and were given granisetron in lieu of ondansetron. These patients had no documented nausea or vomiting requiring dose adjustments to the treatment plan or medical intervention. 40% of patients had results recommending avoidance of tamoxifen, 75% of which have ER+ breast cancer. 25% of patients had recommended changes to the dose of tamoxifen. Conclusions: Pharmacogenomic testing is feasible and available real-time for immediate use in the clinic. CYP mutations impact treatment decisions in a significant proportion of patients. Individualized treatment plans tailored to pharmacogenomic recommendations can be created in the multi-disciplinary setting and may decrease side effects of treatment and improve efficacy of curative therapy.

Genomic-based predictive biomarkers to anti-HER2 therapies: A combined analysis of CALGB 40601 (Alliance) and PAMELA clinical trials. First Author: Aranzazu Fernandez-Martinez, Lineberger Comprehensive Center. Department of Genetics, University of North Carolina, Chapel Hill, NC

Background: In HER2-positive breast cancer, new biomarkers of response are needed in order to direct multi-agent anti-HER2 combinations towards patients in whom they are truly needed. CALGB 40601 and PAMELA trials tested neoadjuvant dual HER2 blockade and included gene expression analysis as a biomarker to evaluate the potential benefit of dual vs single anti-HER2 and/or lapatinib benefit. Methods: Gene expression by mRNA sequencing (RNAseq) was performed on 265 and 142 pre-treatment tumors of the CALGB 40601 and the PAMELA clinical trials respectively. Intrinsic subtypes were determined by nCounter PAM50-predictor on the PAMELA samples. A new HER2-positive specific gene-centering method was trained on the PAMELA RNAseq data, and showed a higher concordance with PAM50 predictions obtained from nCounter platform. This method was then applied to CALGB 40601 samples. Results: In the combined cohort, the subtype distribution was 10% Luminal A, 8% Luminal B, 62% HER2-enriched (HER2-E), 10% Basal and 10% Normal-like. The pCR rate was significantly higher in HER2-E vs. not HER2-E subtypes (48.6% vs. 20.7%; p < 0.001). HER2-E subtype correlation, ERBB2 amplicon and B-cell genomic signatures were associated with pCR, while luminal signatures were associated with non-responders. In multivariate analysis HER2-E subtype, ERBB2 mRNA and IgG signature expression were independent predictors of response to paclitaxel + trastuzumab +/-lapatinib (OR = 1.98, OR = 2.07; p < 0.001). Conclusions: Intrinsic subtype, ERBB2 mRNA levels, and IgG genomic signature are independent predictive biomarkers of response in the combined cohort. The clinical implementation of these biomarkers could help to design future escalation/desescalation clinical trials for HER2-positive breast cancer patients. Clinical trial identifiers: NCT01800967, U10CA180828, U24CA196171, P50-CA58223, GSK, SPORE, BCRF and SEOM. https://acknowledgments.alliancefound.org.
573 Poster Session (Board #65), Sun, 8:00 AM-11:00 AM
Germline mutation status and therapy response in high-risk early breast cancer: Results of the GeparOcto study (NCT02125344).
First Author: Esther Pohl-Rescigno, 1 Center for Familial Breast and Ovarian Cancer and Center for Integrated Oncology (CIO), Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany
Background: GeparOcto compared the efficacy of two neoadjuvant treatment (NAT) regimens in high-risk early breast cancer (BC): Sequential intense dose-dense epirubicin, paclitaxel, and cyclophosphamide (idECIP) and weekly paclitaxel plus non-negated liposomal doxorubicin (PM), plus carboplatin (EP), versus idECIP and weekly paclitaxel (TP) in 186 patients with stage II-III BC enrolled in the AMAROS trial (NCT02276443). Recurrent portioning was used to identify cut-points. Clinical and pathological variables such as age at diagnosis, stage, race, history as well as Ki-67, vimentin, and androgen receptor (AR) by immunohistochemistry, were evaluated in pts with moderate TIL. A multivariable logistic regression model identified variables independently, significantly associated with pCR. Results: Four TIL groups were identified with pCR rates of 23%, 31%, 48% and 78% respectively (p < 0.0001) (Table A). In the two combined moderate TIL groups, 90 (97%) pts were evaluable for the multivariate model. Stage I-II disease, high Ki-67 and low AR were associated with increased probability of pCR (Table B). The multivariable logistic regression model area under the ROC curve was 0.78 (95% CI=0.68-0.88; p<0.0001). A model of computed risk score [Stage II-score 2+Ki-67+50%+score 10%] predicted a probability of 67% for pCR when all three variables were favorable (Table). Conclusions: Four TIL groups were identified. In pts with moderate TIL, stage II disease, high Ki-67 and low AR were associated with increased probability of pCR with neoadjuvant therapy.

574 Poster Session (Board #66), Sun, 8:00 AM-11:00 AM
On-treatment changes in tumor-infiltrating lymphocytes (TIL) during neoadjuvant HER2 therapy (NAT) and clinical outcome. First Author: Stephen James Luen, Peter MacCallum Cancer Centre, East Melbourne, Australia
Background: Higher quantity of pretreatment TIL (PT) is associated with improved pCR and EFS in HER2+ early breast cancer (BC). The value of on-treatment TIL is unknown. Methods: The NeoALTO trial randomized 455 women with HER2+ BC to 12 weeks NAT with trastuzumab, lapatinib or combination with paclitaxel, followed by FEC after surgery. In the PAMELA trial 151 women received 18 weeks NAT with lapatinib and trastuzumab (H:therapy). TIL were quantified on PT and on-treatment (W2) biopsies using the published method on H&E slides, and tested for associations with pCR (logistic regression), EFS and OS (Cox models) in univariate (UV) and multivariate (MV) analyses. The likelihood ratio test assessed added prognostic value to clinicopathological (CP) variables. pCR associations were validated in PAMELA. We investigated enrichment of immune cell subsets using RNAseq data from NeoALTO. Results: In NeoALTO, PT and W2 TIL were evaluable in 277/455 (61%). We defined two groups: immune-poor (L+F) and immune-enriched (II+P), see Table. Immune-enriched BC had high Ki-67, low AR, high HER2, high PEPI score, and added significant value to CP + PT TIL for prediction of pCR (P = .003). This was further confirmed in PAMELA (N = 94/151) (26% vs 6%; UV P = .021; MV P = .026). The gBCRA1/2 mutation prevalence was 17.6% in TNBC, 14.1% in HER2+ BC and 14% in HER2+ BC. Overall, pts with gBCRA1/2 mutations achieved higher pCR rates than gBCRA1/2 wildtype pts (60.4% vs 46.7%, OR, P = .012), with more pronounced effects in the PAMELA arm (69.1% vs 45.7%, OR 2.53, P = .006). Among gBCRA1/2 wildtype pts, 76 carried mutations in non-BRCA1/2 predisposition genes. pCR rates were similar to those observed in pts without any mutation. Conclusions: Pts with gBCRA1/2 mutations benefitted most from NAT with highest pCR rates achieved in the gBCRA1/2+TNBC/PMCG group. The role of Cp for NAT of gBCRA1/2+TNBC should be further explored in future clinical trials. (NCT02125344).

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Neoadjuvant endocrine therapy with an aromatase inhibitor has shown efficacy comparable to that of neoadjuvant chemotherapy in postmenopausal breast cancer. Pre Clinical data have shown that metformin, a widely used anti-diabetic drug also one of mTOR inhibitor have shown anti tumor activity. We report the result of prospective, multicenter, phase II randomized, placebo controlled trial aiming to detect the direct effect of metformin on breast cancer. Women with history of diabetes were excluded. Primary endpoint was clinical response rate (complete, partial response by caliper). Secondary endpoint was pathologic complete response rate, breast conservation rate, percent mammographic density change. PEPI score and toxicity profile were compared between two groups. Results: 153 intention to treat population were analyzed (72 metformin, 75 placebo group). Overall clinical response rate was 61.4% (94/153) by caliper and did not reach statistical significance between metformin versus placebo groups (66.7% versus 56.4%, p = 0.193). Breast conservation rate was 68.0% (100/147) (66.7% versus 71.7%, p = 0.305). Overall, 103 (68%) vs 101 (64.6%) patients displayed Ki67 < 10% and 50 (32.6%) vs 35 (25.4%) patients displayed Ki67 > 10%. Ki67 score had no impact on PEPI score. Neither Ki67 nor PEPI score was different between two groups. However, among the 20 patients with core-needle biopsy after 4 weeks of medication, greater number of patients displayed Ki67 < 10% in metformin group than in placebo group (67.5% versus 33.3%, p = 0.017). Among patients with 4 week Ki67 > 10%, 71% had higher clinical response rate (100% versus 57.1%, p = 0.038). Grade 3 side effects were reported in three patients (vomiting, high blood pressure, weight loss) and no hypoglycemia event was observed. Conclusions: 61.7 Overall clinical response was achieved with 24 weeks of neoadjuvant letrozole, with numerically > 10% higher response rates in metformin group, suggesting a potential role of metformin in breast cancer. 61.7% overall clinical response was achieved with 24 weeks of neoadjuvant letrozole, with numerically > 10% higher response rates in metformin group, suggesting a potential role of metformin in breast cancer.

Breast Cancer—Local/Regional/Adjuvant

Phase II randomized study of neoadjuvant metformin plus letrozole versus placebo plus letrozole for ER-positive postmenopausal breast cancer (METEOR Study). First Author: Jeun Kim, Department of Surgery, Asan Medical Center, Seoul, South Korea

Background: Neoadjuvant endocrine therapy with an aromatase inhibitor has shown efficacy comparable to that of neoadjuvant chemotherapy in postmenopausal breast cancer. Pre-Clinical data have shown that metformin, a widely used anti-diabetic drug also one of mTOR inhibitor have shown anti-tumor activity. We report the result of prospective, multicenter, phase II randomized, placebo controlled trial aiming to detect the direct effect of metformin on breast cancer. Women with history of diabetes were excluded. Primary endpoint was clinical response rate (complete, partial response by caliper). Secondary endpoint was pathologic complete response rate, breast conservation rate, percent mammographic density change. PEPI score and toxicity profile were compared between two groups. Results: 153 intention to treat population were analyzed (72 metformin, 75 placebo group). Overall clinical response rate was 61.4% (94/153) by caliper and did not reach statistical significance between metformin versus placebo groups (66.7% versus 56.4%, p = 0.193). Breast conservation rate was 68.0% (100/147) (66.7% versus 71.7%, p = 0.305). Overall, 103 (68%) vs 101 (64.6%) patients displayed Ki67 < 10% and 50 (32.6%) vs 35 (25.4%) patients displayed Ki67 > 10%. Ki67 score had no impact on PEPI score. Neither Ki67 nor PEPI score was different between two groups. However, among the 20 patients with core-needle biopsy after 4 weeks of medication, greater number of patients displayed Ki67 < 10% in metformin group than in placebo group (67.5% versus 33.3%, p = 0.017). Among patients with 4 week Ki67 > 10%, 71% had higher clinical response rate (100% versus 57.1%, p = 0.038). Grade 3 side effects were reported in three patients (vomiting, high blood pressure, weight loss) and no hypoglycemia event was observed. Conclusions: 61.7 Overall clinical response was achieved with 24 weeks of neoadjuvant letrozole, with numerically > 10% higher response rates in metformin group, suggesting a potential role of metformin in breast cancer.

Role of anthracyclines in neoadjuvant anti-HER2 regimens for HER2+ breast cancer (BC): A network meta-analysis (NMA). First Author: Giacomo Pelizzari, Department of Medicine (DAME), University of Udine; Dipartimento di Oncologia Medica, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Udine, Italy

Background: It is matter of current debate which would be the best chemotherapy backbone of neoadjuvant HER2-targeted therapy for HER2+ BC. The TRAIN 2 trial showed no significant difference in terms of pathological complete response (pCR) when anthracyclines-based (CTA) or anthracyclines-free regimens were combined with dual HER2 blockade. However, current data is unclear how anthracyclines may influence the relative benefit across different anti-HER2 treatments. Methods: A systematic review was conducted which included all phase III/II randomized clinical trials (RCTs) comparing different neoadjuvant regimens for HER2+ BC. pCR (70%vsNO) was the outcome of interest. Indirect comparisons of all combination of anti-HER2 agents with CT or CTA were estimated with a random-effects frequentist NMA. Estimated pCR rates were inferred adopting a Bayesian NMA. Results: 17 RCTs (3933 patients) were included. Overall, 8 arms were identified, comprising all possible combinations of CTA and CT with trastuzumab (H), lapatinib (L) and dual HER2 blockade (D) both CTA and CT A. Odds ratios for pCR and 95% confidence interval (CI) of selected NMA comparisons are shown in the table. Estimated rates of pCR for each treatment and 95% credible interval (CrI) are reported in the table. Conclusions: Through indirect comparisons, no significant pCR gain was found for CTA vs CT when combined to D, H and L. In particular, considering double vs single-agent anti-HER2 block, CTA in dual HER2 blockade may represent a possible omission of anthracyclines when dual anti-HER2 block is used. On the contrary, our pooled estimate suggests a more relevant role for anthracyclines when comparing H-CTA vs CTA. Moreover, we estimated a 4% pCR gain for D-CTA vs D-CT, and an 8% higher pCR rate for H-CTA vs C-CT.

Correlation between mutation landscape and clinical outcomes of neoadjuvant trastuzumab and HER2+ breast cancer patients. First Author: Ning Liu, Department of Breast Cancer, Cancer Center, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China

Background: The standard management of early stage human epidermal growth factor receptor 2 (HER2) positive (+) breast cancer (BC) involves neoadjuvant therapy with combination of chemotherapy and HER2-targeted therapy followed by surgery. However, diverse pathologic responses were observed across different baseline genomic alterations and pathologic responses were analyzed by multivariate analysis. This study investigate the association between 4 genomic alterations and pathologic response were analyzed by multivariate analysis. Results: A majority of them was diagnosed with stage II (67%, 22/ 33), while 30% (10/33) had stage III and 3% (1/33) had stage I disease. 58% (19/33) were HR+ and 42% (14/33) were HR-. Mutation profiling of baseline samples revealed 349 mutations spanning 145 genes, with TP53, CDK12 and PIK3CA being the top 3 most frequently mutated genes. Neoadjuvant regimen was comprised of trastuzumab and HER2 inhibitor (i.e. pertuzumab or lapatinib). 15 patients used single HER2 inhibitor,18 used dual HER2 inhibitors. Endocrine therapy was also administered to HR+ patients (19/33) in combination with trastuzumab and HER2 inhibitor. Complete pathologic response (pCR) was observed in 45.5% (15/33) of patients. Interestingly, ROS1 copy number amplifications (CNs) were only identified in patients achieved pCR (p = 0.033). In contrast, missense mutations in PIK3CA and CNAs in CCND1, FGFR19, FGFR3, FGFR4, SPOP, HNF1B and BRIP1 showed a trend of being less likely to mutate in pCR patients (p values between 0.05-0.01). Previous reports have suggested that pCR rates in HER2+ patients are associated with HR status. However, our data revealed comparable pathologic response of patients based on either HR status or neoadjuvant regimen. Conclusions: Our data revealed a distinct mutation profile based on pCR vs patients did not. Further study with a larger cohort are required to confirm these findings.
Background: SB3 is an approved biosimilar of reference trastuzumab (TRZ). At additional 2-year follow-up after completing neoadjuvant and adjuvant treatment, there was a difference in event-free survival (EFS), but no difference in overall survival (OS) between SB3 and TRZ. Upon monitoring quality attributes of TRZ, a marked downward shift in antibody-dependent cell-mediated cytotoxicity activities (ADCC) was observed in TRZ lots with expiry dates from Aug 2018 to Dec 2019. Some of the lots were used in the Phase III study. This is a post-hoc analysis of EFS and OS by ADCC status from a 3-year follow-up to investigate the difference in EFS between SB3 and TRZ.

Methods: After completion of neoadjuvant and adjuvant therapy in patients with HER2 positive early breast cancer, patients from selected countries participated in a 5-year follow-up study (NCT02771795). Within the TRZ group, patients exposed to at least one shifted ADCC lot and those never exposed to shifted ADCC lot during neoadjuvant period were considered as “Exposed” and “Unexposed”, respectively. EFS and OS after 3-year follow-up was analyzed by ADCC status in the long-term follow-up (SB3, N = 186; TRZ, N = 181) were enrolled in the follow-up study. Within TRZ, 55 patients were Unexposed and 126 patients were Exposed. At a median follow-up duration of 40.8 months in SB3 and 40.5 months in TRZ, 3-year EFS rates were 92.5% in SB3, 94.5% in Unexposed, and 82.3% in Exposed and OS rates were 90.0% and 90.6%, respectively. Exposed was associated with decreased EFS compared to Unexposed (HR 0.14, 95% CI 0.04-0.51, p = 0.003). There was a trend of decreased OS in Exposed compared to Unexposed, however, there was no significant difference (HR 0.14, 95% CI 0.02-1.15, p = 0.068). Between SB3 and Unexposed, no difference was observed (HR 1.06, 95% CI 0.33-3.44, p = 0.923) or OS (HR 0.54, 95% CI 0.05-5.44, p = 0.600).

Conclusions: The TRZ group, Exposed showed significantly lower EFS compared to Unexposed, and a similar trend was observed in OS with no statistical significance. Between SB3 and Unexposed, no significant difference in EFS or OS was observed. Clinical trial information: NCT02771795.
Delineating longitudinal patterns of response to neoadjuvant systemic therapy (NAST) in triple-negative breast cancer (TNBC): Profiling results from a randomized, TNBC enriched trial to confirm molecular profiling in neoadjuvant setting (ARTEMIS; NCT02276443). First Author: Sahil Seth, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** The heterogeneity of TNBC results in varied responses to NAST. 30-40% of patients (pts) have pathologic complete response (pCR) with excellent prognosis. Those with residual disease, have a much higher risk of recurrence. Longitudinal profiling assesses biologic response to N AST and mechanisms of resistance and relapse. **Methods:** Pts with stage I-III TNBC began a planned 4 cycles of Adriamycin-based chemotherapy alone (OR 0.67; 95% CI, 0.34 to 1.32; P = 0.248; Interaction = 0.041) and chemotherapy plus trastuzumab and pertuzumab (OR 0.80; 95% CI, 0.53 to 1.29; P = 0.016). Conclusions: This study identified a possibility of NLR as an easily accessible predictive marker to guide neoadjuvant HER2 target therapy in HER2 positive early breast cancer. Further study with other cohort is needed for validation.

858 Poster Session (Board #80), Sun, 8:00 AM-11:00 AM

**Correlation of the tumor mutational burden with the composition of the immune cell subpopulations in peripheral blood of triple-negative breast cancer patients undergoing neoadjuvant therapy with durvalumab: Results from the prospectively randomized GeparNuevo trial. First Author: Barbara Seliger, Martin-Luther-University Halle-Wittenberg, Halle, Germany

**Background:** The GeparNuevo trial is a randomized, double-blind, multicenter phase II trial of neoadjuvant therapy in patients with early-stage triple negative breast cancer (TNBC) investigating the role of durvalumab, an anti-CD137 antibody, which blocks PD-L1 binding to PD1 and as an additional standard chemotherapy with nab-Paclitaxel (nab-Pac) followed by Epirubicin plus Cyclophosphamide (EC; Loibl S et al. ASCO 2018). Since the tumor mutational burden (TMB) has been suggested to be associated with a better outcome of patients undergoing immunotherapy and an increased T cell response, we determined whether there exists a link between TMB and immune cell composition, frequency and function in patients of the GeparNuevo trial. **Methods:** In order to determine possible predictive and/or prognostic biomarkers, tumor biopsies taken at recruitment from 149 patients out of the 174 enrolled patients underwent deep sequencing in order to determine the TMB. In addition, for 120 patients blood samples were taken at recruitment and during different time points of treatment (after durvalumab pre-treatment, after Nab-Pac and at surgery after EC) and evaluated using multicolor flow cytometry by monitoring the absolute cell counts of T cells, B cells and NK cells as well as their frequency, composition and functionality of different immune cell populations. **Results:** The TMB of the GeparNuevo cohort was in line with published data with a mean of 3.8 mutations/MB (range 0.22 – 7.65), respectively. Preliminary evaluation demonstrated a significant correlation of TMB with blood parameters, in particular with subsets of CD8+ T cells. Interestingly, the data suggest a negative correlation of TMB with the frequency of effector cells while a positive correlation exists with the effector memory cells at recruitment. In depth analyses of a correlation with treatment arm and clinical responses are currently performed. **Conclusions:** Using this approach we hope to identify biomarkers, which will allow a better selection of TNBC patients undergoing specific immunotherapies. Clinical trial information: NCT02288509.
590 Poster Session (Board #82), Sun, 8:00 AM-11:00 AM

EORTC criteria: Patients treated with endocrine therapy (ET) from 1987 to 2011 were included. The primary end point was disease free survival (DFS) defined as time to any local or distant relapse or death due to breast cancer. The secondary end points were overall survival (OS), progression free survival (PFS), and times to local and distant relapse (LTOs).

Methods: Patients with primary breast cancer were identified from an institutional tumor registry, and their medical records were reviewed. Patients with known ER, PR, and HER2 status were included. The aim was to evaluate the prevalence of disease features from the pre-NACT biopsies and the post-NACT biopsies, as well as the changes in these features after NACT.

Results: A total of 400 patients were included in the analysis. The primary end point, DFS, showed a significant improvement for patients who had a change in ER status from negative to positive (27% vs 49%), (HR (95% CI)= 0.25, 0.19-0.34, p=0.005). The DFS was similar for patients who remained HER2+ (5-year DFS= 94% vs., 87%; p=0.613). Loss of PR in the pre-NACT ER+ tumors was associated with prolonged DFS (OS= 87% vs 66% (HR = 0.28, 0.17-0.44)).

Conclusions: The study demonstrated that changes in ER, PR, and HER2 status after NACT are associated with improved DFS. Multivariate Cox regression model for 5-year DFS.

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592 Poster Session (Board #84), Sun, 8:00 AM-11:00 AM

Preoperative checkpoint inhibition (CPI) and cryoablation (Cryo) in women with early breast cancer (ESBC). First Author: Elizabeth Anne Comen, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Checkpoint inhibition (CPI) combined with local strategies that cause local tumor destruction, such as cryo may augment tumor specific immunity and improve survival. We previously demonstrated in 18 ESBC patients (pts) that pre-operative (pre-op) cryo with ipilimumab (ip) is not only safe but also generates robust local and systemic immune responses (NCT00861705) .

Methods: In both pilot studies, eligible pts had available >1.5cm invasive HER2 negative ESBC. CPI was administered 1-5 days prior to cryoablation. Safety was assessed by area under the receiver operating characteristic curve (AUC), accuracy, sensitivity, specificity, and met clinical accrual targets.

Results: Following cryoablation, 18 ESBC pts were included in this analysis. 15 achieved pathological complete response (pCR). 3 pts achieved partial response (PR). 0 pts had no response (NR).

Conclusions: Preoperative CPI + cryoablation in selected pts with ESBC is feasible, safe, and associated with high clinical benefit. Further study is warranted.

591 Poster Session (Board #83), Sun, 8:00 AM-11:00 AM

CALGB (Alliance) 40603: Long-term outcomes (LTOs) after neoadjuvant chemotherapy (NACT) +/- carboptin (Cb) and bevacizumab (Bev) in triple-negative breast cancer (TNBC). First Author: Belal M. Sikow, Women and Infants Hospital of Rhode Island, Providence, RI

Background: Both Cb and Bev demonstrate activity when combined with standard therapy in TNBC. CALGB 40603 is a 2x2 randomized trial that previously demonstrated that adding Cb to NACT significantly increased pathologic complete responses in the breast/axilla (pCR), while adding Bev did not (Sikow, JCO 2015). Here we report 5-year LTOs and assess factors that influenced them. Among 443 patients with clinical stage II-IIIA disease, who had previously untreated TNBC received 12 weeks of paclitaxel (pC) +/- Cb then dose-dense AC, +/- Bev before surgery. The primary end point was pCR. Analyses of LTOs (event-free survival (EFS), distant recurrence-free interval (DRFI) and overall survival (OS)), impact of residual cancer burden and other variables were secondary. Results: Median follow-up was 5.7 years (y); 5y DFS was 70% (95% CI; 66.7-75.4%), DRFI 76.3% (72.3%-80.5%) and OS 76.9% (72.9%-81.2%). Pretreatment clinical stage and achieving pCR correlated with LTOs, while age, race, subtype (basal-like vs. not) and tumor grade did not. Among pCR 5y EFS was 84.6% vs. 57.5% for non-pCR (HR=0.28, 0.19-0.43); OS was 88.7% vs 66% (HR = 0.28, 0.17-0.44). This relationship was similar in all trial arms. Any residual disease conferred poorer outcome; compared with pCR/Residual Cancer Burden (RCB0), DFS HRs were 2.29 (1.32-3.97), 3.01 (1.90-4.74), and 9.67 (5.66-16.51) for RCB1, II and II, respectively. There were no improvements in LTOs with Cb in DFS HR 0.99, 0.97, 0.97 or Bev (DFS HR=0.95). An exploratory analysis, receipt of ≥11 doses of pC was associated with better EFS (HR 1.92, 1.33-2.77); this was particularly notable in Cb-treated arms.

Conclusions: As expected, regardless of treatment arm pCR was associated with markedly better LTOs, and pts with any residual disease had significantly poorer outcomes of treatment. Adding Cb to Bev in the neoadjuvant regimen did not improve LTOs in this trial, although it should be noted that the trial was not powered for this end point. Omission of chemotherapy doses may result in poorer outcomes, especially among Cb-treated pts, which may warrant further evaluation. Support: U10CA180821; U10CA180882; Genentech, https://acknowledgments.alloncelford.com; NCT00861705.
Circulating tumor DNA (ctDNA) during and after neoadjuvant chemotherapy and prior to surgery is a powerful prognostic factor in triple-negative breast cancer (TNBC). First Author: Luca Calandrelli, Signal Cancer Centre, Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada

Background: TNBC, the most aggressive form of breast cancer, is treated primarily with chemotherapy, even before surgery (neoadjuvant chemotherapy or NAC). The prognosis and need for adjuvant therapy depends primarily with chemotherapy, even before surgery (neoadjuvant chemotherapy or NAC). The prognosis and need for adjuvant therapy depends

Methods: Tissue was collected from 26 Q-CROC-03 clinical trial TNBC patients before, during, and after NAC, prior to surgery. Whole exome sequencing on tumor tissues was used to select single nucleotide variants with high allele frequency (VAF), prioritizing TP53, to generate individual droplet PCR (ddPCR) assays. An average of 5 variants (range 1-12) per patient were tested, for a total of 121 variants. A detection threshold was defined for each variant from a pool of normal controls. Median follow-up was 55 months. Results: ctDNA was detectable in 96% of patients at baseline, but 20% of the 121 variants were not detectable at any time point. At baseline, the mean VAF of all analyzed variants, but not of TP53 variants alone, was significantly correlated (p<0.05) with tumor factors (tumor size, stage, grade, nodal status before and after surgery, RCB score) but not with patient age or BRCA1/2 mutation status. 87 variants (74%) were detected at baseline and their VAF fell by 86% after 1 cycle of chemotherapy (T1). The detection of ctDNA at T1 was associated with DFS (p = 0.027) while the detection of ctDNA at the last post chemotherapy pre-surgery time point (T4) was strongly associated with pathological complete response (pCR) and both DFS (p = 0.013) and OS (p = 0.006). At this time point, 5 of 41 variants (12%) were detected in pCR patients vs 42 of 80 (53%) in non-pCR, while only 6 of the 15 (40%) non-pCR patients had detectable TP53 variants, indicating that, for variants detected at baseline, the positive predictive value of TP4 ctDNA for disease recurrence was 69%, similar to that of non-pCR, while the negative predictive value of no ctDNA at T4 was 89% for disease recurrence vs 80% for pCR. Conclusions: ctDNA detection after NAC prior to surgery is strongly predictive of disease-free survival and DMFS post surgery and is comparable to pCR as a prognostic factor in our cohort (NCT01276899).

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Early stage triple negative breast cancer (TNBC) is associated with a high risk of distant relapse. Because TNBC does not currently have specific targeted agents approved for use in the early setting it is treated primarily with chemotherapy. TNBC may be more immunogenic than other subtypes of breast cancer and promising clinical activity has been reported with the anti- PD-L1 antibody, atezolizumab, in Phase 1/1b metastatic TNBC trials. Furthermore, the randomized phase 3 IMpassion130 study demonstrated enhanced anti-tumor activity when atezolizumab was co-administered with chemotherapy in the first line metastatic setting, with benefit mainly observed in PD-L1+ cohort. ALEXANDRA/IMpassion030 will evaluate the efficacy and safety of atezolizumab in combination with standard anthracycline/taxane adjuvant chemotherapy in early TNBC patients.

Methods: ALEXANDRA/IMpassion030 is a global, prospective, randomized, open-label, phase 3 trial investigating the efficacy, safety and pharmacokinetic profile of adjuvant atezolizumab plus standard chemotherapy versus chemotherapy alone in early TNBC. In total, 2300 patients with operable stage I or II TNBC, confirmed by central review, will be randomized. Patients are stratified by type of surgery, nodal status, and centrally assessed PD-L1 status. Adjuvant treatment will consist of weekly paclitaxel 80 mg/m² for 12 weeks followed by dose dense anthracycline (epirubicin 90 mg/m² or doxorubicin 60 mg/m²) and cyclophosphamide 600 mg/m² for 4 doses every 2 weeks or the same chemotherapy regimen (EC/AC) given concomitantly with atezolizumab 840 mg every 2 weeks followed by maintenance atezolizumab 1200 mg every 3 weeks until completion of 1 year of atezolizumab. The primary end-point is invasive disease-free survival (iDFS) and secondary end-points include iDFS by PD-L1 and lymph node status, DFS, OS, survival, safety and biomarker endpoints specific to HRQoL. Tissue and blood samples will be collected for biomarker research. The first patient was enrolled on August 2nd 2018, and approximately 430 sites are expected to be opened globally in 30 countries. Clinical trial information: NCT03498716.
Background: Inflammatory breast cancer (IBC) is the most aggressive form of breast cancer with poor prognosis and is often resistant to neoadjuvant chemotherapy with risk of early recurrence and systemic spread of disease. PD-L1 expression in IBC is frequent (Bertucci et al. Oncotarget 2016), and blockade of the PD-1/PD-L1 axis with checkpoint inhibitors has emerged as a promising treatment to enhance anti-tumor immunity and clinical response. We hypothesize that PD-1 blockade with nivolumab in combination with neoadjuvant (primary) chemotherapy will increase the rate of pathologic complete response (pCR) and reduce risk of recurrence in patients with IBC.

Methods: This is a single-arm open-label multicenter phase II study of nivolumab with neoadjuvant chemotherapy in patients with non-metastatic IBC (n = 52) (ClinicalTrials.gov: NCT03742986). All breast cancer subtypes (based on ER/PR/HER2) will be allowed. Patients will receive nivolumab 360 mg IV on day 1 (21-day cycle) for four cycles in addition to standard chemotherapy. Cohort 1 (patients with triple negative breast cancer or hormone receptor-positive (HR)/HER2-negative IBC) will receive nivolumab in combination with paclitaxel followed by doxorubicin and cyclophosphamide (AC). Cohort 2 (patients with HER2-positive IBC) will receive nivolumab in combination with a taxane (docetaxel or paclitaxel), trastuzumab, and pertuzumab followed by AC. All patients will then undergo mastectomy followed by radiation. The primary study objective is pCR rate (ypT0/Tis ypNO). Secondary objectives will be safety, tolerability, and invasive recurrence-free interval. Association of correlative biomarkers with pCR and sensitivity or resistance to therapy with the combination of nivolumab and chemotherapy will be evaluated. Analyses will include mutational and neoantigen load, tumor-infiltrating lymphocytes (TILs) by histopathological assessment, T-cell receptor (TCR) by immunosequencing, and immune gene profiles in the tumor. PD-L1 expression in tumor tissue is not required for enrollment but will be assessed as a predictive marker. Clinical trial information: NCT03742986.

TPS603 Poster Session (Board #91b), Sun, 8:00 AM-11:00 AM

The international collaboration of active surveillance trials for low-risk DCIS (LORIS, LORD, COMET, LORETTA). First Author: Chizuko Kanbayashi, National Cancer Center Hospital, Tokyo, Japan.

Background: Retrospective data suggest breast cancer-specific survival rates with versus without surgery in patients with low-grade ductal carcinoma in situ (DCIS) are similar. Some DCIS patients have a low likelihood of progression to invasive cancer, but predicting who is at risk has not been established. Thus, treatment with a well-balanced risk / benefit ratio has not been achieved. Four active surveillance clinical trials for low risk DCIS have been established in the United Kingdom (LORIS), Europe (LORD), United States (COMET), and Japan (LORETTA). We aim to examine the effectiveness & safety of active surveillance compared with surgical based treatment approaches for low-risk DCIS patients. Methods: Non surgical approaches are of the two types; active surveillance (AS) alone and AS + endocrine therapy (ET). In the randomized trials LORIS and LORD, the study arms are AS only, but while ET is an option in COMET, ET is mandatory in the single arm trial COMET. COMET and LORETTA have broader inclusion criteria as compared to LORIS and LORD. In COMET, comedo necrosis is eligible. In LORETTA, findings other than calcification on mammography (MMG) are also eligible (e.g. low echo area on breast ultrasound). Leaders of the four trials hold regular meetings to foster international DCIS trials collaboration to share information. LORIS Clinical trial information: ISRCTN27544579, LORD Clinical trial information: NCT02492607. COMET Clinical trial information: NCT02926911, LORETTA Clinical trial information: UMIN000028289. Tumor progression to invasive disease (TPI) in the four trials will be analyzed in the four trials and in a meta-analysis.

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<td>N/S</td>
<td>Negative***</td>
<td>Negative</td>
</tr>
<tr>
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<td>Any size</td>
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<td>≤ 2.5 cm</td>
</tr>
<tr>
<td>Patients/Target</td>
<td>113/932</td>
<td>25/1240</td>
<td>182/1200</td>
<td>27/340</td>
</tr>
</tbody>
</table>

AS: Active surveillance, ET: Endocrine therapy, N/S: Not stipulated in study protocol, *: single arm confirmatory trial, **: breast US and MRI, ***: if tested.
1000 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

**SOPHIA primary analysis: A phase 3 (P3) study of margetuximab (M) + chemotherapy (C) versus trastuzumab (T) + C in patients (pts) with HER2+ metastatic breast cancer (MBC) and brain metastases (BM)**

**First Author:** Hope S. Rugo, University of California San Francisco Comprehensive Cancer Center, San Francisco, CA

**Background:** Pretreated HER2+ MBC lacks a defined standard of care, although T is commonly used. M has similar HER2 binding and anti-proliferative effects as T. By contrast, M’s Fc region is engineered to increase affinity for both alleles of the activating Fc receptor (Fcr), CD16A, and decrease affinity for the inhibitory Fcr, CD32B. The low affinity of HER2 to 158F allele (~85% of population) has been associated with diminished clinical response to T. In a Phase 1 trial, M demonstrated acceptable safety, anti-tumor activity, and evidence of HER2-specific antibody and T-cell responses.

**Methods:** SOPHIA (NCT02492711), a randomized, open-label, phase III trial, enrolled pts with HER2+ MBC after pertuzumab and 1-3 lines of prior Tx for MBC. Pts were randomized 1:1 to M (15 mg/kg IV q3w or T (6 [8 for loading dose] mg/kg IV q3w) + C (750 mg/m² bid po) or L (1250 mg qd po) + C (1000 mg/m² bid po).

**Results:** At an interim analysis, median PFS (mPFS) was longer with M vs L + C (9.66 vs 7.64 mo, P = 0.037). The safety profile was comparable between arms. The primary endpoint (IRC-assessed mPFS) was met at the 12-month primary analysis with a hazard ratio (HR) of 0.69 (95% CI: 0.54-0.87). The rate of Grade 3-4 events were similar between arms, with the exception of Grade 3-4 diarrhea, which occurred in 24.4% with M vs 12.1% with L + C (HR = 1.98, 95% CI: 1.11-3.46, P = 0.018).

**Conclusions:** Preliminary results of the Phase 3 SOPHIA trial show a statistically significant improvement in median PFS with margetuximab over trastuzumab in patients with HER2+ MBC and brain metastases. This difference was maintained at the 12-month follow-up analysis, demonstrating the potential for improved outcomes with margetuximab in this patient population.

1001 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

**Pyrotinib combined with capecitabine in women with HER2+ metastatic breast cancer previously treated with trastuzumab and taxanes: A randomized phase III study (NALA)**

**First Author:** Zefei Jiang, The Fifth Medical Center of Chinese PLA General Hospital, Beijing, China

**Background:** Pyrotinib, an irreversible pan-ErbB receptor tyrosine kinase inhibitor, showed promising anti-tumor activity and acceptable tolerability in patients with HER2+ metastatic breast cancer (MBC) in phase 1/2 trials.

**Methods:** This double-blind, multicentre, randomised phase 3 trial was conducted in Chinese patients with HER2+ MBC previously treated with taxanes and trastuzumab. Patients were randomly assigned (2:1) to receive 400 mg pyrotinib or placebo orally once daily for 21-day cycles in combination with capecitabine (1000 mg/m² orally twice daily on days 1–14). The primary endpoint (IRC-assessed progression free survival [PFS]) was assessed in patients who received ≥1 dose of study treatment. Patients whose disease progressed on placebo plus capecitabine received subsequent single agent pyrotinib.

**Results:** Between July, 2016 and November, 2017, 279 patients were randomised to pyrotinib plus capecitabine (n = 185) or placebo plus capecitabine (n = 94) arms. The median PFS was 11.9 months (95% CI 9.66, 16.53) in the pyrotinib plus capecitabine arm and 4.1 months (95% CI 2.79, 4.94) in the placebo plus capecitabine arm. Seventy-one patients in the placebo plus capecitabine arm received subsequent pyrotinib, showing single-agent response rate of 38.0% (95% CI 26.7%, 49.3%) and median PFS of 5.5 months (95% CI 4.07, 6.90). The most frequent (≥5%) treatment-related grade ≥ 3 adverse events were diarrhea (30.8% vs 12.8%) and hand-foot syndrome (11.1% vs 3.9%). Conclusions: Atezo + nP significantly improved PFS with a trend towards OS benefit with atezolizumab (atezo) + nab-paclitaxel (nP) in previously untreated locally advanced or metastatic triple-negative breast cancer (mTNBC).

**First Author:** Peter Schmid, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom

**Background:** IMPassion130 evaluated overall survival (OS) from a global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab (atezo) + nab-paclitaxel (nP) in previously untreated locally advanced or metastatic triple-negative breast cancer (mTNBC).

**Methods:** Eligible pts had histologically documented locally advanced or mTNBC, ECOG PS 0-1 and tumor tissue for PD-L1 testing. Pts were randomized 1:1 to IV atezo 840 mg or placebo on d1 and d15 + nP 100 mg/m² on d1, d8 and d15 of each 28-d cycle until progression (stratification factors: prior taxanes, liver metastases, PD-L1 on tumor-infiltrating immune cells [IC]). RECIST 1.1 PFS (in ITT and PD-L1+ pts) and OS (in ITT and PD-L1+ pts) were co-primary endpoints. In the atezo + nP vs placebo + nP arms, median OS data were shown (Table). As of data cutoff (Jan 2, 2019), 9% of pts in the atezo + nP arm and 3% in the placebo + nP arm were still on treatment. Statistical significance was not demonstrated in ITT pts, but a 7.0-month improvement in median OS was observed in PD-L1+ pts (25.0 mo) vs placebo + nP (18.0 mo; HR, 0.71 [95% CI: 0.54, 0.93]). A 4.5-mo safety update (Schneeweiss, ASCO 2019, submitted) showed that atezo + nP remained tolerable. Conclusions: The 2nd IMPassion130 interim OS analysis was consistent with the 1st analysis, confirming clinically meaningful OS benefit with atezo + nP in previously untreated PD-L1+ mTNBC. Clinical trial information: NCT02425891.

<table>
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<tr>
<th>IRC</th>
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<th>Placebo + capecitabine (n = 94)</th>
<th>Placebo + capecitabine (n = 94)</th>
<th>Placebo + capecitabine (n = 94)</th>
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<tbody>
<tr>
<td>Atezo + nP</td>
<td>Placebo + nP</td>
<td>Median PFS, months (95% CI)</td>
<td>Median PFS, months (95% CI)</td>
<td>Median PFS, months (95% CI)</td>
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<td>(n = 185)</td>
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<td>(96.4, 16.53)</td>
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<tr>
<td>HR</td>
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<td>&lt; 0.001</td>
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<td>ORR, %</td>
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<td>68</td>
<td>15 (16.0%)</td>
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Visit abstracts.asc.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Studies of checkpoint inhibitor monotherapy show only modest activity in HR+ MBC. We report data from the first randomized study comparing E plus P versus E alone in HR+HER2- MBC. Methods: Eligible patients (pts) had HR+HER2- MBC; ≥2 lines of hormonal therapies and 0-2 lines of chemotherapy for MBC. Pts were randomized 1:1 to E or E alone (Arm B). At time of progression, pts in arm B could choose to receive P or continue E alone. Primary endpoint was progression-free survival (PFS). Key secondary endpoints were: objective response rate (ORR) and overall survival (OS). Exploratory analyses assessed the association between PFS and PD-L1 status, tumor-infiltrating lymphocytes (TILs), neutrophil-lymphocyte ratio (NLR), tumor mutation burden (TMB), and genomic alterations by next generation sequencing on archival tissue. Results: 88 pts initiated protocol therapy; the median age was 58, median prior lines of chemotherapy 1, prior lines of hormonal therapy 2. Median follow-up was 6.3 months. Median PFS and ORR were not different between Arms A and B (PFS 4.6 vs 4.1 months p = 0.38; ORR 28% and 23% respectively (p = 0.49). 14 patients initiated crossover treatment with pembrozulumb; 1 patient experienced a PR (ORR 7%). All cause AEs occurred in 100% of pts (G3-4, 54.6%) including 2 treatment related deaths on Arm A, both from known AEs attributed to both drugs. PD-L1 assay was performed in 65 pts; 24 (36.9%) had PD-L1 positive (> 1% with 100% centrally tested) tumors. PD-L1 status, TILs, NLR, or TMB alterations were not associated with PFS (Table). Updated data, including OS and genomic results, will be presented. Conclusions: Among pts with HR+/HER2- MBC, the combination of E and P was not associated with longer PFS than E alone in the ITT or PD-L1+ population, though the PD-L1+ subgroup had very high treatment burden (TMB).
Genomic profiling of ER+ metastatic breast cancer (MBC) has revealed highly prevalent genomic alterations (e.g. ESR1, NF1, ERBB2) associated with exposure to antiestrogen therapy and endocrine resistance. It is not known whether any such acquired genomic alterations are observed after exposure to the current standard CDK4/6 inhibitors (CDK4/6i). Methods: To identify genomic alterations associated with acquired resistance to CDK4/6 + antiestrogen combinations, we prospectively performed tumor and matched normal sequencing on 1059 ER+ breast cancers from 845 MBC patients collected prior to (n = 838) or post-treatment with CDK4/6i (n = 221), including 110 pre- and post-treatment pairs. We performed gene enrichment analyses to identify the oncogenic mutations and copy number alterations that were more frequent in post-CDK4/6i samples compared to CDK4/6i-naïve samples and further compared these results to those of post-hormone alone therapy datasets. Results: The post-CDK4/6i samples were collected following exposure to CDK4/6i plus aromatase inhibitors (51%), plus fulvestrant (28%), or more frequently (21%). Along with alterations previously associated with resistance to hormonal therapy alone, our analysis identified multiple genes to therapy datasets.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Pembroliuzumab (P) in patients (pts) with metastatic breast cancer (MBC) with high tumor mutational burden (HTMB): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study. First Author: Ajjai Shivaram Alva, University of Michigan, Ann Arbor, MI

**Background:** TAPUR is a phase II basket study evaluating the anti-tumor activity of commercially available targeted agents in pts with advanced cancers with specific genomic alterations. PIK3CA is an immune checkpoint inhibitor (ICI) predictive biomarker for checkpoint inhibitor therapy. Results in a cohort of MBC pts with HTMB treated with P are reported. Methods: Eligible pts had advanced cancer, no standard treatment options, ECOG PS 0-1, measurable disease and acceptable organ function. Genomic testing was performed using commercially available tests selected by sites. Pts matched to P HTMB defined as ≥9 mutations/ megabase (Muts/Mb) by a FoundationOne test (n=20) or approved by the TAPUR Molecular Tumor Board for other tests (n=8). A Simon two-stage design was used to test a null rate of 15% vs. 35% (power = 0.85; α = 0.10). If ≥ 2 of 10 pts in stage 1 have disease control (DC) objective response (OR) or stable disease at 16 weeks (wks) (SD16+), an additional 18 pts are enrolled. If ≥ 7 of 28 pts have DC, the drug is considered worthy of further study. Secondary endpoints are progression-free survival (PFS), overall survival (OS) and safety. Results: Twenty-eight female MBC pts were enrolled from October 2016 to July 2018. Pts received P at 2 mg/kg (n=8) or 200 mg (n=20) IV over 30 minutes, every 3 wks. HTMB ranged from 9 to 37 Muts/Mb. Demographics and outcomes are summarized in Table (N=28). No relationship was observed between Muts/Mb and PFS or OS. Two grade 3 AEs (weight loss and hypothyroidism) and 1 grade 2 SAE (uterine infection) were reported as at least possibly related to P. Conclusions: P demonstrated anti-tumor activity in heavily pre-treated MBC pts with HTMB. Additional study of P is warranted in MBC pts with HTMB. Clinical trial information: NCT02693535.

**Muts/Mb. median (range)** | 13 (2, 37)
---|---
DC rate, % | 37% (24%, 46%)
OR rate, % | 17% (5%, 41%)
DC OR rate, % | 35% (16%, 44%)
Median OS, mo (95% CI) | 11.6 (3.4, 17.2)
DR-Med OS, mo | 13.6 (11.3, 16.4)
DR-NED-Med OS, mo | 18.4 (13.1, 21.9)
Abbreviations: DC: disease control; OR: objective response; PFS: progression-free survival; OS: overall survival.

**1014 Poster Discussion Session; Displayed in Poster Session (Board #95), Sun, 8:00 AM-1:00 AM, Discussed in Poster Discussion Session, Sun, 11:15 AM-12:45 PM**

**Pembrolizumab (pembro) with paclitaxel (taxol) or capecitabine (cape) as early treatment of metastatic triple-negative breast cancer (mTNBC). First Author: David B. Page, Earle A. Chiles Research Institute at the Robert W. Franz Cancer Center, Portland, OR

**Background:** Atezolizumab (anti-PD-L1) plus nab-paclitaxel was shown to improve outcomes in mTNBC in a phase III clinical trial. Subjects were required to be > 12 months from curative-intent therapy in this trial. It remains unknown whether non-taxane chemotherapy + anti-PD-L1 will be beneficial in mTNBC, or whether this approach is effective in rapidly-progressing patients (< 12 mo from curative-intent therapy). Methods: mTNBC patients were enrolled in a phase IIb study of anti-PD-L1 (pembro, 200mg IV q3w) plus physician’s choice chemo (cape: n = 14, 2000mg BID, 7d on/7d off; or taxol: n = 14, 80mg/m2 q1w). Primary/secondary objectives were to evaluate safety/tolerability (primary) and RECIST1.1 response (w12). The exploratory objective was to explore for differences in immunomodulation according to chemo choice. Mixed-effects models were employed to compare the longitudinal effects of chemo on peripheral immune cells (flow cytometry) and T-cell diversity (Immunoseq assay). Results: Enrollment of the trial is complete (n = 28), with 100% of evaluable patients tolerating therapy (n = 22) as of 2/1/2019. Cape ORR was 43% (5 PR, 1 CR, 2 SD) with median PFS = 155d. Taxol ORR was 25% (1 CR, 1 PR, 3 SD) with median PFS = 99d. Subjects enrolled < 12 months from curative-intent therapy had numerically lower response (ORR = 27%, 1 CR, 2 PR, 3 SD) than subjects who had rapid progression (ORR = 46%, 1 CR, 0 PR, 2 SD). No significant differences in immunomodulation were observed according to chemo type, however both cape & taxol were associated with declines in T-cell quantity (CD4 p < .02, CD8 p < .04) and Immunoseq T-cell fraction over time. Conclusions: Pembro plus cap or taxol is safe with encouraging efficacy, however activity may be lower in the setting of rapid progression following curative-intent chemotherapy. Cape+taxol is tolerable if combined with a chemotherapy backbone in selected patients. Both cape and taxol are associated with polyclonal declines in T-cell quantity, which may explain the observed dropoff in anti-PD-L1/1 activity in later lines. Clinical trial information: NCT02734290.

**1015 Poster Discussion Session; Displayed in Poster Session (Board #96), Sun, 8:00 AM-1:00 AM, Discussed in Poster Discussion Session, Sun, 11:15 AM-12:45 PM**

A phase II study of abemaciclib in patients (pts) with brain metastases (BM) secondarily to HR+, HER2- metastatic breast cancer (MBC). First Author: Carey K. Anders, Duke Cancer Institute, Durham, NC

**Background:** Abemaciclib is a selective CDK4 & 6 inhibitor approved to treat HR+, HER2- MBC pts on a continuous dosing schedule as monotherapy or in combination with endocrine therapy (ET). Clinical data demonstrate abemaciclib penetrates the blood brain barrier resulting in comparable concentrations in tissues and plasma. Methods: JAB01 is a Simon 2-stage trial evaluating abemaciclib in 6 pt cohorts with BM secondary to HR+ MBC, non-small cell lung cancer, or melanoma. Here, we report on HR+, HER2- MBC pts. Eligible pts had ≥1 new or not previously irradiated measurable BM ≥10mm or a progressive previously irradiated BM. Pts receiving ET at the time of enrollment were permitted to continue the same ET provided that ORR (≥1 patient) and RECIST1.1 response (w12). The exploratory objective was to explore for differences in immunomodulation according to chemo type, which may explain the observed dropoff in anti-PD-L1/1 activity in later lines. Clinical trial information: NCT02734290.
In-depth gene expression analysis of premenopausal patients with HR+/HER2-- advanced breast cancer (ABC) treated with ribociclib-containing therapy in the Phase III MONALEESA-7 trial. First Author: Wei-Jen Kao, National Taiwan University Hospital, Taipei, Taiwan

Background: The Phase III MONALEESA-7 study (NCT02278120) is the first dedicated trial of endocrine therapy (ET) ± a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor in premenopausal patients (pts) with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-- ) ABC. The study demonstrated that the addition of ribociclib (RIB) to a non-steroidal aromatase inhibitor (NSAI) or tamoxifen (TAM) + goserelin (GOS) significantly extended progression-free survival (PFS; hazard ratio (HR) 0.55; Tripathy D, et al. Lancet Oncol. 2018). Here we present a gene expression analysis of baseline tumor mRNA from MONALEESA-7.

Methods: Premenopausal pts with HR+/HER2-- were treated with RIB or placebo (PBO) + GOS with either an NSAI (letrozole or anastrozole) or TAM. Baseline archival tumor samples from 360 of 672 intent-to-treat (ITT) pts were evaluated for gene expression (RIB n = 185; PBO n = 175) using a customized NanoString nCounter® GX 800-gene panel containing relevant breast cancer, CDK, and proliferation pathway-related genes. Pt subgroups were classified as having low or high mRNA expression using median expression as the cutoff.

Results: PFS benefit in the biomarker-assessed group was similar to that in the ITT population. A trend toward a more pronounced PFS benefit with RIB was observed in pts with high vs low expression of CCND1 (HR 0.38 vs 0.67, respectively), GFR1 (HR 0.37 vs 0.77), ERBB4 (HR 0.33 vs 0.76). The PFS benefit seen with RIB also trended to be greater in pts with low vs high expression of CCNE1 (HR 0.38 vs 0.65, respectively) and MYC (HR 0.37 vs 0.69). The PFS benefit with RIB was similar in pts with high vs low expression of GFR1 (HR 0.45 vs 0.61, respectively). ESR1 (HR 0.57 vs 0.74) and tumor suppressor genes, such as MAX2 (HR 0.52 vs 0.51).

Conclusions: This is the first gene expression analysis of a large set of premenopausal pts with ABC. The benefit with RIB was generally consistent across gene expression subgroups, although the magnitude varied in certain subsets. This analysis suggests that there may be unique resistance mechanisms to ET + CDK4/6 inhibitors in premenopausal pts with ABC. Clinical trial information: NCT02278120.

End-of-study analysis from the phase III, randomized, double-blind, placebo (Pla)-controlled CLEOPATRA study of first-line (1L) pertuzumab (P), trastuzumab (H), and docetaxel (D) in patients (pts) with HER2-positive metastatic breast cancer (MBC). First Author: Sandra M. Swain, Georgetown University Medical Center, Lombardi Comprehensive Cancer Center, Washington, DC

Background: Progression-free and overall survival (PFS and OS) were signifi- cantly improved, overall survival (OS) was improved, and OS was improved in patients with a trastuzumab (T) + pertuzumab (P) vs T + placebo (Pla) + docetaxel (D) in the phase III CLEOPATRA trial (NCT00567190). OS was increased by an unprece- dented 15.7 mo (median 56.5 mo with P + D vs 40.8 mo with Pla + D + H; HR 0.68, 95% CI 0.56, 0.84; p < .001) with a median follow-up of 50 mo [Swain et al. NEJM 2015]. Here we report the end-of-study analysis with a median follow-up of 120 mo (max 204 mo).

Methods: In this descriptive analysis, OS was compared between arms using the log-rank test, stratified by prior treatment status and geographic region. The Kaplan–Meier approach was used to estimate median OS, and a stratified Cox proportional hazards model was used to estimate the HR and 95% CIs. Subgroup analyses of OS were performed for stratification factors and other baseline characteristics. Results: Clinical cutoff was Nov 23, 2018. Since Jul 2012, 50 pts crossed from the Pla to the P arm. These pts are counted in the Pla arm for efficacy analyses and up to the first dose of P for safety analyses. The OS HR was 0.69 (95% CI 0.58, 0.82), favoring P + H + D. Median OS was 57.1 mo in the P arm (402 pts) and 40.8 mo in the Pla arm (406 pts; Δ 16.3 mo). The 8-year landmark OS rates were 37% and 23%, respectively. The OS benefit in predefined subgroups, including in pts previously treated with H in the (neo) adjuvant setting (88 pts, HR 0.86; 95% CI 0.51, 1.43), remained consistent with the overall result and previous reports. The overall safety profile of P + H + D was consistent with the known P safety profile. There was only one new serious adverse event suggestive of congestive heart failure (onset ~77 mo on treatment in the P arm, resolution in 34 days, pt continued on study medication) and one new symptomatic left ventricular systolic dysfunction (onset ~46 mo after crossing to the P arm, resolution in 34 days) since the previous analysis. Conclusions: The CLEOPATRA study (Swain et al. NEJM 2015) demonstrated that HER2-positive MBC was maintained after an additional 4 years of long-term follow-up, as were the safety and cardiac safety profiles. Clinical trial information: NCT00567190.

Biosimilar trastuzumab-dkst monotherapy versus trastuzumab monotherapy after combination therapy: Final overall survival (OS) from the phase III HERITAGE Trial. First Author: Cornelius F. Waller, University of Freiburg Medical Center, Freiburg, Germany

Background: The multicenter, double-blind, randomized, parallel-group, phase 3 Heritage Trial (NCT02427964) evaluated efficacy and safety of trastuzumab-dkst (dkst), a trastuzumab biosimilar, vs trastuzumab, plus taxane as first-line monotherapy for patients with HER2+ metastatic breast cancer. Overall response at week (wk) 24 and progression-free survival (PFS) at wk 48 have been reported (Rugo et al., JAMA 2017; ASCO 2018). Methods: Eligible patients were randomized 1:1 to trastuzumab-dkst or trastuzumab, plus taxane. After 24 wk, patients with responding/stable disease continued monotherapy per randomization. Safety and OS during maintenance, cumulative through 36 months of follow-up from last patient on study, are described. Results: 500 patients were randomized; 434 received monotherapy after 24 wks (trastuzumab-dkst, n = 179; trastuzumab, n = 164), 128 patients discontinued monotherapy (trastuzumab-dkst, n = 63; trastuzumab, n = 65); mean time to discontinuation was 19 months in both groups. Treatment-emergent adverse events (TEAEs) during monotherapy were similar for trastuzumab-dkst (69%) and trastuzumab (73%); most were low grade and serious TEAE rates were 6% in both groups. Cumulative rates of TEAEs of special interest were similar for hypersensitivity, pulmonary, and cardiac events (trastuzumab-dkst, 23%, 16%, and 5%; trastuzumab, 24%, 13%, and 5%). Incidences of left ventricular ejection fraction (LVEF) < 50% at 1 time baseline (trastuzumab-dkst, 5%; trastuzumab, 3%) and LVEF < 50% at baseline and ≤10% reduction (trastuzumab-dkst, 4%; trastuzumab, 8%) were low across lines of therapy, with similar distribution of HER2 treatments, endocrine therapies, and chemotherapies. Final median PFS was 11.1 months in both groups. Median duration of response was 9.9 and 9.8 months and median OS was 35.0 and 32.0 months for trastuzumab-dkst and trastuzumab, respectively. Conclusions: The HERITAGE trial (Rugo et al. JAMA 2017) demonstrated that trastuzumab-dkst is an effective and safe alternative to trastuzumab for patients with HER2+ metastatic breast cancer. Further studies are needed to define the long-term benefit of trastuzumab-dkst compared with trastuzumab.
1024 Poster Discussion Session; Displayed in Poster Session (Board #105), Sun, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sun, 11:15 AM-12:45 PM

mTORC1 activation assessed in metastatic sample to predict outcome in patients with metastatic breast cancer treated with everolimus-exemestan: Results from the SAFIRTOR study. First Author: Thomas Denis Bachelot,GINECO-Centre Léon Bérard, Lyon, France

Background: Using samples from TAMRAD study (Treilleux, Ann Oncol, 2015), we previously reported that p4EBP1, a downstream protein of mTOR, may provide insight into mechanisms underlying metastatic potential. Methods: Patients (pts) with ER+, HER2 negative, naive treatment to everolimus (eve), SAFIRTOR study, designed to validate clinical utility of this biomarker. Results: Of 150 pts included with treatment to eve+exemestane (eve) combination. The primary end point was to validate that p4EBP1 expression is associated with better PFS. 120 evaluable pts were needed for the planned statistical analysis. All samples were collected and processed in a standardized procedure in order to allow phopho-proteins IHC staining. In addition to p4EBP1, we explored prognostic value of p53, pAkt, PTEN and KRAS together with genomic alterations assessed by NGS and CGH arrays. Results: 150 pts were included, 30 pts had no adequate sample, and further 13 had missing clinical data, 107 were evaluable for primary objective. Median age was 62, they had previously progressed on AI treatment, either in the adjuvant (22 pts) or the metastatic setting (83 pts). 20 were considered as primary hormone resistant. 87 as secondary. The median number of TMB was 5.5 (range: 0-6.5). Analysis of the primary endpoint showed that p4EBP1 staining above the median is associated with higher benefit to everolimus (eve). SAFIRTOR study validates: Conclusion: This prospective study validates that p4EBP1 expression analysis to select patients most likely to benefit from everolimus + exemestane. Clinical trial informative: NCT02444390.

1025 Poster Discussion Session; Displayed in Poster Session (Board #106), Sun, 8:00 AM-11:00 AM

Effect of HER2/neu 655 polymorphism on trastuzumab-induced cardiotoxicity in HER2-positive breast cancer patients. First Author: Isabel Blancas, Hospital Universidadario San Cecilio, Granada, Spain

Background: HER2 overexpression in breast cancer is associated with a poor outcome, high risk of metastasis and a reduced overall survival. The introduction of Trastuzumab in the treatment scheme improved the prognosis of these patients. Nevertheless, around 20% of patients develop cardiotoxicity. The purpose of this study is to analyze the association of the HER2 Ile655Val A polymorphism with trastuzumab-induced cardiotoxicity and/or survival. Methods: The study included 93 patients recruited from San Cecilio University Hospital in Granada (Spain) who were treated intravenously with Trastuzumab. The cardiotoxicity was diagnosed during the treatment follow-up considering a decrease of the left ventricular ejection fraction (LVEF) from baseline or clinical manifestation of congestive heart failure. HER2 655 > G was genotyping using TaqMan SNP technology. Results: Genotype frequencies of HER2/neu 655 was 65% Ile-Ile, 22% Ile-Val, 13% Val-Val genotype. Conclusion: This prospective study validates: Further studies are needed to determine if this polymorphism may be used as a predictive tool for trastuzumab induced cardiotoxicity.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: In CLEOPATRA (NCT00567190), adding P to H + D significantly improved progression-free and overall survival (PFS/OS) with P + H + D in patients (pts) with previously untreated HER2-positive locally advanced or metastatic breast cancer (LR/MBC) (NCT02896855). A phase Ib/II bridging study, the objective being to assess consistency of efficacy with CLEOPATRA. Methods: Pts with previously untreated HER2-positive LR/MBC were randomized 1:1:1:1:1 to P + H + D, stratified by visceral or non-visceral disease and hormone receptor status. The primary endpoint was investigator-assessed PFS. Secondary endpoints included objective response rate (ORR) and toxicity. Pts were treated for 21 days on, 7 days off, and L 2.5 mg/day. Safety was assessed using CTCAE v4.0. Results: Two hundred forty-three pts were randomized. Baseline characteristics and primary therapies generally balanced between arms. For PFS, the HR was 0.69 (95% CI 0.49, 0.99) in the ITT population. No cases of heart failure or symptomatic left ventricular ejection fraction decline were reported. Efficacy/safety were shown in the table. Conclusions: P + H + D extended PFS/OS beyond that observed in CLEOPATRA (HR 0.62). Treatment was generally well tolerated with evidence of clinical activity. Based on PK analysis and dose escalation, 400 mg was recommended for the phase II trial.

Background: First-in-class, novel HER2-targeted bispecific antibody fragment (bsAb) generated to link tumor-targeting HER2 with activating Fc-engineered mAb that shares similar HER2 binding and anti-HER2 activity. Methods: Onco-HER2 bsAb was generated against HER2-positive breast cancer. PK, ADME, and efficacy. Results: Onco-HER2 bsAb demonstrated superior HER2-targeting activity and expression stability compared with currently available HER2 inhibitors. BSAb was highly cleared by tumor (T), liver (P), and lung (L) in vivo. Conclusions: Onco-HER2 bsAb is a promising novel HER2 inhibitor with high anti-tumor activity and favorable pharmacokinetics.

Background: Previous studies have shown that 44-71% of trastuzumab (T)-treated pts develop HER2-specific immunity (Cancer Res 2007, 13: 5133; Cancer Res 2016, 76:3702; Breast Cancer Clin 2018, 20:5). M is an Fc-engineered mAb that shares similar HER2 binding and anti-HER2 activity as T. Methods: M was administered to metastatic HER2+ cancer pts who progressed on prior therapy. Results: M treatment increased affinity to the activating FcRIIα (CD16A) and lower binding to inhibitory FcγRIIB (CD32B), which may enhance the mAb’s immune function, such as antigen presentation. Conclusions: HER2+ patients who were refractory to prior therapy received M. The mAb’s active immunogenicity is enhanced by the mAb’s immune function, such as antigen presentation.
Background: In MA.31 the trastuzumab-taxane combination led to longer PFS than lapatinib-taxane in HER2+ metastatic breast cancer (MBC). In MA.31 we previously reported the prognostic/predictive utility of pretreatment serum PD-L1 (SABCS 2018, PD3-10) and serum activin A (SABCS 2016, P6-07-06) separately; here we evaluate them combined. Methods: MA.31 accrued 652 centrally and/or locally-identified HER2-positive patients, and pretreatment serum was available for 382 patients (184 in trastuzumab arm, 198 in lapatinib arm). The ELLA immunoassay platform (ProteinSimple, San Jose, CA) was used to quantitate serum PD-L1, and ELISA for activin A (R&D Systems, Minneapolis, MN). Results: In correlation analysis, pretreatment serum PD-L1 was moderately correlated with serum activin A (r = 0.21, p = 0.004). In univariate analysis for OS, the combination of higher serum PD-L1 and higher serum activin A (median cutpoints) (vs. both low) was significant for shorter OS in the trastuzumab arm (HR 6.62, p=0.0005) and in the lapatinib arm (HR 3.25, p=0.0003)(Table). In multivariate analysis for OS (17 covariates included), elevated serum activin A at PD-L1 combination remained the most significant independent predictor of survival in the trastuzumab arm (HR 12.40, p=0.0001), and in the lapatinib arm (HR 5.2, p=0.0001). Conclusions: In the CCTG MA.31 trial, elevated pretreatment serum activin A (TGF-B superfamily) and PD-L1 was associated with a shorter OS to HER2-targeted treatment. Multiple mechanisms, including immune evasion, may decrease the effectiveness of HER2-targeted agents. Elevated serum activin A and PD-L1 may identify HER2-positive MBC patients who would benefit from inhibitors of the HER2, PD-L1, and activin A pathways.

Univariate analysis of OS of serum activin A and PD-L1 combined.

<table>
<thead>
<tr>
<th>TRAS arm</th>
<th>LAPT arm</th>
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<td>Serum biomarker (ActA &amp; PD-L1)</td>
<td>HR</td>
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<td><img src="image1.png" alt="Graph" /></td>
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<td>ActA high &amp; PD-L1 low vs both low</td>
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<tr>
<td>ActA low &amp; PD-L1 high vs both low</td>
<td>3.16</td>
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* Referent cohort

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1033 Poster Session (Board #114), Sun, 8:00-11:00 AM

Real-world treatment patterns and outcomes in ER+/PR+/HER2+ metastatic breast cancer (MBC): A National Cancer Database analysis. First Author: Abby Statler, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Background: Treatment patterns and clinical outcomes are unclear for MBC patients diagnosed with estrogen receptor-positive (ER+) and/or progesterone receptor-positive (PR+) human epidermal growth factor 2 positive (HER2+) disease (i.e. triple positive). This study aimed to: 1) examine the utilization of de-escalation of systemic therapy in this subgroup of patients and future research to identify biomarkers to determine which patients can avoid chemotherapy were warranted.

Univariate analysis of OS of serum activin A and PD-L1 combined.

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* Referent cohort

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1034 Poster Session (Board #115), Sun, 8:00-11:00 AM

Clinical characteristics of patients with no evidence of disease (NED) versus residual disease (RES) to anti-HER2 therapy in metastatic breast cancer (MBC): A multi-institutional analysis. First Author: Zachary William Veitch, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Anti-HER2 therapy has improved survival in HER2+ MBC. Yet, large patient cohorts with no evidence of disease (NED) with long-term follow up are incompletely described in the literature. We evaluated the clinical characteristics of patients with HER2+ MBC and prolonged response to anti-HER2 therapy, excluding RES vs Residual disease on anti-HER2 therapy. Patients treated with chemotherapy plus trastuzumab (CT) from 2005-2013, or taxane plus trastuzumab-pertuzumab (TTP), or trastuzumab-emtansine (TDM1) from 2012-2016 for HER2+ MBC at Princess Margaret Cancer Centre in Toronto, Ontario or in Alberta, Canada were included. Duration on anti-HER2 therapy (without switch) was collected. Patients with median duration of response (MDR; months) 2x higher than phase III/III trials for each regimen (CT = 18.2; TTP = 40.4; TDM1 = 25.2) were included to select for prolonged response. Clinical features (ie: stage at diagnosis, survival, etc) and oncologist/radiologist reported best response were collected. Responses were grouped as NED (including sclerotic bone metastases) or RES. Clinical variables were evaluated by Chi-square and survival by Kaplan-Meier (log-rank) Results: 2403 patients (CT = 1830; TTP = 394; TDM1 = 179) were evaluated. After cut-off, 119 patients (5%) were included in the analysis; of these, 3770 (60%) received CT and 2464 (40%) received chemo. Of those with complete survival data, there was no difference in median OS between patients treated with chemo vs. CT; however, those who received anti-HER2 therapy had significantly better OS than those who did not (median OS 49.4 vs. 41.0 months, p < 0.0001). Median OS stratified by ET or chemo with and without anti-HER2 further supported these findings, revealing the addition of anti-HER2 therapy to chemotherapy and CT resulted in superior median OS (Table). Conclusions: This is the first study to evaluate treatment utilization and OS among real-world triple positive MBC patients treated with CT or chemo. Our results suggest the majority of patients in the United States are treated with first-line CT; furthermore, the reported OS outcomes support the consideration of CT plus anti-HER2 therapy as a first-line treatment option for ER+/PR+/HER2+ MBC. Prospective trials evaluating de-escalation of systemic therapy in this subgroup of patients and future research to identify biomarkers to determine which patients can avoid chemotherapy were warranted.
Survival at 3 years, %

| Follow-up, mos | 56.5 | 39.2 | 30.9 | 15.4 |

Follow-up, mos

HF, n (%)

plus capecitabine 1000mg/m² twice daily on days 1 to 14 of a 21-day cycle. Oral pyrotinib 160 mg, 240 mg, 320 mg, or 400 mg once daily continually.

HER2-positive metastatic breast cancer (MBC).

improved efficacy to block HER2 signaling in trastuzumab-resistant breast cancer. This phase I study evaluated the safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics, antitumor activity and predictive biomarkers of pyrotinib in combination with capecitabine in patients with HER2-positive metastatic breast cancer (MBC).

**Methods:** Patients received oral pyrotinib 160 mg, 240 mg, 320 mg, or 400 mg once daily continually targeting EGFR/HER1, HER2 and HER4, which may offer the potential for crossing and targeting EGFR/HER1, HER2 and HER4, which may offer the potential for crossing.

**Background:** Cross-signaling in the ErbB family is an important mechanism targeted by pyrotinib. Phosphotyrosine is an irreversible pan-ErbB inhibitor targeting EGFR HER1, HER2 and HER4, which may offer the potential for crossing.

**Results:** A total of 28 patients were enrolled. All 28 (100%) patients experienced at least one treatment-related adverse event (AE), which were predominantly grade 1 or 2. Grade 3 treatment-related AE occurred in 12 (42.9%) patients; anemia (14.3%) and diarrhea (10.7%) were the most common grade 3 AEs. Three (10.7%) patients discontinued capecitabine administration due to AEs. The overall response rate (ORR) was 78.6% (95% CI: 59.0% to 91.7%), and the disease control rate was 94.6% (95% CI: 81.7% to 99.9%). The median progression-free survival (PFS) was 22.1 months (95% CI: 9.0 to 26.2 months). ORR was 70.6% (12/17) in trastuzumab-prefatented patients and 90.9% (10/11) in trastuzumab-naive patients. NGS analysis of all genetic alterations of HER2 bypass signaling pathway, PIK3K/PI3K and TRP5 in baseline blood samples suggested that concomitant (two or more) genetic alterations were significantly associated with poorer PFS compared to none or one genetic alteration (median, 15.8 vs. 26.2 months, P = 0.006). **Conclusions:** Pyrotinib in combination with capecitabine are well-tolerated and demonstrate promising antitumor activity in HER2-positive MBC patients. Clinical trial information: NCT02361112.

**Background:** Little data exist for comparing cardiac safety and survival outcomes of anti-HER2 therapy with concurrent trastuzumab (T) and pertuzumab (P) or ado-trastuzumab emtansine (TDM1) in metastatic breast cancer (MBC) patients enrolled in randomized clinical trial (RCT) vs those in the real world. Furthermore, whether older women have worse outcomes is unknown. **Methods:** This was a retrospective population-based cohort of all women with MBC treated with concurrent T or TDM1 in Ontario (between 2012 and 2017), identified from New Drug Funding Program and linked to Ontario Cancer Registry and other administrative datasets. Outcomes were incident heart failure (HF), defined as hospitalization or emergency room visit for HF) and overall survival (OS). RCT data were obtained from digitizing survival curves as per established methods and compared with cohort OS data using log-rank test. Age-based comparison of outcomes was conducted for women ≥ 65 years old vs younger. **Results:** Our cohort comprised of 833 (28% > 64 years old), and 397 (28% > 64 years old) women treated with P and TDM1, respectively, of which 46 and 30 had baseline HF, respectively. 49% and 99.5% of women received T prior to P and TDM1, respectively. Incident HF following P or TDM1 initiation was low (P 26 women, TDM1 8 women; Table). HF events was not more in women ≥ 65 years old vs younger. **Conclusions:** On average, older women did not experience worse outcomes compared to younger women. Differences in survival were not statistically significant. Cross-section of data analyzed, TDM1 was associated with worse survival compared to P in women ≥ 65 years old. **Clinical trial information:** NCT02361112.

**Background:** Alpelisib (ALP) with fulvestrant (FUL) in patients (pts) with PIK3CA-mutated hormone receptor-positive (HR+)-IRMA1 (preclinical model of endocrine resistance). **Methods:** This was a phase 1b/2 trial in postmenopausal women receiving endocrine therapy (ET) who had progressed on/after an aromatase inhibitor. PFS was estimated by Kaplan-Meier method and median PFS (mPFS) presented by tx arm. A stratified Cox proportional hazards model estimated HR and 95% CI. **Results:** Of 341 pts in the PIK3CA mutant cohort, 39 (11%) were ETS, 302 (90%) were ETR. mPFS in the ALP vs PBO arms was 22.1 vs 19.1 mo (HR 0.87; 95% CI, 0.35-2.17) for ETS pts and 9.4 vs 4.2 mo (HR 0.64; 95% CI, 0.48-0.84) for ETR pts. For EFS pts, mPFS for 1L (n=138) was 9.0 vs 4.7 mo (HR 0.69; 95% CI, 0.46-1.05) and for 2L (n=161) was 10.9 vs 3.7 mo (HR 0.61; 95% CI, 0.42-0.89). **Conclusions:** In SOLAR-1, mPFS was significantly improved with ALP + FUL vs PBO + FUL across ETR pts in 1L and 2L. Representation of ETS pts was low in SOLAR-1, which included more ETR pts. Analysis of the PI3K mutation based on on using liquid biopsy tests monitoring the metastatic prognosis and endocrine resistance.
Background: Approximately 40% of pts with HR+, HER2-ABC have tumors with a PIK3CA mutation, resulting in phosphatidylinositol 3-kinase (PI3K) pathway hyperactivation. Use of the oral α-specific PI3K inhibitor alpelisib (ALP) + fulvestrant (FUL) in SOLAR-1 significantly improved vs placebo (PBO) + FUL both progression-free survival (PFS) (median 11.0 vs 5.7 mo, respectively; HR 0.65; 95% CI, 0.50-0.85; P< 0.001) and objective response rate (ORR) (measurable disease: 36% vs 16%; P< 0.001) in the PIK3CA mutant cohort. In addition to primary efficacy and safety measures, PROs offer valuable insight into therapeutic benefit by measuring whether quality of life (QoL) is maintained during treatment. Methods: Postmenopausal women or men with HR+, HER2-ABC whose disease progressed on/after an aromatase inhibitor were randomized to receive ALP 300 mg once daily or PBO, + FUL 500 mg every 28 days + Cycle 1, Day 15. Secondary objectives included PROs using the EORTC QLQ-C30, EQ-5D-5L, and BPI-SF scales. PROs were collected at screening, every 8 wk for 18 mo then every 12 wk thereafter, at end of treatment, and during follow-up for efficacy. Adjusted effects models were used to assess score changes from baseline. Time to 10% deterioration (TTD), an established measure of clinically meaningful change in QoL, was compared between the treatment arms’ survival distribution using Kaplan-Meier methodology. Results: At baseline, 93% of pts in the PIK3CA mutant cohort (n = 341) completed questionnaires; 75% completed them at baseline and 75% at post-baseline. Adjusted mean changes from baseline in EORTC global health/QoL status/QoL scores were < 10% for all visits through wk 96 for both arms, with a mean difference between arms of < 3% for all visits. There was no difference between arms in TTD in global health/QoL status (HR 1.03; 95% CI, 0.72-1.45). Analysis of TTD in EORTC physical (P < 0.001), role (P < 0.05), and emotional (P = 0.05) functional scores revealed no meaningful differences between arms. Conclusions: In addition to significantly improving PFS and ORR, overall QoL was maintained in pts treated with ALP + FUL. Clinical trial information: NCT02437318.

Background: Approximately 40% of pts with HR+, HER2-ABC have tumors with a PIK3CA mutation, resulting in phosphatidylinositol 3-kinase (PI3K) pathway hyperactivation. Use of the oral α-specific PI3K inhibitor alpelisib (ALP) + fulvestrant (FUL) in SOLAR-1 significantly improved vs placebo (PBO) + FUL both progression-free survival (PFS) (median 11.0 vs 5.7 mo, respectively; HR 0.65; 95% CI, 0.50-0.85; P< 0.001) and objective response rate (ORR) (measurable disease: 36% vs 16%; P< 0.001) in the PIK3CA mutant cohort. In addition to primary efficacy and safety measures, PROs offer valuable insight into therapeutic benefit by measuring whether quality of life (QoL) is maintained during treatment. Methods: Postmenopausal women or men with HR+, HER2-ABC whose disease progressed on/after an aromatase inhibitor were randomized to receive ALP 300 mg once daily or PBO, + FUL 500 mg every 28 days + Cycle 1, Day 15. Secondary objectives included PROs using the EORTC QLQ-C30, EQ-5D-5L, and BPI-SF scales. PROs were collected at screening, every 8 wk for 18 mo then every 12 wk thereafter, at end of treatment, and during follow-up for efficacy. Adjusted effects models were used to assess score changes from baseline. Time to 10% deterioration (TTD), an established measure of clinically meaningful change in QoL, was compared between the treatment arms’ survival distribution using Kaplan-Meier methodology. Results: At baseline, 93% of pts in the PIK3CA mutant cohort (n = 341) completed questionnaires; 75% completed them at baseline and 75% at post-baseline. Adjusted mean changes from baseline in EORTC global health/QoL status/QoL scores were < 10% for all visits through wk 96 for both arms, with a mean difference between arms of < 3% for all visits. There was no difference between arms in TTD in global health/QoL status (HR 1.03; 95% CI, 0.72-1.45). Analysis of TTD in EORTC physical (P < 0.001), role (P < 0.05), and emotional (P = 0.05) functional scores revealed no meaningful differences between arms. Conclusions: In addition to significantly improving PFS and ORR, overall QoL was maintained in pts treated with ALP + FUL. Clinical trial information: NCT02437318.

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1043  Poster Session (Board #124), Sun, 8:00 AM-11:00 AM
A GINECO randomized phase II assessing addition of an aromatase inhibitor to oral vinorelbine in pretreated metastatic breast cancer patients. First Author: Pierre Haustel, GINECO/Centre Lion Bérard, Lyon, France.

**Background:** For ER+/HER2- metastatic breast cancer (mBC), efficacy of endocrine therapy + chemotherapy combination remain an open question. We hypothesized that continuing ER targeted therapy after progression in combination with chemotherapy may improve disease control. The objective of the CHEOPS trial was to assess the benefit of adding aromatase inhibitor (AI) to metronomic chemotherapy,oral vinorelbine, 50mg/3 time a week (OV) for AI-pre-treated, ER+/HER2- mBC patients. **Methods:** Eligible patients had to have progressed on endocrine therapy and one or two lines of chemotherapy. They were randomized between vinorelbine (OV) and vinorelbine + AI (OV+AI). Primary end point was progression-free survival (PFS). To show an increase of median PFS (from 3.5 to 5.5 month, HR 0.636), with alpha = 5% and power = 80%, 130 evaluable patients were needed. **Results:** 121 patients were Included (OV = 61; OV+AI = 60). Median age was 68: (range: 49-87), Median time from metastatic diagnosis was 3.2 years (range 0-16.9). 109 patients (90%) had visceral metastases. They all had previously received an AI and had been treated with one line (N = 66, 54.5%), or 2 lines (N = 59, 45.5%) of chemotherapy. Median PFS was increased 2.3 months with OV to 3.7 months with OV+AI, but this difference was not significant (HR 0.73 (95% CI 0.50-1.06), log-rank test: P = 0.09) 81 patients (67%) had at least one adverse event (AE) of grade ≥ 3 (40% (66%) for OV vs 41% (68%) for OV+AI). The most common grade ≥ 3 AE were: GT gynecologic (17%), acute arterial hypertension and lymphopenia (17%). The occurrence of 3 toxic deaths (OV = 1; OV+AI = 2) secondary to febrile apleasia motivated the early cessation of this clinical trial. 9 patients (5 OV (10%) and 4 OV+AI (8%) presented an incomplete objective or partial response. **Conclusions:** The addition of AI to OV over OV alone in AI resistant mBC was associated with a non-significant improvement of PFS, but both PFS are lower than expected. Metronomic OV schedule, at 50 mg three times a week, requires close biological monitoring. The question of hormonal treatment and chemotherapy combination remains open. Clinical trial information: EudraCT Number: 2015-000431-09.

1045  Poster Session (Board #126), Sun, 8:00 AM-11:00 AM
A phase Ib/II trial of lenatinib (len) and letrozole (let) incorporating pharmacodynamics studies in postmenopausal women with hormone receptor positive (HR+) locally advanced/metastatic breast cancer (LABC/mBC). First Author: Joline Si JIng Lim, National University Cancer Institute, Singapore, Singapore.

**Background:** Endocrine blockade (EB) is standard of care for patients (pts) with HR+ LABCMBC. RET over-expression (RET+) occurs in up to 75% of HR+ breast cancers and is a postulated mechanism of endocrine resistance. Preclinical studies show cross talk between RET and estrogen receptor, and at least additive treatment (Tx) effect of Len+EB. **Methods:** We performed a phase Ib trial (3+3 dose escalation) to study safety, tolerability, pharmacodynamics and efficacy of Len+Let. Both drugs were given as continuous daily dosing with 2 weeks (wks) of Len alone, followed by len+let for 12 wks then surgery (LABC) or disease progression (PD) (MBC). Serial tumor biopsies (n = 15) were done at baseline, after Len alone, 4 wks post Len+Let, and at surgery (LABC) upon PD (MBC). **Results:** 16 pts were treated (4 LABC, 12 MBC); Among MBC pts, median lines of prior Tx was 3 (range 0-10); 84.6%, 66.7%, and 58.3% had prior EB, EB+CDK4/6 inhibitor (i), and chemotheraphy (CT) respectively. At dose level (DL) 1, 2/4 pts had dose-limiting toxicities (DLT). There was no DLT at DL-1, but 6/6 pts needed dose reductions (DR), with 4/6 DR within 5 wks of Len+Let (G3 hypertension; HTN), 1 G3 wound pain), deeming DL-1 intolerable. At DL-2, 3/6 pts had DLT; this was declared recommended phase 2 dose level (DL2). Most frequent toxicities (TOX), were HTN (6/16), proteinuria (2/16), hypertension (PD) (16) and palmar-plantar erythrodysesthesia (PPE) (2/16), with no G4/5 tox. Len+Let was active with 93.8% overall disease control rate (DCR) (50% partial response (PR), 43.8% stable disease (SD)). Among MBC pts (8/12 had prior EB+CDK4/6), DR ≥ 12 wks was 91.7%; 1 pt had sustained PR for 48 wks and 1 ongoing PR at 40 wks. 9/16 pts had RET+ tumors on immunohistochemistry at baseline, and 66.7% showed down-regulation with Tx (RECIST 4. PR, 2 SD). **Conclusions:** Len+Let showed significant anti-tumor activity, even in pts who failed prior CT or EB+CDK4/6. RP2D of 14mg Len and 2.5mg Let is tolerated with efficacy; dose expansion is currently underway. Clinical trial information: NCT02926118.

1044  Poster Session (Board #125), Sun, 8:00 AM-11:00 AM
Efficacy and safety of talazoparib (TALA) or placebo (PCT) in United States patients (pts) with HER2- germline BRCA1/2-mutated (gBRCAm) locally advanced/metastatic breast cancer (LABC/mBC) in the EMBRACA study. First Author: Sami Diab, University of Colorado Cancer Center, Aurora, CO.

**Background:** TALA is a poly(ADP-ribose) polymerase (PARP) inhibitor approved in the US for HER2- gBRCAm LABC/mBC. Approval was based on results from the Phase 3 EMBRACA trial comparing efficacy/safety of TALA (1 mg/d) to PCT (capcitabine, eribulin, gemcitabine, vinorelbine) in HER2- gBRCAm LABC/mBC pts. This analysis describes outcomes of US pts included in the pivotal study. **Methods:** Clinical findings from US pts enroled in EMBRACA were analyzed. Pt characteristics, progression-free survival (PFS), objective response rate (ORR), clinical benefit rate (CBR), and safety/adverse events (AE) were among the parameters assessed. **Results:** Of 431 randomized pts, 156 pts (36%) were from the US (TALA: 99; PCT: 57). Pt characteristics were balanced, although a higher percentage in the TALA arm had more poor prognostic features (eg, triple-negative breast cancer, disease-free interval < 12 mo, and more disease sites). TALA improved PFS, ORR, CBR, and duration of response (DOR) vs PCT (Table). 22% of pts in the TALA arm had a continued objective response at month 12 vs 0 pts in the PCT arm. The most common AEs in the TALA arm included anemia, neutropenia, thrombocytopenia, fatigue, nausea, alopecia, and headache; hematologic grade 3/4 AEs occurred more often than nonhematologic AEs. **Conclusions:** In US pts with HER2- gBRCAm LABC/mBC, TALA demonstrated significant improvements in outcomes vs PCT with a manageable safety profile. Clinical trial information: NCT01945775.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
A phase II study of pembrolizumab in combination with palliative radiotherapy (RT) for hormone receptor-positive (HR+) metastatic breast cancer (MBC).  
First Author: Romualdo Barroso-Sousa, Hospital Sirio-Libanês, Brazil  
Background: RT is frequently used for palliation in MBC. In animal models its use has been reported to induce distant (abscopal) tumor responses when combined with immune checkpoint inhibitors. Here, we report the safety and efficacy of palliative RT plus pembrolizumab in a phase II single-arm study in patients (pts) with HR+ HER2- MBC.  
Methods: Eligible pts had HR+/HER2- MBC, ECOG PS ≤2, indication for palliative RT, and ≤1 measurable lesion outside of the RT field; there was no limit on prior lines of therapy. A total RT dose of 20 Gray was delivered over 5 daily fractions. Pembrolizumab was given at 200 mg IV 2-7 days before day 1 of RT, then every 3 weeks until disease progression. The primary endpoint was objective response rate (ORR) outside the field of radiation by RECIST v1.1. Using the Simon’s “optimal” method, if ≤1/8 pts responded during the first stage, 19 more would be enrolled. If ≤3/27 responded, the null hypothesis (ORR≤3%) would be rejected in favor of a 20% ORR. Predefined secondary endpoints included progression free survival (PFS) and toxicity. Analyses associating PD-L1 expression, tumor-infiltrating lymphocytes (TIL), and neutrophil/lymphocyte ratio (NLR) with outcomes were exploratory.  
Results: Eighty-three pts were enrolled into the first stage of the trial; no objective responses were seen, and the study was closed to further accrual. The median age was 59y (37-68y), 6 pts: 4 had ECOG PS 0, 2 had PS 1. The median number of prior cytotoxic therapies for MBC was 2 (range 0 to 8). Of 343 pts treated, 294 had CTC data and were included in this analysis. Of 293 PRAGNANT patients, 576 were HER2- and received first-line ctx. Of those 529 patients with gBRCA1/2 mutations and follow up information could be analyzed, 24 patients (4.5%) had a gBRCA1 (11 BRCA1, 13 BRCA2). Mutation rate in HR positive patients was 3.9% (17/432) and 7.2% (79/11) in HR negative patients. Most patients received ctc+ cxt either as the first or second-line chemotherapy in the metastatic setting. The ORR of pembrolizumab combined with RT was well-tolerated, and no unexpected adverse events were observed; however, clinical benefit of the combination was not demonstrated in this heavily pretreated HR+ population. Clinical trial information: NCT03051672.

1049  
Poster Session (Board #130), Sun, 8:00 AM-11:00 AM  
Clinical significance of circulating tumor cells (CTCs) in hormone receptor positive (HR+) metastatic breast cancer (MBC): Patients with letrozole+Bev (L+Bev) versus letrozole (L) alone.  
First Author: Mark Jesus Mendoza Magbanua, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco  
Background: CALGB 40503 randomized HR+ MBC postmenopausal pts to L+Bev or L alone as first-line therapy. Adding Bev to L prolonged progression-free survival (PFS) and overall survival (OS) in this overall population. Dickler IC-2012 performed a retrospective study to assess prognostic and predictive value of CTCs in this population.  
Methods: Blood was collected prior to initiation of treatment. CTCs were enumerated using US FDA-cleared CellSearch assay samples with ≥5 CTCs per 7.5 mls of blood were considered positive. correlates with CTC counts. CTCs correlated with PFS assessed using Cox regression analysis. Median follow-up was 39 months (mo). Results: Of 343 pts treated, 294 had CTC data and were included in this analysis. Original study results that showed improved PFS (HR = 0.75; 95%CI 0.59-0.96) but not OS (HR = 0.87; 95% CI: 0.65-1.18) in pts receiving L+Bev compared to L were recapitulated in this subset. In multivariable analysis, CTC+ pts (31%) had significantly reduced PFS (HR = 1.49; 95% CI: 1.12-1.97) and OS (HR = 2.08; 95% CI: 1.49-2.93) compared to CTC- pts. Moreover, CTC+ pts who did not receive Bev had worse PFS (HR = 2.31; 95% CI: 1.54-3.47) and OS (HR = 2.64; 95% CI: 1.59-4.40) (Table). CTC+ pts who received Bev had numerically lower median PFS (18.0 vs. 7.0 mo) and OS (33.6 vs. 27.1 mo) compared to CTC- pts with no Bev; however, tests for interaction between CTC and Bev were not statistically significant for PFS (p=0.70) or OS (p=0.84). Conclusions: CTCs were highly prognostic in this study involving addition of Bev to first-line L in postmenopausal HR+ MBC. Further research to determine the potential predictive value of CTCs in the setting of both metastatic disease and early breast cancer is warranted. Support: U10CA180821, U10CA180882, Genentech; https://acknowledgments.alliancefound.org; NCT00601900. Survival in HR+ MBC pts receiving L+Bev stratified by CTC status. Clinical trial information: NCT00601900.

<table>
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<tr>
<th>CTC Status</th>
<th>Events</th>
<th>Median survival in mo (95% CI)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>Adjusted Likelihood-Ratio p-value</th>
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<tr>
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<td>108</td>
<td>74 (15.0-23.5)</td>
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<tr>
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1050  
Poster Session (Board #131), Sun, 8:00 AM-11:00 AM  
Exploratory analysis of the effect of taselisib on downstream pathway mediators and correlation with tumor response in ER-positive/HER2-negative early-stage breast cancer from the LORLEI trial.  
First Author: Paolo Nuñociforo, Molecular Oncology Group, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain  
Background: Taselisib (T) is an oral, potent, selective inhibitor of Class I PI3-kinase with enhanced activity against PIK3CA mutant cancer cells. Results from the LORLEI trial have demonstrated a significant improvement in ORR (objective response rate) compared to placebo (P) in patients with ER positive/HER2 negative metastatic breast cancer (mBC). In mBC patients the TNT-study showed bioactivity of taselisib as indicated by downstream pathway suppression. Translational research aiming to integrate these results with additional exploratory biomarkers data is currently ongoing. Clinical trial information: NCT02273973.
1051 Poster Session (Board #132), Sun, 8:00 AM-11:00 AM
PIPA: A phase Ib study of β-isofumarap reprogram phosphatidylinositol 3-kinase (PI3K) inhibitor bataisib (T) plus palbociclib (P) and fulvestrant (FUL) in PIK3CA-mutant (mt) ER-positive and negative (PIK3CA–mt BC) models. Efficacy and safety. Preliminary data of P + T in PIK3CA-mt BC patients (pts). Methods: The primary objective was to assess the confirmed objective response rate (ORR) of the P + T + FUL triplet in pts with measurable PIK3CA-mt ER+ HER2- advanced BC, with up to two prior lines of chemotherapy for advanced disease. PIK3CA mutation was assessed in tissue or plasma DNA analysis. Exploratory objectives included assessment of efficacy of P + T + FUL in a cohort of pts with PIK3CA-mt advanced ER+ BC. Safety is reported overall for 44 patients including an additional cohort of 7 PIK3CA-uncommon ER– BC pts treated with P + T + Iletrozole (LET). For the P + T + FUL triplet a Simon mimmax design was used, with 6 responses in 25 patients required to declare efficacy. Results: We recruited 24 assessable patients with PIK3CA-mt ER+ HER2- advanced BC, median age 57 (42-74), median 3 (1-9) prior therapy lines for advance disease, with 24 (100%) receiving prior endocrine therapy and 23 (96%) prior aromatase inhibitor. ORR was 33% (8/24, 95% CI 16-55%), with median progression-free survival (PFS) 12.4 m (95% CI 6.0-19.9). Three (7%) of 39 assessable PIK3CA-mt ER- pts (8 HER2-2, 3 HER2+) receiving P + T, ORR was 0% (0/11), clinical benefit rate (CBR) 27% (3/11) and median PFS 4.3m (95% CI 1.8-6.1). Most common AEIs across all cohorts were neutropenia (80%), fatigue (50%), mucositis (50%) and thrombocytopenia (30%). Median cycles of P + T were 6 (3-11). Rare AEIs included 3/4 AEs were neutropenia (57%) and rash (11%). Translational research is ongoing. Conclusions: The triplet of P + T + FUL has promising efficacy in pre-treated PIK3CA-mt ER+ advanced BC. A subset of patients with PIK3CA-mt ER- advanced BC had clinical benefit from P + T. The combination of P + T + FUL/LET was well tolerated with anticipated AEs. Clinical trial information: NCT03898492.

1052 Poster Session (Board #133), Sun, 8:00 AM-11:00 AM
Molecular characterization and monitoring of patient ctDNA in phase I study of H3B-6545 in ER+ MBC. First Author: Vicki Rimkunas, H3 Biomedicine, Cambridge, MA
Background: Because of lack of effective treatment in endocrine resistant metastatic breast cancer (MBC), we developed H3B-6545, a novel selective ERα covalent antagonist, capable of irreversibly inactivating both wild-type and mutant ERα. The aims of this study are to 1) characterize hot spot mutation profiles in heavily pretreated MBC and correlate ESR1, PIK3CA and AKT1 mutations in plasma vs tumor tissue 2) determine if mutations in ESR1 or PIK3CA predict response to H3B-6545 and 3) evaluate if longitudinal tracking of ctDNA correlates with response to H3B-6545. Methods: Fresh plasma samples were collected at baseline (predose), cycle 1 day 15 (CD15), CD21, CD31 and every 8 weeks thereafter with a final sample collection at disease progression. At baseline, BEAMing digital PCR was used to evaluate hotspot mutations in ESR1, PIK3CA and AKT1. Patient specific ctDNA mutations were subsequently monitored by ddPCR. Baseline tumor biopsies were subjected to a targeted Next Generation Sequencing (NGS) panel to identify hotspot mutations. Results: In 77% of patients (30/39), mutations were detected at baseline by the BEAMing assay and of those, 21/39, 16/39 and 14/39 had mutations in ESR1, PIK3CA and AKT1, respectively. 20% (9/39) of patients exhibited co-mutations in ESR1 and PIK3CA. In 60% (9/15) of patients, DNA mutations identified by the plasma BEAMing assay were also detected in the tumor biopsy whereas; DNA mutations found in tissue were also detected in plasma in 86% (12/14) of cases. Serial ctDNA monitoring revealed that in patients with confirmed partial responses (3/3), ctDNA levels were undetectable by C2D1. In contrast, ctDNA levels increased from baseline in 3/4 patients with progressive disease. Exploration of ctDNA ratios (day 15/baseline and day 30/baseline) and correlations of PIK3CA and ESR1 mutations with response to H3B-6545 will be presented. Conclusions: ctDNA is a robust sample type for monitoring ESR1, PIK3CA and AKT1 mutations in MBC, overcoming the challenges of obtaining biopsies in the metastatic setting. In addition, ctDNA dynamics may be a useful tool to monitor the efficacy of H3B-6545. Clinical trial information: NCT03250676.

1053 Poster Session (Board #134), Sun, 8:00 AM-11:00 AM
A large retrospective analysis of CDK 4/6 inhibitor retreatment in ER+ metastatic breast cancer (MBC). First Author: Carlos-Henrique dos Anjos, Memorial Sloan Kettering Cancer Center, New York, NY
Background: Sequential retreatment with endocrine therapy (ET) has been the clinical paradigm for ER+ MBC due to persistent dependence on hormone signaling. Recently CDK4/6i + ET have improved PFS and are routinely utilized in the first-second-line setting. Whether this paradigm of sequential retreatment holds for CDK 4/6i is unknown. To evaluate the potential benefit of CDK4/6i re-treatment we conducted this retrospective analysis. Methods: We identified ER+/HER2- MBC pts treated with ≥ 2 lines of CDK4/6i at our institution between 2015-2018. We categorized pts based on reason for CDK4/6i re-treatment we conducted this retrospective analysis. Results: In 18FES-PET scans, signal inhibition and decreased appetite (31.3%). There were no DLTs at any of the five dose levels. In 7 patients with confirmed partial responses (3/3), ctDNA levels were undetectable by C2D1. In contrast, ctDNA levels increased from baseline in 3/4 patients with progressive disease. Exploration of ctDNA ratios (day 15 baseline and day 30/baseline) and correlations of PIK3CA and ESR1 mutations with response to H3B-6545 will be presented. Conclusions: ctDNA is a robust sample type for monitoring ESR1, PIK3CA and AKT1 mutations in MBC, overcoming the challenges of obtaining biopsies in the metastatic setting. In addition, ctDNA dynamics may be a useful tool to monitor the efficacy of H3B-6545. Clinical trial information: NCT03250676.

1054 Poster Session (Board #135), Sun, 8:00 AM-11:00 AM
Dose-escalation study of SAR439859, an oral selective estrogen receptor (ER) degrader (SERD), in postmenopausal women with ER+/HER2- metastatic breast cancer (mBC). First Author: Aditya Bardia, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA
Background: SERDs result in ER competitive antagonism and degradation and can block signaling in ER-dependent tumors resistant to other endocrine therapies. This study investigates SAR439859, a potent oral SERD, +/- palbociclib in ER+/HER2- mBC. Here are preliminary results, as of 28 Nov 2018, for single-agent SAR439859 dose escalation. Methods: Part A of this Phase I/2 study (NCT03284957; TDEL4856) assessed SAR439859 dose escalation (dose range: 20-600 mg once daily [QD]; 3 + 3 design) in postmenopausal women with ER+/HER2- mBC treated for ≥ 6 months with prior endocrine therapy and ≤ 3 chemotherapies in the advanced setting. Endpoints: dose-limiting toxicities (DLTs); maximum tolerated dose (MTD); safety; pharmacokinetics (PK); tumor response (RECIST 1.1); pharmacodynamic (PD) inhibition of ER occupancy (18F-FES-PET scan). Results: Patients (n = 16) had a median age of 59.5 years (range 40-79), ECOG performance status of 0 (62.5%) or 1 (37.5%) and a median of three prior anticancer therapies (range 1–8) in the advanced setting (endocrine therapy n = 16; chemotherapy/targeted therapy n = 13). All pts had ≥ 1 treatment emergent adverse event (mostly grade 1–2); most frequent were asthenia/fatigue (43.8%), hot flushes (37.5%), nausea (37.5%), diarrhea (31.3%), constipation (31.3%), and decreased appetite (31.3%). There were no DLTs at any of the five dose levels (maximum administered dose: 600 mg QD): MTD was not reached. In 18F-FES-PET scans, signal inhibition > 87% occurred with plasma concentrations > 100 ng/mL. There was a dose proportional increase of exposure up to 400 mg after repeated QD doses. Average Ctrough was reached after repeated 400 mg QD allowing 90% of 18F-FES-PET signal inhibition. One pt (6.3%) had confirmed partial response (150 mg QD); 85% (50%) had stable disease (SD) including three (18.8%) long-term SD (> 24 weeks); seven (43.8%) had progressive disease. Conclusions: SAR439859 had a favorable safety profile, high ER occupancy and encouraging antitumor activity (to be confirmed in dose expansion) in pretreated pts with ER+/HER2- mBC. No DLTs were seen in continuation doses based on safety, PD and PK data. Funding: Sanofi. Clinical trial information: NCT03284957.
Background: The rarity of BC in men limits the feasibility of randomized clinical studies in this population. Treatment guidelines recommend that men with BC be treated similarly to postmenopausal women. PAL, a cyclin-dependent kinase 4/6 inhibitor, is used in men with metastatic BC (mBC) in real-world clinical practice, presenting an opportunity to utilize real-world evidence to enable healthcare providers to assess novel agents in this space.

Methods: Two parallel approaches were taken. In the first approach, pharmacy and medical claims data from IQVIA Inc were retrospectively analyzed to describe the treatment patterns and duration of PAL + ET (aromatase inhibitor or fulvestrant) compared to ET in men with mBC. The second approach was a retrospective analysis of data derived from electronic health records in the Flatiron Health database to understand real-world clinical response to PAL + ET vs ET alone. Median duration of treatment (mDOT) was estimated by the Kaplan-Meier method. Results: Between Feb 2015 and Apr 2017, 12.9% (147/1139 [IQVIA dataset]) of men receiving treatment for mBC were prescribed PAL + ET for any line of therapy. The mDOT in the first-line setting was numerically longer in the PAL cohort (n=37) compared with the non-PAL cohort (n=214; 8.5 vs 4.3 mo, respectively). In particular, mDOT in the first-line setting was longer with PAL + letrozole (LET; n=26) than with LET alone (n=63; 9.4 vs 3.0 mo, respectively). In the Flatiron Health dataset between Feb 2015 and July 2017, the real-world maximum response rate in the PAL + ET cohort across all lines of therapy in the first setting (n=12) was 33.3% (2 complete responses [CR], 2 partial responses [PR]) vs 12.5% (0 CR, 1 PR) for the ET alone cohort (n=8). Conclusions: The real-world data sources used in this study support that men with mBC derive clinical benefit from the addition of PAL to ET. Given the challenges of conducting randomized clinical trials in men with mBC, real-world evidence data appear to be useful to delineate the benefit of such therapies in this setting. Funding: Pfizer.

Background: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) are widely used for pts with HR+/HER2- MBC. The MONARCH-1 trial of abemaciclib and fulvestrant for pts with hormone receptor-positive (HR+)/HER2- metastatic breast cancer (MBC) in February 2017 revealed RB1 and FGFR1 alterations in pts with PD on abemaciclib. Additionally, the median progression-free survival (PFS) of 6.0 months, leading to approval as monotherapy in a CDK4/6i-naive population. The MONARCH-1 trial of abemaciclib in women with HR+/HER2- MBC demonstrated improved PFS compared with placebo (PAL) + exemestane (EXE). The MONARCH-2 trial compared EVE + EXE to PAL + EXE in pts with hormone receptor-positive (HR+)/HER2- MBC. First Author: Seth Andrew Wander, Massachusetts General Hospital Cancer Center, Boston, MA

Methods: Two parallel approaches were taken. In the first approach, pharmacy and medical claims data from IQVIA Inc were retrospectively analyzed to describe the treatment patterns and duration of PAL + ET (aromatase inhibitor or fulvestrant) compared to ET in men with mBC. The second approach was a retrospective analysis of data derived from electronic health records in the Flatiron Health database to understand real-world clinical response to PAL + ET vs ET alone. Median duration of treatment (mDOT) was estimated by the Kaplan-Meier method. Results: Between Feb 2015 and Apr 2017, 12.9% (147/1139 [IQVIA dataset]) of men receiving treatment for mBC were prescribed PAL + ET for any line of therapy. The mDOT in the first-line setting was numerically longer in the PAL cohort (n=37) compared with the non-PAL cohort (n=214; 8.5 vs 4.3 mo, respectively). In particular, mDOT in the first-line setting was longer with PAL + letrozole (LET; n=26) than with LET alone (n=63; 9.4 vs 3.0 mo, respectively). In the Flatiron Health dataset between Feb 2015 and July 2017, the real-world maximum response rate in the PAL + ET cohort across all lines of therapy in the first setting (n=12) was 33.3% (2 complete responses [CR], 2 partial responses [PR]) vs 12.5% (0 CR, 1 PR) for the ET alone cohort (n=8). Conclusions: The real-world data sources used in this study support that men with mBC derive clinical benefit from the addition of PAL to ET. Given the challenges of conducting randomized clinical trials in men with mBC, real-world evidence data appear to be useful to delineate the benefit of such therapies in this setting. Funding: Pfizer.

Background: Osteosarcoma is an aggressive bone tumor that affects primarily teenagers and young adults. Aggressive osteosarcoma is mainly treated with surgery, followed by chemotherapy, which includes cisplatin, doxorubicin, and ifosfamide. However, cisplatin is associated with significant toxicity, and doxorubicin may result in neurotoxicity. Therefore, the development of less toxic and more effective therapies for treatment of aggressive osteosarcoma is needed. A previous phase II study showed a promising activity of the HDAC inhibitor belinostat (BO) when combined with doxorubicin and ifosfamide in advanced osteosarcoma patients. We sought to explore the efficacy of the combination of BO and ifosfamide in a phase II study in patients with aggressive osteosarcoma.

Methods: This was a phase II single-arm study of the combination of BO + ifosfamide + doxorubicin (BO-IF-AD) in patients with aggressive osteosarcoma resistant to standard treatment. The primary endpoint was the objective response rate (ORR) in patients with chemo-refractory osteosarcoma after at least 3 cycles of treatment. The secondary endpoints included disease control rate (DCR), duration of response (DOR), overall survival (OS), and safety profile.

Results: From February 2018 to December 2019, 13 patients were enrolled. The median age was 17 years (range: 11-24). The median Karnofsky performance status score was 90%. All patients had received at least one prior chemotherapy regimen. The most common prior chemotherapy regimens included cisplatin (85%), doxorubicin (85%), and ifosfamide (85%). The median number of prior regimens was 2 (range: 1-6). The median duration of prior chemotherapy regimens was 4 months (range: 1-24). The proportion of patients with a clinical benefit was 77% (10/13), with 4 complete responses and 6 partial responses. The median duration of response was 8.0 months (range: 2.0-22.0). The median overall survival was 17.5 months (range: 6.0-44.0). The median time to progression was 8.0 months (range: 2.0-20.0). The most common treatment-related adverse events were hematological (anemia, neutropenia, thrombocytopenia) and gastrointestinal (nausea, vomiting, diarrhea). One patient developed grade 4 neutropenia and febrile neutropenia, requiring hospitalization. No treatment-related deaths were reported.

Conclusions: The combination of BO + IF-AD demonstrates promising activity in patients with chemo-refractory osteosarcoma. The median duration of response, overall survival, and disease control rate were longer than expected for patients with aggressive osteosarcoma who failed to respond to standard therapy. Further studies are needed to confirm these results and to explore the role of BO-IF-AD in the upfront setting.
Phase I dose escalation of H3B-6545, a first-in-class highly Selective ER Covalent Antagonist (SERCA), in women with ER-positive, HER2-negative breast cancer (HR+ BC). First Author: Enka Pakhomov, Fitzgerald Oncology, PLLC and Sarah Cannon Research Institute, Nashville, TN

Background: H3B-6545 inactivates both wild-type and mutant ERα by targeting cysteine 530 and enforcing a unique antagonist conformation. Methods: Women with locally advanced or metastatic HR+ BC are treated (tx) with H3B-6545 administered once daily orally over a 28 day cycle after progression on at least one hormonal therapy and at least one additional therapy regimen. Dose escalation uses a 3+3 design with dose levels for each cohort to backfill previously cleared doses and allows for intrapatient dose escalation. This phase 1 explores the safety, pharmacokinetics and pharmacodynamics of H3B-6545 in women with HR+ BC to identify the recommended Phase 2 dose. Results: As of 10-Dec-2018, 32 pts have been tx with H3B-6545 at doses of 100 to 450 mg/day; 97% had prior tx with a CDK4/6 inhibitor and 56% had received >=3 lines of prior anti-cancer therapy. No dose-limiting toxicities and only one Grade 3 treatment related adverse event (TRAE) have been observed (lymphocyte count decrease). The most common (>10%) TRAEs include asymptomatic sinus bradycardia, diaphoresis, nausea, fatigue, anemia, decreased appetite, and weight loss. H3B-6545 was rapidly and extensively absorbed with a tmax of 2-4 h. Plasma concentration increased with dose from 100 to 450 mg, and was similar on C1D1 and C1D15. Consistent with the H3B-6545 mechanism of action and preclinical data, H3B-6545 inhibits ER target gene expression and shows a 50% decrease in Ki67 levels across all treatment levels. Therapeutic drug monitoring of H3B-6545 is recommended with early signs of single-agent anti-tumor activity in a post CDK4/6 setting. Conclusions: H3B-6545 has demonstrated single agent activity in HR+ HER2- breast cancer, irrespective of their menopausal status. The primary objectives include: progression free survival (PFS), overall survival (OS), safety and changes in quality of life. We describe the baseline characteristics, safety data and the clinical benefit rate (CBR) at 24 weeks, of patients (pts) with at least 24 weeks of therapy. Analysis was 12 months after the last patient was enrolled in the pretreated and metastatic setting.

Association of drug-related polymorphisms with palbociclib-related neutropenia: Pharmacogenetic analysis of PALOMA-2A-3 (P2A3). First Author: Hirojo Iwata, Aichi Cancer Center Hospital, Nagoya, Japan

Background: The most common PAL treatment related adverse event is neutropenia. ABCB1 and ERCC1 variants are associated with increased chemotherapy drug exposure and CYP3A7*1C may be associated with reduced exposure. Pharmacogenetic analyses of these variants in patients (pts) from P2A3 may reveal associations between single nucleotide polymorphisms (SNPs) and early occurrence of grade 3/4 (G3/4) neutropenia. Methods: ABCB1 (rs1045642, rs1128503, ERCC1/rs3212986, rs11615), and CYP3A7*1C (rs45446698) variants were analyzed in germline DNA from pts with HR+/HER2- advanced breast cancer from P2 (n=584) and P3 (n=442) by TaqMan assay. Association between variants and incidence of G3/4 low absolute neutrophil count (ANC) at Cycle 1 Day 15 (C1D15) was assessed with the exact Cochran-Armitage trend test. Odds ratios (OR) and 95% confidence intervals (CI) were estimated by logistic regression. Results: In total, 652 PAL-treated pts had SNP, race, and C1D15 ANC data. Minor allele frequencies (MAF), incidence rates, and relative risk of G3/4 C1D15 ANC for ABCB1 and ERCC1 variants are given in the Table. CYP3A7*1C was only found in non-Asians (MAF 6%). Conclusions: This is the first comprehensive assessment of pharmacogenetic data from P2A3. ABCB1 and ERCC1 SNP allele frequencies differ between Asians and non-Asians. Despite combining P2/P3 data, we lacked power to detect moderate associations; further investigation of these SNPs with G3/4 C1D15 ANC is warranted. Pfizer clinical trial information: NCT01740427, NCT01942135.

Association of drug-related polymorphisms with palbociclib-related neutropenia: Pharmacogenetic analysis of PALOMA-2A-3 (P2A3). First Author: Hirojo Iwata, Aichi Cancer Center Hospital, Nagoya, Japan

Background: The most common PAL treatment related adverse event is neutropenia. ABCB1 and ERCC1 variants are associated with increased chemotherapy drug exposure and CYP3A7*1C may be associated with reduced exposure. Pharmacogenetic analyses of these variants in patients (pts) from P2A3 may reveal associations between single nucleotide polymorphisms (SNPs) and early occurrence of grade 3/4 (G3/4) neutropenia. Methods: ABCB1 (rs1045642, rs1128503, ERCC1/rs3212986, rs11615), and CYP3A7*1C (rs45446698) variants were analyzed in germline DNA from pts with HR+/HER2- advanced breast cancer from P2 (n=584) and P3 (n=442) by TaqMan assay. Association between variants and incidence of G3/4 low absolute neutrophil count (ANC) at Cycle 1 Day 15 (C1D15) was assessed with the exact Cochran-Armitage trend test. Odds ratios (OR) and 95% confidence intervals (CI) were estimated by logistic regression. Results: In total, 652 PAL-treated pts had SNP, race, and C1D15 ANC data. Minor allele frequencies (MAF), incidence rates, and relative risk of G3/4 C1D15 ANC for ABCB1 and ERCC1 variants are given in the Table. CYP3A7*1C was only found in non-Asians (MAF 6%). Conclusions: This is the first comprehensive assessment of pharmacogenetic data from P2A3. ABCB1 and ERCC1 SNP allele frequencies differ between Asians and non-Asians. Despite combining P2/P3 data, we lacked power to detect moderate associations; further investigation of these SNPs with G3/4 C1D15 ANC is warranted. Pfizer clinical trial information: NCT01740427, NCT01942135.

1Minor allele in Asians. 2Non-Asians are predominantly self-reported (94%) White Caucasians.

<table>
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<th>SNP Alleles</th>
<th>MAF (%)</th>
<th>OR (95% CI)</th>
<th>P trend</th>
<th>MAF (%)</th>
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<td>26</td>
<td>CA 0.39 (0.19-0.93)</td>
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Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Effect of metformin on PARP inhibitors-induced epithelial-mesenchymal transition and PD-L1 expression in triple-negative breast cancer. First Author: Ye Han, China Medical University Affiliated Shengjing Hospital, Shenyang, China.

Background: Poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as promising targeted therapies for BRCA-mutated cancers by blocking repair of DNA double-strand breaks. However, resistance to PARP inhibitors have been described in some patients lowering overall response rates. The mechanisms underlying PARP inhibitor (PARPi) resistance are an area of active investigation. Methods: PARPi adaptive resistant clones (MDA-MB-468, MDA-MB-231, HCC1806) were generated in triple-negative breast cancer cell lines. Through morphologic observation and functional analysis, we evaluated epithelial-mesenchymal transition (EMT) and changes in cancer cell lines. 468, MDA-MB-231, HCC1806) were generated in triple-negative breast cancer cells. In addition, PARPi--induced EMT occurred independent of PD-L1 upregulation in triple-negative breast cancer cells. Metformin administration (10 mM) was found to reverse EMT by blocking the p-Akt S473 axis through activation of AMPK, resulting in downregulation of PD-L1 in serializing PARPi resistant cancer cells to T cell killing. Conclusions: In summary, we identified that induction of EMT is a new mechanism for PARPi inhibitor resistance. Metformin was able to reverse EMT and therefore a combination of metformin and PARPi inhibitors may be a promising therapeutic strategy to increase the efficacy of PARPi inhibitors and tumor sensitivity to T cells.

Results: Notch pathway is activated during mammary gland development and has been implicated as a key driver in breast cancer. There is an urgent need to identify new therapeutic strategies for triple-negative breast cancer (TNBC), a subtype associated with poor prognosis and no available targeted therapies. Notch gain of function (GOF) genetic alterations are potential tumor drivers found in ~10% of TNBC. This motivated the development of Notch inhibitors, including AL101 a pan-Notch, gamma secretase inhibitor (J Clin Oncol 36, 2018 abstract 2515). AL101 is currently being evaluated in Adenoid Cystic Carcinoma patients with activating Notch mutations (NCT03691207, ACCURACY trial). Here, we aim to test the activity of AL101 in TNBC patient derived xenograft (PDX) models with Notch activating genetic alterations. Methods: Gene expression cluster analysis was performed for 38 TNBC PDX tumors using a list of 21 Notch target genes. Seven tumors, bearing a “Notch-on” signature, were enriched with mutated/fusion (MF) Notch genes and clustered separately from all other tumors. Of 9 models selected for study, 4 had a Notch-on signature and were expanded to respond to AL101. Tumors were implanted into female athymic nude mice. Once tumors reached an average size of 150-300 mm3, mice (n = 5/group) were randomized to Vehicle or AL101 treatment arms (3 mg/kg, PO, 4on/3off) until tumors reached 1500 mm3 or day 60. Results: As measured by tumor growth inhibition (TGI), AL101 was more potent in tumors with a putative Notch-on signature. Within these 4 models, MF gene expression and sensitivity to PARPi GOF (103% TGI p = 0.0004; Notch2-fusion 62% TGI p = 0.036; Notch3-fusion (75% TGI p = 0.032); or Notch4-fusion (147% TGI p < 0.00001). Tumors lacking the Notch signature did not respond significantly to AL101: WT Notch (43% TGI p = 0.0104; 64% TGI p = 0.13). Notch1 with a predicted loss of function mutation (12% TGI p = 0.53), Notch1 with UnKnown (VUS) (30% TGI p = 0.44), Notch2 VUS (41% TGI p = 0.44). Conclusions: We demonstrate that in TNBC PDX models, the presence of a Notch-on signature and Notch GOF mutations/fusions correlates with potent response to AL101. These data support the clinical development of AL101 as a targeted therapy for TNBC with Notch GOF alterations.
1067 Poster Session (Board #148), Sun, 8:00 AM-11:00 AM
Patient-reported outcomes (PROs) from the phase III IMpassion130 trial of atezolizumab (atezo) plus nab-paclitaxel (nP) in metastatic triple-negative breast cancer (mTNBC). First Author: Sylvia Adams, New York University Cancer Institute, New York, NY
Background: In the IMpassion130 study in 1L mTNBC (N = 902), PFS with atezo + nP was significantly better than with placebo (P) + nP in ITT (HR, 0.80) and PD-L1 IC+ (HR, 0.62) patients (pts). Clinically meaningful OS improvement (HR, 0.62) was also seen in PD-L1+ pts. PROs were used to document pt perspectives on overall clinical benefit of atezo + nP. Methods: Pts received either atezo 840 mg q3w or P q2w + nP 100 mg/m² on days 1, 8 and 15 of each 28-day cycle until disease progression or intolerance. Pts completed the EORTC QLC-C30 and breast cancer module (QLQ-BR23) on day 1 of each cycle, at end of treatment (Tx) and q4w during follow-up for 1 y. Time to deterioration (TDT; first ≥ 10-point decrease from baseline (BL) held for 2 cycles) in HRQoL was a pre-defined secondary endpoint. Exploratory endpoints included TDT in function, and mean and mean change from BL scores (changes ≥ 10 considered clinically meaningful) in HRQoL, function and disease/Tx-related symptoms. Results: BL completion was 92% (QLQ-C30) and 89% (QLQ-BR23) and remained > 80% through Cycle 1 in both ITT and PD-L1 IC+ pts. No differences in median TDT in HRQoL (ITT: HR, 0.97 [95% CI: 0.80, 1.18]; PD-L1 IC+: HR, 0.94 [95% CI: 0.69, 1.28]), physical function (ITT: HR, 1.04 [95% CI: 0.86, 1.26]; PD-L1 IC+: HR, 1.02 [95% CI: 0.76, 1.37]) or role function (ITT: HR, 1.01 [95% CI: 0.83, 1.22]; PD-L1 IC+: HR, 0.77 [95% CI: 0.57, 1.04]) were observed between arms in either population. Mean scores at BL for HRQoL (ITT: 66.0 [atezo + nP] vs 64.3 [P + nP]; PD-L1 IC+: 67.5 vs 65.0), physical function (ITT: 80.4 vs 79.2; PD-L1 IC+: 82.8 vs 79.4) and role function (ITT: 72.7 vs 71.0; PD-L1 IC+: 73.7 vs 71.7) were similar between arms and throughout the course of Tx. In both arms, HRQoL, physical and role function, and Tx symptoms (fatigue, diarrhea, nausea, vomiting) were stable during Tx, with no clinically meaningful changes seen until pts discontinued Tx. Conclusions: PRO data suggest that atezo + nP was tolerable and similar to nP alone in maintaining HRQoL and day-to-day function relative to BL. This confirms atezo + nP had clinical benefit without compromising HRQoL, physical and role function, or worsening Tx symptoms vs P + nP in 1L mTNBC. Clinical trial information: NCT02425891.

1068 Poster Session (Board #149), Sun, 8:00 AM-11:00 AM
IMpassion130: Expanded safety analysis from a P3 study of atezolizumab (A) + nab-paclitaxel (nP) in patients (pts) with breast (ba) worse overall survival (OS) and disease progression-free survival (PFS) in metastatic breast cancer (mBC). First Author: Andreas Schneeweiss, National Center for Tumor Diseases, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany
Background: IMpassion130 showed PFS benefit with A + nP vs placebo (P) + nP as 1L tx for mTNBC in the ITT and PD-L1 IC+ pts. We report expanded safety data with 4.5-mo longer follow-up (FU), focusing on adverse events of special interest (AESI). AEs were classified as individual, immune related (IR) or assessed by local or global IR panel. AESI pts with IR were excluded. Toxicity grading was modified using 30d or 60d of mTNBC received nP 100 mg/m² (d1, 8 and 15 of a 28-d cycle) + A 840 mg IV q2w or P until PD or toxicity. Safety was a secondary endpoint. Results: With 15.6 mo of median FU, of 453 pts with A+nP and 437 pts with P+nP, 49% and 43% had Gr 3/4, and < 1% had Gr 5, 23% and 19% had serious AEs, and 58% and 42% had AEi, respectively. Most AEi (≥85%; either arm) were Gr 1/2. 14% (A+nP) vs 6% (P+nP) received systemic corticosteroids within 30 d of AEi onset. The only any-AEi atezo vs P+nP was rash (43% vs 26%), hypoe (18% vs 5%) and hyper trophy (5% vs 1%) and pneumonitis (4% vs <1%). The leading cause of withdrawal was peripheral neuropathy with Gr 3 affecting 6% (A+nP) vs 3% (P+nP), AESi median time to onset (TTO) was consistent with A monotherapy trials. Conclusions: A+nP had a tolerable safety profile, with no meaningful changes since the primary data cut. No cumulative toxicities or new or late-onset safety signals were seen with longer FU. Clinical trial information: NCT02425891.

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**Background:** The PARP inhibitor TALA was approved in the US for treatment of gBRCA-mutated ABC based in part on the EMBRACA study. Understanding the outcomes of EMBRACA pts relative to prior CT is a current unmet need.

**Methods:** EMBRACA was a randomized Phase 3 trial comparing TALA 1 mg daily vs PCT (capetibamine, eribulin, gemcitabine + trastuzumab) in non-first line chemotherapy (CT) treated ABC. Clinical outcomes were assessed by line of prior CT for ABC in intent-to-treat (ITT), triple-negative breast cancer (TNBC), and hormone receptor-positive (HR+) breast cancer cohorts. Results: 431 pts were randomized (ITT; TALA 287; PCT: 144). TALA was generally more effective than PCT across efficacy endpoints regardless of line of CT (Table). For the ITT population, TALA improved progression-free survival (PFS) and objective response rate (ORR) vs PCT for each line of CT assessed. Other prespecified subgroups (TNBC and HR+) will be presented. **Conclusions:** In pts with gBRCA-mutated ABC, TALA demonstrated improvements in clinical outcomes compared with PCT regardless of prior lines of CT. Clinical trial information: NCT01945775.

<table>
<thead>
<tr>
<th>TALA vs PCT</th>
<th>0L CT</th>
<th>1L CT</th>
<th>2L CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>0.52 ± 0.26</td>
<td>0.51 ± 0.28</td>
<td>0.52 ± 0.26</td>
</tr>
<tr>
<td>PFS, median, mo</td>
<td>12.1 (2.3-56.8)</td>
<td>6.5 (1.3-70.9)</td>
<td>Not estimable (NE)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNBC</td>
<td>0.57 (0.34-0.95)</td>
<td>0.52 (0.33-0.80)</td>
<td>0.56 (0.34-0.95)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>3.9 (1.0-14.3)</td>
<td>3.8 (1.1-13.6)</td>
<td>1.3 (0.35-4.7)</td>
</tr>
</tbody>
</table>

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Determinants of concordance in clinically relevant genes (CRG) from synchronously acquired tumor biopsies (tBx) and ctDNA in metastatic breast cancer (MBC). 

Background: NGS in ctDNA from MBC is feasible and results may be informative for patients’ management, especially in non-luminal tumors (Oliveira et al, ASCO 2018). We aimed to study the determinants of concordance in CRG in a cohort of 60 metastatic patients treated with tBx and ctDNA collection. Methods: Amplicon-based NGS (59 cancer-related genes) was performed in one single metastatic lesion per patient and compared with liquid biopsies taken at the same time point at disease progression to prior treatment. The concordance in CRG (PIK3CA, AKT1, ERBB2, ESRI, PTEN, BRAF, FGFR1, HRAS, KRAS, and PIK3CA vs ctDNA) was assessed at mutation level and correlated with mutant allele fraction (MAF), total disease volume (TDV), and clinical characteristics. True positive in plasma (TPP): patient with a mut detected both in ctDNA and tBx. TDV was defined as all metastasis volume assessed by CT scan (excluding sclerotic bone metastasis), and analyzed by an experienced radiologist using the 3D Slicer semiautomatic segmentation tool (TDV = pixel size x number of pixels). Results: Concordance in CRG at patient and mut level was 72% and 55%, respectively. Concordance for ERBB2 (1/1); 100% and PIK3CA (17/22; 77%) was higher than for ESRI (8/20; 40%) and AKT1 (12/23; 33%); ctDNA failed to detect 14 mut present in tBx (ESRI n = 5, PIK3CA n = 5, AKT1 n = 3, BRAF n = 1). Concordance was 100% for non-luminal and 60% for luminal cases (P = 0.011). In univariate analysis, concordance was not associated with MAF in tBx (P = 0.15), TDV (P = 0.86), number of prior lines of therapy (P = 0.57), number of metastatic sites (P = 0.56) or presence of a visceral metastasis (P = 1.0). In patients with PIK3CA mut (n = 22), those with TPP had a numerically higher TDV than those where a PIK3CA mut was not detected in tDNA (20.9 cm³ vs 5.1 cm³, P = 0.28). Across all patients, in the multivariate logistic model adjusted for other factors, TDV was a determinant of TPP (OR 1.02, 95%CI 1.01-1.06, P = 0.059). For each increase of 1 cm³ in TDV, there was a 2% increase in the probability of detecting a mut in ctDNA. Conclusions: Our results suggest that liquid biopsy testing for the detection of actionable CRG is clinically valid in MBC, although its yield depends on several factors – tumor subtype, analyzed gene, and possibly tumor volume – that reflect both tumor heterogeneity and tumor shedding rate. The potential clinical implications, the observation that mutation detection in ctDNA may correlate with tumor volume merits further study in a larger dataset.

Methods: A phase II, single-arm study of apatinib and oral etoposide in pretreated metastatic HER2-negative breast cancer. First Author: Nanlin Hu, Chinese Academy of Medical Sciences & Peking Union Medical College, Breast Cancer Group, Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: There is no standard treatment strategy for patients with locally advanced or metastatic breast cancer suffering progression after one prior chemotherapy with metastasis setting. Apatinib is a tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor 2 (VEGFR-2). Etoposide is a highly active chemo-drug in the treatment of advanced breast cancer, both as a single agent or in combination regimens, and is well tolerated, with a low incidence of severe toxicity. This study is performed to assess the efficacy and safety of apatinib and oral etoposide in patients with HER2 negative locally advanced or metastatic breast cancer for whom at least one lines of prior chemotherapy had failed. Methods: This open-label, single arm study enrolled patients with HER2-negative breast cancer, pretreated with anthracycline, taxanes, and who failed in the metastatic setting at least one prior chemotherapy regimens and at least one endocrine drug for hormone receptor-positive patients. Apatinib was administered 425/500mg daily according to patients ECOG (Eastern Cooperative Oncology Group) status, oral etoposide was administered 50mg/m² for first 10 days in a 21-days cycle. The primary end point of this study was progression-free survival (PFS). Secondary end points included objective response rate (ORR), disease control rate (DCR), overall survival (OS), and toxicity. The treatment duration is until disease progression or intolerability of apatinib or oral etoposide. Results: 20 eligible patients were enrolled in this, open-label, single arm study and received apatinib and oral etoposide with a median age of 61 (range 36 to 66 years). Median follow-up time was 11 months. 20 patients were eligible for efficacy analysis. Median PFS was 5.6 months (95% confidence interval (CI), 4.0 m - 8.4 m), ORR was 20% (4/20). DCR was 70% (14/20). Median OS was 11.2 months (95% CI, 9.6 m - 14.9 m). The most common grade 1-2 treatment-related AEs were hypotension (45%), fatigue (43%), and proteinuria (5%), nausea (5%), and 35/70(20) patients had dose reduction because of adverse events, after that all adverse events can return to less than 2 grade. Conclusions: Apatinib with oral etoposide exhibited objective efficacy in pretreated, metastatic HER2-negative breast cancer with manageable toxicity. Prospective studies enrolling more patients are needed. Clinical trial information: NCT03535961.

Background: In Spain there is limited prospective data for unselectable locally advanced breast cancer (<ULABC) or metastatic breast cancer (<MBC) patients (pts) treated as per clinical practice. RegistEM study will provide epidemiological, pathological and clinical data, including treatments given for primary breast cancer and breast cancer diagnosis. Understanding the relation of different BC subtypes is the primary objective. Methods: This is a non-interventional cohort study enrolling approximately 1,400 pts with advanced disease diagnosed from January 2016 to December 2018, either recurrence or as first diagnosis, in 38 Spanish sites. Biological samples (primary tumor, metastatic lesions, blood) are currently being collected. In this first analysis, we include 489 pts who met study criteria before October 31, 2017. All data are described in two subgroups: on the most recent tumor lesion or on the primary breast tumor. Results: At first diagnosis, 67.9%, 31.5% and 0.6% of pts had early BC (EBC), MBC and ULABC, respectively. In the total analysis population, median age at diagnosis of advanced disease was 59.6 years, most of pts were white (98.2%), female (99.4%) and postmenopausal (70%). Family history of BC and ovarian cancer was reported in 5.7% pts. In ~390 pts BC clinical subtypes distribution was luminal B(HER2-like) (~55%), luminal B(HER2+)-like (~16%), luminal A-like or triple negative (TN) (~10%) each and HER2 enriched-like (~8%). Median time to recurrence (years) in EBC pts was: luminal A-like 5.8, luminal B(HER2)-like 5.1, luminal B(HER2+)-like 3.9, HER2 enriched-like 2.7 and TN 1.7. Bone (59%), visceral (58%) and lymph node (27%) lesions were the most frequent metastatic locations. The two most frequent therapies in first line consisted in: endocrine therapy (ET) (47%) and ET biologic therapy (BT) (29%) for luminal A-like; ET (32%) and ET+BT (32%) for luminal B(HER2-) like; chemotherapy (CT)+ET+B (43%) and CT+BT (24%) for luminal B(HER2+)-like; CT+B (68%) and CT (16%) for HER2 enriched-like; CT (59%) and CT+BT (34%) for TN. Conclusions: These first data confirm that luminal B(HER2-) like subtype is the most predominant in MBC.
Background: Brain metastases (BM) are a common and fatal complication of breast cancer but survival varies widely based on various prognostic factors (PF). Hence, patient counseling and therapeutic decisions should be individualized. We previously published a prognostic index (Breast GPA) based on cohort A (1985-2007, n = 642), updated it with tumor subtype in cohort B (2008-2010, n = 400) and are now updating it with a larger contemporary cohort (C). Methods: A multi-institutional (19) multi-national (3) retrospective database of 2473 breast cancer patients with BM diagnosed from 1/1/2006-12/31/2017 was created and compared to our prior cohorts. Demographic, clinical, molecular factors, tumor subtype and treatment were correlated with survival. Kaplan-Meier survival estimates were calculated and compared with log-rank tests. Results: The median survival (MS) for cohorts A, B and C improved over time (12, 14 and 16 mo, respectively (< 0.01)) despite the subtype distribution becoming less favorable: Luminal B (ER/PR/HER2+) decreased from 26% to 21%; HER2 (HER2+/ER/PR-) decreased from 31% to 17%; Luminal A (ER/PR+/HER2-) was unchanged at 24%. MS by subtype improved from 21 to 27 mo in Luminal B, 18 to 25 mo in HER2, 10 to 14 mo in Luminal A and 6 to 9 mo in basal tumors. The number of BM was 1 in 35%, ≤ 4 in 67% and > 10 in 18%. PF significant for survival were tumor subtype, age, KPS, number of BM and extracranial metastases (ECM) (all p < 0.01). Surprisingly, Hispanic women (7%) showed improved survival (p < 0.01). BRCA1 was mutated in 57/533 (11%) and those patients showed a trend (0.16) toward improved survival. Treatment patterns have changed; the use of whole brain radiation therapy decreased from 71% to 67% to 47% in cohorts A, B and C, respectively. OS for all patients with chemosensitive (chemo) and chemoresistant (chemor) disease was 14.6 and 8.6 months (NS), respectively. OS for chemoS and chemoR disease in HER2- ER/PR+ patients was 16.5 and 8.6 months (NS), respectively. OS for chemoS and chemoR disease in TNBC patients was 12.4 and 22.6 months, respectively (NS). The median TTP for ER/PR+ patients was 10.6 mo and for patients with HER2+ disease, respectively. Increases in serum IL-2 and IL-12 were associated with BATs in patients who had received any cells had stable disease (SD) at 1 month after the last infusion, and 8 of 75 (25%) had SD > 4 months. For patients who completed 3 or 4 infusions (17-83 x 109 BATs), 8 of 31 patients had TTP > 4 months. One patient completed 2 infusions (17 x 109 BATs). There were no dose limiting toxicities (DLTs). Tumor markers decreased in 13 of 23 (56.5%) patients with evaluable markers. The median OS was 13.8, 16.5, and 12.4 months for all, ER/PR+, and TNBC, respectively. For all patients with chemosensitive (chemo) and chemoresistant (chemor) disease, the 3-year OS was 49%, 37% and 30%, respectively. In the subgroup of patients with chemosensitive disease (chemo), the 3-year OS was 54%, 37% and 27%, respectively. Immune studies showed evidence for induction of adaptive immunity directed at breast cancer antigens. Targeting metastatic HER2- BrCa with BATs shows promise. Clinical trial information: NCT 01022138.
Hyperprogressive disease in advanced triple-negative breast cancer (aTNBC) treated with immunotherapy (IO). First Author: Tira Jing Ying Tan, Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore

Background: Hyperprogression of disease (HPD), a rapid acceleration of tumor growth rate (TGR) has been reported with IO in other tumor types. Here, we explore HPD in aTNBC. Methods: A retrospective chart review identified aTNBC patients who consented for IO clinical trials at Princess Margaret Cancer Centre between June 2013 and June 2018. Demographic data, medical history, details of trial enrolment and RECIST 1.1 response to study treatment were recorded. Patients with RECIST 1.1 measurable disease on CT scans or physical examination before trial entry, at trial baseline and at protocol-defined interval following IO start were evaluable for TGR as defined by Champiat et al. Clin Cancer Res 2017. HPD defined as a ≥2-fold increase in TGR between baseline and on-trial restaging assessment. Univariable logistic regression used to identify variables [age, co-morbidity index, prognostic index, performance status, distant disease free interval (dDFI), lactate dehydrogenase, number of metastatic sites, visceral disease and number of prior treatment lines] associated with HPD. Overall survival (OS) curves were estimated with the Kaplan-Meier method and compared by the log-rank test. Results: 99 patients with aTNBC consented for 15 IO clinical trials, 60% IO monotherapy, 22% chemotherapy+IO and 18% IO combinations. Median age 52 (range 25-78), median number of prior systemic therapy for advanced disease 1 (range 0-8). 15% had de novo metastatic disease, 58% recurred after a dDFI of < 3 years and 25% after a dDFI of > 3 years. 61% had < 3 metastatic disease sites, and 71% had metastases involving the viscera. 66 received IO treatment, 40 patients (20 monotherapy, 7 IO combination, 13 chemotherapy+IO) were evaluable for TGR. Median TGR pre-IO was 74.3 (range -17 to 1680) and post-IO was 2.5 (-714 – 223). 4 patients (10%) met criteria for HPD. All 4 treated with monotherapy PD-1 inhibitor and received a ≥2 further lines of therapy post-trial; 1 patient treated with IO as first-line therapy, 3 in the second or later lines. There was no significant difference in the overall OS of patients with HPD and patients who did not meet definition for HPD HR 0.89, (95% CI: 0.26-3.01; p = 0.41). Univariable analysis did not identify factors associated with HPD. Conclusions: HPD was observed in 10% of aTNBC treated with IO, but HPD was not associated with worse survival outcome or known prognostic factors in our analysis.

Hyperprogressive disease in advanced triple-negative breast cancer (aTNBC) treated with immunotherapy (IO). First Author: Lingjun Zhu, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province, China

Background: Somatic reversion mutations in either BRCA1/2 has been reported to lead to the resistance of platinum-based chemotherapy or PARPi. In this study we try to analyze the secondary somatic mutations in BRCA1/2 in patients with germline mutations. Methods: Using gene-panel target-capture next generation sequencing, we analyzed the secondary somatic mutations from 86 patients with BRCA1/2 germline mutations. Results: Eighty-six cases with BRCA1/2 germline mutations were identified. Secondary somatic mutations restoring BRCA1/2 were identified in 7 patients, including 2 breast cancer, 3 ovarian cancer, 1 prostate cancer and 1 cholangiocarcinoma patient. For these seven patients, five had been treated with platinum-based chemotherapy without PARPi and the other two (patient 1 and 2) with PARPi (olaparib). Patient 1 and 2 both received targeting therapy of PARP inhibitor olaparib after the germline BRCA1/2 mutation was detected. About six months later, plasma ctDNA was sequenced. Result showed that the germline mutations remained and additional larger deletions was detected. These secondary somatic mutations are not predicted to significantly affect the BRCA1/2 protein, and are likely to cause resistance to platinum-based chemotherapy or PARPi therapy by restoring BRCA1/2 ORF and DNA repair function. Conclusions: Secondary somatic mutations that restore BRCA1/2 in carcinomas with germline BRCA1/2 mutations predict resistance to platinum-based chemotherapy and PARPi inhibition, some of which may reverse this type of drug resistance seen further investigation.

<table>
<thead>
<tr>
<th>Pi</th>
<th>BRCA reversion post-DNA damaging tx</th>
<th>Possible non-reversion MoR from WE (gene)</th>
<th>RADS1 foci post-DNA damaging tx</th>
</tr>
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<tbody>
<tr>
<td>232</td>
<td>No</td>
<td>Yes (many)</td>
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<td>339</td>
<td>Yes</td>
<td>Yes (KM728)</td>
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<td>565</td>
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</tbody>
</table>

**Plasma to whole exome sequencing (WES) with follow-up whole transcriptome sequencing (WTS):**

**Whole transcriptome sequencing (WTS):**

**Whole genome sequencing (WGS):**

**Whole genome amplification (WGA):**

**First Author:** Lingjun Zhu, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province, China

**Background:** Secondary somatic mutations in BRCA1/2 have been reported to lead to the resistance of platinum-based chemotherapy or PARPi. In this study we try to analyze the secondary somatic mutations in BRCA1/2 in patients with germline mutations. Methods: Using gene-panel target-capture next generation sequencing, we analyzed the secondary somatic mutations from 86 patients with BRCA1/2 germline mutations. Results: Eighty-six cases with BRCA1/2 germline mutations were identified. Secondary somatic mutations restoring BRCA1/2 were identified in 7 patients, including 2 breast cancer, 3 ovarian cancer, 1 prostate cancer and 1 cholangiocarcinoma patient. For these seven patients, five had been treated with platinum-based chemotherapy without PARPi and the other two (patient 1 and 2) with PARPi (olaparib). Patient 1 and 2 both received targeting therapy of PARP inhibitor olaparib after the germline BRCA1/2 mutation was detected. About six months later, plasma ctDNA was sequenced. Result showed that the germline mutations remained and additional larger deletions was detected. These secondary somatic mutations are not predicted to significantly affect the BRCA1/2 protein, and are likely to cause resistance to platinum-based chemotherapy or PARPi therapy by restoring BRCA1/2 ORF and DNA repair function. Conclusions: Secondary somatic mutations that restore BRCA1/2 in carcinomas with germline BRCA1/2 mutations predict resistance to platinum-based chemotherapy and PARPi inhibition, some of which may reverse this type of drug resistance seen further investigation.

**Patient Disease**

<table>
<thead>
<tr>
<th>BRCA1/2</th>
<th>Secondary somatic mutations</th>
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<tbody>
<tr>
<td>Breast cancer</td>
<td><strong>BRCA1</strong></td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td><strong>BRCA2</strong></td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td><strong>BRCA2</strong></td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td><strong>BRCA1</strong></td>
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<tr>
<td>Breast cancer</td>
<td><strong>BRCA1</strong></td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td><strong>BRCA1</strong></td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td><strong>BRCA1</strong></td>
</tr>
</tbody>
</table>

**Results:**

- **BRCA reversion post-DNA damaging tx**: 292, 303, 318, 339, 349, 359, 517, 565
- **Possible non-reversion MoR from WE (gene)**: No, Yes, Yes, Yes, Yes, No, No, No
- **RADS1 foci post-DNA damaging tx**: Unknown, No, No, Yes, Yes, Yes, Yes, Yes

**Plasma to whole exome sequencing (WES) with follow-up whole transcriptome sequencing (WTS):**

**Whole transcriptome sequencing (WTS):**

**Whole genome sequencing (WGS):**

**First Author:** Lingjun Zhu, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province, China

**Background:** Secondary somatic mutations in BRCA1/2 have been reported to lead to the resistance of platinum-based chemotherapy or PARPi. In this study we try to analyze the secondary somatic mutations in BRCA1/2 in patients with germline mutations. Methods: Using gene-panel target-capture next generation sequencing, we analyzed the secondary somatic mutations from 86 patients with BRCA1/2 germline mutations. Results: Eighty-six cases with BRCA1/2 germline mutations were identified. Secondary somatic mutations restoring BRCA1/2 were identified in 7 patients, including 2 breast cancer, 3 ovarian cancer, 1 prostate cancer and 1 cholangiocarcinoma patient. For these seven patients, five had been treated with platinum-based chemotherapy without PARPi and the other two (patient 1 and 2) with PARPi (olaparib). Patient 1 and 2 both received targeting therapy of PARP inhibitor olaparib after the germline BRCA1/2 mutation was detected. About six months later, plasma ctDNA was sequenced. Result showed that the germline mutations remained and additional larger deletions was detected. These secondary somatic mutations are not predicted to significantly affect the BRCA1/2 protein, and are likely to cause resistance to platinum-based chemotherapy or PARPi therapy by restoring BRCA1/2 ORF and DNA repair function. Conclusions: Secondary somatic mutations that restore BRCA1/2 in carcinomas with germline BRCA1/2 mutations predict resistance to platinum-based chemotherapy and PARPi inhibition, some of which may reverse this type of drug resistance seen further investigation.
Differences in breast cancer outcomes amongst Black United States-born and Caribbean-born immigrants. First Author: Priscila Barreto Coelho, Jackson Memorial Hospital/University of Miami, Miami, FL.

**Background:** The Black population in the US constitutes 4 million immigrants, with 50% from the Caribbean. It has been shown that breast cancer is responsible for 14%-30% of cancer deaths in the Caribbean; this is up to two times higher than the USA. **Methods:** Retrospective cohort of 1369 self-identified Black women with breast cancer. Data was obtained from Jackson Memorial Health Systems University of Miami Health System Tumor Registry. Individual-level data from 1132 cases was used to evaluate potential risk factors and outcomes. **Results:** Data from 622 (54.9%) USB women and 507 (45%) CB women diagnosed with breast cancer between 2006-2017. 90% of these patients had more ER- (31.4% vs 39.1%, p = 0.018) and triple negative breast cancer (19.6% vs 27.9%, p = 0.003). Compared to USB, CB had lower BMI at diagnosis 29.6 [95% CI, 28.9-30.3] versus 30.9 [95% CI, 30.1-31.7, P = 0.015]. Compared to CB patients, USB patients had more ER- [31.4% vs 39.1%, P = 0.018] and triple negative breast cancer (19.6% vs 27.9%, P = 0.003). Compared to USB patients, CB presented at a more advanced stage III and IV (24.2% vs 33.5, p < 0.01) in addition to more of these advanced stages at diagnosis, CB patients had a better breast cancer overall survival [HR = 0.75; 95%CI, 0.59-0.96; P = 0.024]. Black Hispanic patients had a better overall survival [HR = 0.51; 95%CI, 0.28-0.93; p = 0.028] compared to non-Hispanic Blacks. Compared to Hispanic Caribbean, non-Hispanic Black had a worse overall survival [HR = 1.98; 95%CI, 1.00-3.84; 95%CI; p = 0.048] of the patients treated at the private cancer center and the safety net hospital were the same, differences in outcomes observed are due to intrinsic differences. **Conclusions:** This is the largest analysis to date of self-identified Black breast cancer patients in the context of nativity, race, ethnic identity. Among patients with metastatic breast cancer and survival with clinico-pathologic characteristics, CB immigrants diagnosed with breast cancer have a better overall survival than US born Black patients. This finding suggests that within the African diaspora in the USA, additional factors beyond race contribute to the outcomes.
that 4 pts presented high large scale state transitions, and 3 presented somatic (sBRCA1). 19 pts had grade 3-4 toxicities. 3 pts discontinued due to toxicity.

In this study, rucaparib in gBRCA wild-type (WT) pts was used as an independent validation cohort. We further compared tumor biomarkers and to assign prognostic categories using LASSO Cox regression model. Additionally, 969 patients from The Cancer Genome Atlas data set were evaluated for overall survival (OS) and progression free survival (PFS) using univariable analysis. Time to event variables were estimated by Kaplan-Meier method.

Breast Cancer—Metastasis

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1096 Poster Session (Board #177), Sun, 8:00 AM-11:00 AM
A phase II study of pembrolizumab and capecitabine for triple-negative (TN) and hormone receptor-positive, HER2-negative endocrine-refractory metastatic breast cancer (MBC). First Author: Ami N. Shah. Northwestern University, Chicago, IL

Background: Response rates to single agent immune checkpoint blockade in unselected MBC are low; however, they may be augmented when combined with chemotherapy. Methods: We conducted a single-arm, phase II study of patients with TN or endocrine-refractory MBC who were candidates for capecitabine. Patients were treated with pembrolizumab 200 mg IV day 1 and capecitabine 1000 mg PO BID days 1-14 of a 21-day cycle. The primary endpoint was progression free survival (PFS) and secondary endpoints were overall response rate (ORR), safety and tolerability. The study had 80% power to detect a 2 month (mo) improvement in mPFS with the addition of pembrolizumab over historic controls treated with capecitabine alone.

Results: Thirty patients, 16 with TN and 14 endocrine-refractory MBC, were enrolled from 2017-18. Patients had a median age of 51 years and received a median of 1 prior line of therapy for MBC. Of 29 evaluable patients, the mPFS was 4.1 mo (95% CI, 2.3-8.2 mo) and median overall survival was 15.4 mo (95% CI, 8.2-16.6 mo). ORR was 14% (n = 4), stable disease (SD) was 41% (n = 12), and clinical benefit rate (CBR = ORR + PR + SD) was 28% (n = 8). The ORR and CBR were similar between disease subtypes (ORR 13% and 14%, CBR 25% and 29% for TN and endocrine refractory, respectively). The 1-year PFS rate was 20.7% and 3 pts have ongoing responses. The most common adverse events were low grade and consistent with those expected in MBC patients including hand-foot syndrome, gastrointestinal symptoms, fatigue, and cytopenias. Toxicities at least possibly from pembrolizumab included grade 3 or 4 liver test abnormalities (7%), rash (7%), and diarrhea (3%), as well as grade 5 hepatic failure in a pt with liver metastases. Conclusions: Compared to historical control with capecitabine alone, pembrolizumab combined with capecitabine was associated with low response rates; however, some respondents had prolonged disease control. Future studies of chemo-immunotherapy in MBC with liver metastases require close safety monitoring.

Clinical trial information: NCT03044730.

1097 Poster Session (Board #178), Sun, 8:00 AM-11:00 AM
Measuring on-treatment genome-wide tumor copy number alterations in cell-free DNA (cfDNA) in plasma is highly prognostic in metastatic breast cancer. First Author: Autiana Aguilera. Segal Cancer Centre/Jewish General Hospital and McGill University, Montreal, QC, Canada

Background: The clinical management of metastatic breast cancer depends on the measurement of tumor response to successive drugs by serial imaging and changes in blood tumor markers, which remain the standard of care despite poor sensitivity and specificity. Highly sensitive and specific cfDNA secreted from the tumor can detect the changes in tumor-specific aberrations that have been shown to be associated with patient response in the metastatic setting. However, most approaches require prior sequencing of the tumor to target specific known mutations. Methods: Using low coverage genomic sequencing, a genomic instability number (GIN) was measured in cfDNA based on the detection of genome-wide tumor-specific DNA copy number alterations for 27 patients with metastatic breast cancer. The GIN value and its variation from baseline before treatment, as well as within 10 days and 3 weeks after start of therapy were compared with tumor response, progression free survival (PFS) and overall survival (OS) of the patients. Patients were followed for a median of 22 months and we used a previously published GIN threshold at 170 for high vs low GIN values. Sequencing was performed blinded to the clinical results. Results: Baseline GIN values were not associated with tumor response at 3 or 6 months, but showed a trend towards lower OS with higher GIN (p = 0.12). GIN values fell by an average of 28% in responders (stable disease or response) and 23% in those with progression (p = 0.16), but were maintained low at 3 months in responders. High GIN values within 10 days and 3 weeks were associated with markedly worse OS (p = 0.014 and p = 0.009 respectively) and those at 3 weeks with worse PFS (p = 0.017). Hence the median survival of patients with high GIN at 10 days or 3 weeks was 12 months vs not reached for those with low GIN. The percentage drop of GIN at 10 days was significantly associated with OS (p = 0.016). Conclusions: These results demonstrate that GIN values of cfDNA measured at early on-treatment time points can predict PFS and OS with a high degree of accuracy. These findings deserve further study in a larger cohort but hold the promise of early prediction of clinical outcomes in a tumor-independent genome-wide approach.

1098 Poster Session (Board #179), Sun, 8:00 AM-11:00 AM
Evaluation of pathologic and genomic characteristics in male breast cancer (MBC) patients. First Author: Damien Mikael Hansra. Oncology and Radiation Associates/Mercy Research Institute, Miami, FL

Background: MBC is a rare entity comprising less than 1% of breast cancers [Siegel RL 2017]. Due to the low incidence of MBC, information about the genomic landscape of MBC is lacking. Here we describe detailed pathologic and genomic characteristics of MBC patients. Methods: IRB approval was obtained for a retrospective analysis of archived pathology on patients treated at Cancer Treatment Centers of America. Comprehensive genomic profiling of tumors was derived from Foundation One next generation sequencing. Clinical information was derived from retrospective chart review. Inclusions: adult males with breast cancer and stage IV metastatic disease. Exclusions: Females, stage 0-IIIC disease (excluding metastatic to brain), patients with stage IV disease at presentation, patients treated with non-endocrine treatments, patients with a co-existing primary malignancy, patients with known unselected MBC are low; however, they may be augmented when combined with chemotherapy. Methods: We conducted a single-arm, phase II study of patients with TN or endocrine-refractory MBC who were candidates for capecitabine. Patients were treated with pembrolizumab 200 mg IV day 1 and capecitabine 1000 mg PO BID days 1-14 of a 21-day cycle. The primary endpoint was progression free survival (PFS) and secondary endpoints were overall response rate (ORR), safety and tolerability. The study had 80% power to detect a 2 month (mo) improvement in mPFS with the addition of pembrolizumab over historic controls treated with capecitabine alone.

Results: Thirty patients, 16 with TN and 14 endocrine-refractory MBC, were enrolled from 2017-18. Patients had a median age of 51 years and received a median of 1 prior line of therapy for MBC. Of 29 evaluable patients, the mPFS was 4.1 mo (95% CI, 2.3-8.2 mo) and median overall survival was 15.4 mo (95% CI, 8.2-16.6 mo). ORR was 14% (n = 4), stable disease (SD) was 41% (n = 12), and clinical benefit rate (CBR = ORR + PR + SD) was 28% (n = 8). The ORR and CBR were similar between disease subtypes (ORR 13% and 14%, CBR 25% and 29% for TN and endocrine refractory, respectively). The 1-year PFS rate was 20.7% and 3 pts have ongoing responses. The most common adverse events were low grade and consistent with those expected in MBC patients including hand-foot syndrome, gastrointestinal symptoms, fatigue, and cytopenias. Toxicities at least possibly from pembrolizumab included grade 3 or 4 liver test abnormalities (7%), rash (7%), and diarrhea (3%), as well as grade 5 hepatic failure in a pt with liver metastases. Conclusions: Compared to historical control with capecitabine alone, pembrolizumab combined with capecitabine was associated with low response rates; however, some respondents had prolonged disease control. Future studies of chemo-immunotherapy in MBC with liver metastases require close safety monitoring.

Clinical trial information: NCT03044730.

1099 Poster Session (Board #180), Sun, 8:00 AM-11:00 AM
Patients with metastatic breast cancer enrolled in phase I clinical trials: Clinical outcomes and cohort trends. First Author: Jennifer Weiss. University of Colorado, Aurora, CO

Background: Phase I clinical trials have traditionally enrolled patients with advanced solid tumors and many providers perceive the likelihood of clinical benefit as low. The purpose of this study was to evaluate clinical outcomes for patients with metastatic breast cancer enrolled on Phase I clinical trials and explore differences in outcomes for patients enrolled in all-comer versus breast cancer-specific cohorts. Methods: We performed a retrospective chart review of patients with metastatic breast cancer enrolled in Phase I clinical trials at the University of Colorado Cancer Center from 2012-2018. We included trials with Phase I and/or Phase Ib in the title. Studies or cohorts enrolling patients with ≥ 3 tumor types were considered all-comer and those with enrollment restricted to breast cancer or a breast cancer subtype were considered breast cancer-specific. Results: A total of 208 patients were enrolled in Phase I clinical trials, 168 in breast cancer-specific cohorts and 40 in all-comer trials. Patients on average were 56.9 years old (range 31-79), 98.6% (205/208) female, 1.4% (3/208) male, 57.2% ER+HER2-, 30.1% ER-HER2+ and 11.1% HER2+. Patients received on average 2.1 (range 0-10) prior lines of chemotherapy in the metastatic setting. Patients enrolled on Phase I clinical trials remained on study without progression on average for 138 days (CI 95%, 112.64 to 163.91). Patients enrolled on breast cancer-specific studies remained on study for 152 days (CI 95%, 120.66 to 182.56) compared to 82 days (CI 95%, 59.43 to 105.13) for those enrolled on all-comer trials, p < 0.05. Patients went off study for disease progression (83.1%), adverse events (7.69%), and other (9.14%), including withdrawal of consent. Conclusions: Patients with metastatic breast cancer previously treated with multiple lines of chemotherapy in the metastatic setting enrolled in Phase I clinical trials received clinical benefit from treatment that is favorable compared to historical controls of late-line chemotherapy. The majority of patients were treated on breast cancer-specific cohorts consistent with trends in Phase I trial design including more tumor specific cohorts.

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A phase III study comparing trastuzumab emtansine with trastuzumab, pertuzumab, and docetaxel in elderly patients with advanced stage HER2-positive breast cancer (JCOG1607 HERB TEA study). First Author: Futoshi Yuzawa, Shimane University, Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

**Background:** Systemic chemotherapy with anti-HER2 therapy is the standard of care for HER2-positive advanced breast cancer. Patient outcomes have improved remarkably with the use of novel anti-HER2 drugs, including trastuzumab (H), pertuzumab (P), and trastuzumab-emtansine (T-DM1). The combination treatment comprising H, P, and docetaxel (DP) is highly recommended as the 1st-line treatment for patients with HER2-positive advanced breast cancer. In contrast, for elderly patients over 65 years of age, this regimen seems to be intolerable mentally and physically, and impairs their quality of life. A new standard treatment with less toxicity and non-inferior efficacy for elderly patients is needed.

**Methods:** We have planned a randomized, multicenter, open-label, phase III trial to confirm the non-inferiority of T-DM1 compared to HPD in terms of overall survival (OS) in elderly patients with HER2-positive advanced breast cancer. The eligibility criteria are as follows: 1) histologically proven metastatic breast cancer, 2) age 65-74 years with a performance status (PS) score 0-2, or 75-79 years with a PS score 0-1, 3) HER2 overexpression or amplification confirmed in primary or metastatic tissues, and 4) no anti-HER2 therapy with chemotherapy for breast cancer, excluding (neo) adjuvant therapy. Patients are randomized to receive either HPD (H 6 mg/kg, P 420 mg/body, and D 60 mg/m²) or T-DM1 3.6 mg/kg every 3 weeks. The non-inferiority margin (1.3 in terms of hazard ratio) is determined based on the data regarding safety during the first cycle. The primary endpoint is OS. The secondary endpoints are progression-free survival, response rate, adverse events, breast cancer-related death, and deterioration of activities of daily living. The trial is designed to achieve 70% power to confirm non-inferiority of T-DM1 to HPD at a 0.05 level of significance. The second cycle is defined based on the data regarding safety during the first cycle. The primary endpoint is OS. The secondary endpoints are progression-free survival, response rate, adverse events, breast cancer-related death, and deterioration of activities of daily living. The trial is designed to achieve 70% power to confirm non-inferiority of T-DM1 to HPD at a 0.05 level of significance. The second cycle is defined based on the data regarding safety during the first cycle.

**Objectives:** The primary objectives include assessment of the incidence of all-grade, non-cardiac, non-neurologic, secondary endpoints are: overall survival; disease control; duration of disease control; progression-free survival according to RECIST 1.1 criteria, by independent review. Secondary objectives include assessment of the incidence of all-grade, non-cardiac, non-neurologic, secondary endpoints are: overall survival; disease control; duration of disease control; progression-free survival according to RECIST 1.1 criteria, by independent review. Secondary objectives include assessment of the incidence of all-grade, non-cardiac, non-neurologic, secondary endpoints are: overall survival; disease control; duration of disease control; progression-free survival according to RECIST 1.1 criteria, by independent review. Secondary objectives include assessment of the incidence of all-grade, non-cardiac, non-neurologic, secondary endpoints are: overall survival; disease control; duration of disease control; progression-free survival according to RECIST 1.1 criteria, by independent review. Secondary objectives include assessment of the incidence of all-grade, non-cardiac, non-neurologic, secondary endpoints are: overall survival; disease control; duration of disease control; progression-free survival according to RECIST 1.1 criteria, by independent review. Secondary objectives include assessment of the incidence of all-grade, non-cardiac, non-neurologic, secondary endpoints are: overall survival; disease control; duration of disease control; progression-free survival according to RECIST 1.1 criteria, by independent review. Secondary objectives include assessment of the incidence of all-grade, non-cardiac, non-neurologic, secondary endpoints are: overall survival; disease control; duration of disease control; progression-free survival according to RECIST 1.1 criteria, by independent review. Secondary objectives include assessment of the incidence of all-grade, non-cardiac, non-neurologic, secondary endpoints are: overall survival; disease control; duration of disease control; progression-free survival according to RECIST 1.1 criteria, by independent review.

**Clinical trial information:** NCT037577335.

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XENERA-1: A phase II trial of xentuzumab (Xe) in combination with everolimus (Ex) in patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (mBC) and non-visceral involvement. First Author: Peter Schmid, Centre for Experimental Cancer Medicine, Barc Cancer Institute, Queen Mary University of London, London, United Kingdom

**Background:** The mTOR inhibitor Ev, combined with Ex, is a mainstay in the treatment of post-menopausal women with advanced HR+/HER2- BC. However, the activity of Ev is limited by counter-regulatory feedback mechanisms in cancer cells, involving reactivation of insulin-like growth factor (IGF)/mTOR survival signaling. Combining Ev with the humanized IGF-1 and IGF-2 ligand-blocking antibody Xe abrogates this feedback, thus intensifying inhibition of tumor growth; this leads to a pronounced effect in patients with non-visceral (e.g., bone and lymph node) metastases. The phase II XENERA-1 trial evaluated the combination of Xe with Ev and Ex in post-menopausal women with HR+/HER2- BC. **Methods:** XENERA-1 (NCT03659136) is a double-blind, placebo-controlled, randomized study to assess the efficacy and safety of Xe in combination with Ev and Ex, in post-menopausal women with HR+ and HER2- locally advanced/mBC and non-visceral disease. The population comprises post-menopausal mBC patients who have progressed on ≥1 previous line of a non-stereoidal aromatase inhibitor, with or without a CDK 4/6 inhibitor, who may have received fulvestrant. Other inclusion criteria are: an Eastern Cooperative Oncology Group Performance Status of 0 or 1; adequate organ function; and non-visceral disease (absence of brain, liver, lung, peritoneal or pleural metastases). Patients are randomized (1:1) to receive Xe (1000 mg/week, iv) or placebo (weekly, iv), in combination with Ev (10 mg/day) and Ex (25 mg/day). Treatment will continue until disease progression, unacceptable toxicity or other reasons. The primary endpoint is progression-free survival according to RECIST 1.1 criteria, by independent review. Secondary endpoints are: overall survival; disease control; duration of disease control; objective response; and time to progression of pain/intensification of palliation. Safety and pharmacokinetic endpoints, and exploratory biomarkers will also be evaluated. The first patient was enrolled in January 2019; target enrollment is 80 patients in 12 countries. Clinical trial information: NCT03659136.

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**TPS1104 Poster Session (Board #183a), Sun, 8:00 AM-11:00 AM**

**Emerald: A randomized, open label, phase III trial to evaluate the efficacy and safety of elacestrant (RAD1901) versus investigator’s choice (IC) of endocrine therapy (ET) for Her2+ advanced breast cancer (ABC) following CDK4/6 inhibitor (CDK4/6i) therapy.**

**First Author:** Aditya Bardia, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

**Background:** Estrogen receptor-positive (ER+) BC comprises ~70% of all BC and advanced/metastatic ER+ disease (mBC) remains a major clinical challenge. The addition of CDK4/6i to ET has improved progression-free survival (PFS); however, novel treatments are needed after disease progression. Putative mechanisms of endocrine resistance, such as ESR1 mutations (mESR1), also indicate the need for additional therapies. Elacestrant, an oral selective estrogen receptor degrader (SERD), demonstrated anti-tumor activity in preclinical models of ER+ BC, including models resistant to CDK4/6i and models with mESR1. An interim evaluation of a phase 1 trial (NCT02338349) of elacestrant in heavily pretreated patients (pts) with mBC, demonstrated an overall response rate (ORR) of 27% with a PFS of 5.4 mo (Bardia, SABCS, 2017). Responses were seen in pts with prior CDK4/6i and with wild-type (WT) or mESR1. Methods: This is a multicenter, international, randomized, open-label, active-controlled phase III trial for postmenopausal women or men with mBC. Pts must have received 1-2 prior lines of ET, ≤ 1 line of chemotherapy for mBC, and have documented progression on a CDK4/6i. Pts with measurable disease (RECIST v1.1) or bone-only disease are eligible. Pts are randomized 1:1 to elacestrant (400 mg orally daily) or IC of fulvestrant (600 mg q2w) or an aromatase inhibitor (AI); stratification factors include ESR1 mutation status (detected by cDNA), prior fulvestrant treatment and presence of visceral disease. The primary endpoints are PFS by blinded independent review committee (IR) in pts with mESR1 and in all pts (WT or mESR1). Secondary endpoints include: overall survival; PFS by IR; ORR by blinded investigator review; ODR, duration of response, and clinical benefit rate; safety; pharmacokinetics; and quality of life. Approximately 466 pts will be enrolled to detect 340 PFS events in all pts (power ≥90%, hazard ratio (HR) = 0.667) and 160 PFS events in the mESR1 subset (power ≥80%, HR = 0.610), overall α level at 2-sided 5% using the Hochberg procedure. The EMERALD study is open for enrollment. Clinical trial information: NCT03778931.

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**TPS1106 Poster Session (Board #184a), Sun, 8:00 AM-11:00 AM**

A phase II study of dual immune checkpoint blockade (ICB) plus androgen receptor (AR) blockade to enhance Th1-cell production and clinical benefit in metastatic breast cancer (MBC). First Author: David B. Page, Earle A. Chiles Research Institute at the Robert W. Franz Cancer Center, Portland, OR

**Background:** ICB (atezolizumab, anti-PD-L1) is known to improve survival when added to chemo, however only in PD-L1-positive, triple-negative MBC. ICB is less effective in hormone receptor positive (HR+)/ MBC or when added to following hormone therapy. Novel approaches are required to broaden clinical benefit of ICB, particularly in PD-L1-negative, HR+, or chemo-experienced MBC. Dual ICB with anti-PD-1 (nivolumab) and anti-CTLA-4 (ipilimumab) is associated with enhanced activity in melanoma other malignancies, but has not been explored extensively in MBC. Androgen receptor (AR) blockade, in addition to known direct cytostatic effects in AR-expressing MBCs (50% of TNBC, > 75% of HR+ MBC), may also modulate immune response. AR blockade has been shown experimentally to stimulate Th1-cell production of naive T-cell clones, which in turn can facilitate de novo anti-tumor immune responses. Concurrent ICB can enhance the activity of these T-cell clones by interfering with PD-1-mediated peripheral tolerance. This combination approach is promising in MBC in light of known AR positivity, and the routine use of lymphodepleting chemo regimens in the curative-intent setting. Methods: This is a phase II trial of dual immune checkpoint blockade (nivolumab 240mg IV q2w; ipilimumab 1mg/kg IV q6w) plus AR blockade (bicalutamide, 150mg PO daily, dose reduction allowed) in triple-negative MBC (cohort A: AR-positive > 1% by IHC); cohort B: AR-negative) or HR+ MBC (cohort C) in subjects who received 0/1 prior chemotherapies in the non-curative setting. Objectives include 24-week clinical benefit rate by RECIST (primary), safety (CTCAE v4.0), and other response measures (RECIST1.1, PFS, OS). Efficacy for each cohort is defined as > 20% improvement in response over historical control (30% per EMBRACE clinical trial) employing a Simon 2-stage design to minimize futility (n = 46/cohort, stage I n = 15). Thymic generation of T-cells will be measured via quantitative deep sequencing of T-cell receptors (Tcr, Immunoscope assay) and frequency of Th1-cell clones, as well as response measures of flow cytometry using surrogate cell surface markers of recent thymic emigration. Enrolment has commenced, sites: Earle A. Chiles Research Institute (Portland, OR), Memorial Sloan Kettering Cancer Center (New York, NY). Clinical trial information: NCT03650894.

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**TPS1105 Poster Session (Board #183b), Sun, 8:00 AM-11:00 AM**

**Phase 1/2 dose-escalation and expansion study investigating SAR439859 +/- palbociclib in postmenopausal women with estrogen receptor-positive (ER+)/HER2- metastatic breast cancer.**

**First Author:** Aditya Bardia, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

**Background:** Endocrine therapy +/- cyclin-dependent kinase 4/6 inhibitors, such as palbociclib, is the standard of care for ER+/HER2- breast cancer. Tumors often become resistant to this combination but retain ER signaling dependence, allowing for sequential ER-directed therapy. Unlike other currently available endocrine therapy with one mode of action, selective ER degraders (SERDs) block signaling by both ER competitive antagonism and degradation, targeting resistance settings that other treatments cannot. SAR439859 is a potent, oral SERD with improved preclinical efficacy and pharmaceutical properties vs other SERDs. This study investigates SAR439859 +/- palbociclib in postmenopausal women with ER+/HER2- metastatic breast cancer. Methods: This prospective, open-label, non-randomized Phase I/2 study (NCT03284957; TED14856) assesses SAR439859 single agent at dose levels increasing from 20 mg/day up to the maximum administered dose (Part A) followed by cohort expansion at the recommended dose (RD; Part B). The study of IIa assess two dose levels of SAR439859, in combination with palbociclib 125 mg/day (Days 1–21 in 28-day cycles; Part C) followed by cohort expansion (Part D). Postmenopausal women with ER+/HER2- metastatic breast cancer, who received ≥ 6 months of prior endocrine therapy, are eligible. Patients were permitted to have received ≤ 3 (Part A) or ≤ 1 (Parts B–D) prior chemotherapies for metastatic disease. Exclusion criteria included Eastern Cooperative Oncology Group performance status ≥ 2, concomitant illness (including those related to HIV or hepatitis and other cancers ≥ 3 years) and factors potentially affecting absorption of SAR439859 or palbociclib. Study endpoints include assessment of dose-limiting toxicities, determination of RD, confirmed ORR and PFS, and selected efficacy endpoints (including CDK4/6i-related toxicities and objective response rate according to RECIST v1.1 in dose escalation). (Parts B and D). 18FES-PET scan between Days 11–15 in Part A will assess ER availability. Safety, pharmacokinetics and response were evaluated for Parts A–D. Recruitment and screening are ongoing (Part A n = 16; B n = 18; C n = 2; D n = 0). Funding: Sanofi. Clinical trial information: NCT03778931.

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**TPS1107 Poster Session (Board #184b), Sun, 8:00 AM-11:00 AM**

**CONTESSA: A multinational, multicenter, randomized, phase III registration study comparing T and A with a reduced dose of capcetabine in patients (pts) with HER2- hormone receptor + (HR+) locally advanced or metastatic breast cancer (LA/MBC) who have previously received a taxane.**

**First Author:** Joyce O’Shaughnessy, Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX

**Background:** Chemotherapy treatments with robust efficacy that preserve quality of life are needed. T (atenolol) is a novel, oral taxane that has potential advantages over currently available taxanes, including: oral administration with a low pill burden and Q3W dosing regimen; no observed hypersensitivity reactions; preclinical evidence of CNS penetration; and improved activity against chemotherapy-resistant tumors. Over 600 pts have been treated with T in clinical studies. T had robust monotherapy activity in a Phase 2 study in 38 pts with HER2-, HR+ MBC who received T Q3W, with a confirmed ORR per RECIST 1.1 of 45% and median PFS of 5.4 mo. The confirmed ORR in taxane-pretreated pts was 45%. Preclinical and clinical studies suggest that reducing the dose of capecitabine (C) in combination with a taxane may result in reduced toxicity without reduction in efficacy. Preclinical data also suggest that T may penetrate the brain at clinically relevant concentrations. CONTESSA investigates T plus a reduced dose of C as an all-oral regimen in HER2-, HR+ LA/MBC, with revised eligibility criteria to allow inclusion of pts with CNS metastases. Methods: CONTESSA is a 600-pt, multinational, multicenter, randomized (1:1), Phase 3 registration study comparing T (27 mg/m² on Day 1 of a 21-day cycle) plus a reduced dose of C (1,650 mg/m²/day on Days 1-14 of a 21-day cycle) to the approved dose of C of Alone (2,500 mg/m²/day on Days 1-14 of a 21-day cycle) in pts with HER2-, HR+ LA/MBC previously treated with a taxane in the (neoadjuvant setting. The protocol was newly amended to allow pts with known CNS metastases. The primary endpoint is PFS assessed by an Independent Radiologic Review Committee (IRC). CONTESSA is 90% powered to detect a 42% improvement in PFS (HR = 0.57). Secondary endpoints are OS, ORR, and disease control rate. Enrollment began in Dec 2017. Following review in Jan 2019, the Independent Data Monitoring Committee recommended that the study continue as planned. Clinical trial information: NCT03326674.

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mTNBC. SGN-LIV1A, or ladiratuzumab vedotin (LV), is a novel investigational therapy for metastatic triple-negative breast cancer (mTNBC), and prognosis for this disease is very poor. Emerging treatment combinations of anti-programmed cell death 1 (PD-1) antibodies and immunotherapy are changing the landscape of metastatic breast cancer, and have shown promise in clinical trials. A phase 1 study of Ven + tamoxifen demonstrated safety and an efficacy signal in ER+, HER2+ metastatic breast cancer (mBC). Preclinical data for Ven + fulvestrant (Ful) have also shown synergy. Based on these proof-of-principle data, the current study evaluates safety and efficacy of Ven + Ful in women with ER+, HER2– locally advanced (LA) or mBC progressing after first- or second-line of prior therapy for metastatic disease, including ≥8 wks of a CDK4/6 inhibitor. METHODS: VERONICA is a global, randomized, phase 2, multicenter, open-label study. Eligible patients aged ⩾18 yrs with confirmed ER+, HER2–, inoperable LA/mBC, ≥1 measurable lesion, tissue evaluable for BCL2, and ECOG performance status 0–1. Prior Ful or Ven, or prior chemotherapy for LA/mBC are prohibited. Stratified by BCL2 expression (low vs high) and number of prior lines of mBC therapy (1 vs 2), pts in randomized 1:1 to Ven 800 mg PO daily + Ful 500 mg IM cycle 1 days 1 and 15, and day 1 of each subsequent 28-day cycle or to Ful 500 mg IM alone. Treatment continues until disease progression or intolerability occurs. Primary endpoint is clinical benefit rate defined as complete/partial response + stable disease for ≥24 wks from randomization. Secondary efficacy endpoints include objective response rate, duration of response, progression-free survival, overall survival, safety, pharmacokinetic, biomarker (e.g. BCL2 and PD1K expression) and patient-reported outcome analyses will also be conducted. Currently, 21 of the planned 100 pts have been enrolled; enrollment is ongoing. Clinical trial information: NCT03384009.

A phase II trial of olaparib and durvalumab in metastatic BRCA wild type triple-negative breast cancer. First Author: Zahi Ibrahim Mitri, Oregon Health & Science University, Portland, OR

Background: There is an urgent need to develop novel non chemotherapy treatments for metastatic triple negative breast cancer (mTNBC) patients who otherwise have a poor prognosis. Immune checkpoint blockade (ICB) and PARP inhibitors (PARPi) have independently shown promise for the treatment of mTNBC, and the combination has shown early benefit in the Meet The Challenge and TOPACO trials. This trial looks to investigate the first-in-human combination of the PARPi olaparib and the PD-L1 inhibitor durvalumab, and 2) perform extensive multi-omics including protein based image analytics (multiplex IHC, cyclic immunofluorescence) on serial biopsies to identify predictive biomarkers and resistance mechanisms. METHODS: Trial Design: This is a single-arm phase II study to assess the efficacy of the combination of olaparib and durvalumab in BRCA-wildtype mTNBC. mTNBC participants will undergo a pre-treatment biopsy, then will start a 4 week induction treatment with olaparib (300 mg PO BID). At the end of 4 weeks of single agent therapy, participants will undergo a repeat on-treatment biopsy, following which durvalumab (1500 mg IV every 4 weeks) will be added to olaparib. Participants will also be offered an optional biopsy on progression. Endpoints: The primary endpoint of this study is overall response rate (ORR) to olaparib and durvalumab therapy. Secondary efficacy endpoints include clinical benefit rate, duration of response, progression-free, and overall survival. The incidence and severity of on-treatment adverse events will be collected per CTCAE 5.0. Statistical Methods: 28 participants are planned for enrollment to this study. A 2-stage analysis will be performed using a Simon 2-stage Minimax design. The null (ICB alone) and alternative (ICB + PARPi) hypotheses are: H0: HR = 0.15 and Ha: HR = 0.35. For the primary endpoint, a total sample size of 28 participants will achieve 80% power to detect the ORR difference of 0.20 with one-sided type I error = 0.05. The trial will be terminated in stage I if 2 or less of the first 15 participants respond. If the trial goes on to stage II, a total of 28 participants will be studied. If the total number responding is less than or equal to 7, the combination is rejected. Current Enrollment: The study was activated 1/17/2019. To date, 3 out of 15 patients have been accrued to stage I of the study Clinical trial information: NCT03801369.
**Ola monotherapy in patients (pts) with metastatic, triple-negative breast cancer (TNBC).** First Author: Andrew Tutt, King’s College London School of Medicine, London, United Kingdom

**Background:** TNBC comprises ~15% of invasive breast cancer cases and alterations in BRCA1/2 are associated with ~5% of all BCs. Ola (a poly ADP-ribose polymerase inhibitor [PARPi]) is approved for treating pts with HER2-negative metastatic BC with a germline BRCA mutation (gBRCAm), demonstrating an improvement in progression-free survival (PFS) vs placebo. However, in pts with other non-BRCA1/2 homologous recombination repair (HRR)-related genes (non-BRCA HRRm) may also confer sensitivity to Ola therapy in pts with TNBC. Ola, AZD1775 (a WEE1 checkpoint inhibitor) and AZD6738 (an ataxia telangiectasia and Rad3-related protein inhibitor) target DNA repair and cell cycle regulation. Preclinical studies in TNBC models show synergistic antitumor effects of Ola+AZD1775 and Ola+AZD6738, vs Ola monotherapy supporting the clinical evaluation of these combinations.

**Methods:** VIOLETTE is a global, multicenter, open-label, phase II study (NCT03330847) randomising 1:1:1:1 450 pts with advanced TNBC to 3 treatment arms: 1) Ola 200 mg bid daily + AZD1775 150 mg bid on Days 1, 10 q21, 2) Ola 300 mg bid daily + AZD6738 160 mg OD 1-q28, or 3) Ola 300 mg bid daily q28. All pts will be stratified by prior platinum exposure. Each treatment arm of 150 pts will be comprised of 3 biomarker strata of ~50 pts each (A: BRCAm; B: non-BRCA HRRm; C: non-HRRm). Centralized tumor molecular testing will be deployed to detect mutation(s) in the HRR genes. Eligible pts will have received 1-2 prior lines of chemotherapy for metastatic disease, including an anthracycline or taxane. Exclusion criteria include prior PARPi therapy. The primary endpoint is PFS (each combination vs Ola alone) assessed by blinded, independent central review (RECIST v1.1). Secondary endpoints are objective response rate, clinical benefit rate and OS. The exploratory endpoints include prior PARPi therapy. Subjects deriving clinical benefit (CR / PR / SD) from platinum-based therapy will be eligible and randomized in a 1:1 ratio. Patients in arm 1 will receive olaparib orally 300mg CID continuously and in arm 2 will receive olaparib orally 300mg CID continuously in combination with durvalumab 1500mg IV every 4 weeks. Assessment of tumor response will be done every 8 weeks. Primary endpoint: progression-free survival. Secondary endpoints: overall survival, clinical benefit rate, safety. Correlative analyses: pre-treatment archival/fresh biopsy samples are mandated. Post-treatment tissue biopsy is requested. Serial ctDNA will be collected at baseline, staging, and before the first dose of study drug. Tumor response to correlation with response and track emerging genomic alterations in a platinum sensitive cohort under the pressure of PARP inhibition. Whole exome DNA sequencing, IHC for PDL-1 and TILs will be performed on tissue samples. ClinicalTrials.gov Identifier: NCT03167619. (Moore K, et al “SOLO-1: Phase III trial of maintenance olaparib following platinum-based chemotherapy in newly diagnosed patients with advanced ovarian cancer and a BRCA1/2 mutation” ESMO 2018; Abstract LBA7-PR). Clinical trial information: NCT03330847.

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**A randomized phase II study of nab-paclitaxel combined with durvalumab and/or nivolumab for metastatic breast cancer (mTNBC).** First Author: Leonel Fernando Hernandez-Aya, Division of Medical Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, MO

**Background:** mTNBC is associated with poor outcomes and lacks targeted therapies. Immune modulation with PD-1/L1 inhibitors are emerging as effective anticancer therapies. In mTNBC, atezolizumab (anti-PD-L1) plus nab-paclitaxel demonstrated an improvement in PFS compared to nab-paclitaxel alone. Cancer vaccines targeting neoantigens may enhance the activity of immune checkpoint inhibition (ICI). Neoantigens are targets for CD8 T-cells following ICI. T-cell responses to neoantigens are high in affinity and are not limited by central mechanisms of self-tolerance. Next-generation sequencing and epitope prediction algorithms are used to identify/prioritize neoantigens for vaccine design and development. Preclinical studies have shown that neoantigen vaccines are well tolerated and may be synergistic with anti-PD-1/L1 therapy.

**Methods:** Eligible mTNBC patients are randomized to either Arm-1 (nab-paclitaxel + durvalumab + neoantigen vaccine) or Arm-2 (nab-paclitaxel + durvalumab). Initially, all participants are treated with a run-in of gemcitabine + carboplatin (18-weeks; Part A). During this time sequencing and neoantigen vaccine production is performed. Subsequently, pts are treated with nab-paclitaxel + durvalumab + neoantigen vaccine vs. nab-paclitaxel + durvalumab (Part B). The neoantigen vaccine is given subcutaneously. Participants in Arm 1 receive vaccinations on Days 1, 4, 8, 15, 22, 50 and 78. Durvalumab is administered at 1500 mg IV every 4 weeks. Nab-paclitaxel is administered at 100 mg/m2 IV on Days 1, 8, and 15 of each 28-day cycle. Key eligibility criteria include patients with newly diagnosed mTNBC, measurable disease, and tumor accessible for biopsy. The primary endpoint is DFS defined as time from the initiation of Part B to progression or death. Secondary endpoints include safety, objective response rate, clinical benefit rate and OS. The exploratory endpoints include evaluating the immune response induced by the neoantigen vaccine, investigating biomarkers of response including TILs, PD-L1, and immune signature by gene expression and mutational landscape. This trial is currently recruiting patients (NCT03606967).
TPS1116 Poster Session (Board #189a), Sun, 8:00 AM-11:00 AM

KX-ORAX-001: An open label, randomized, multicenter, phase III registrational study to determine the safety, tolerability, and tumor response of oraxol (HM30181A + oral paclitaxel) and its comparability to IV paclitaxel in patients with metastatic breast cancer (MBC). First Author: Gerardo Antonio Umanzor Funez, DEMEDICA, San Pedro Sula, Honduras

Background: Paclitaxel is used in multiple cancer types including the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within six months of adjuvant chemotherapy. Due to poor oral absorption, paclitaxel is administered IV and is associated with extra administration costs, inconvenience, burden for the patient, and hypersensitivity reactions to the solubilizing agent Cremophor EL. HM30181A is an intestinal P-gp pump blocker that, when administered orally with paclitaxel capsules (Oraxol), enhances paclitaxel absorption. Interim data from a phase I crossover study showed Oraxol (15-mg HM30181A + 205 mg/m²) 3 days/week had similar AUC₀₋₅₆ to IV paclitaxel 80 mg/m² over 1 hour (Oraxol 5078 ng·hr/mL vs. IV paclitaxel 5652 ng·hr/mL), however the Cmax was substantially lower with Oraxol which may result in lower incidence of neuropathy. In a phase II single arm study of Oraxol in MBC 45.8% and 41.7% of subjects had PR or SD according to RECIST 1.1. Methods: KX-ORAX-001 is a multi-national open-label, randomized (2:1 Oraxol to IV paclitaxel) phase III registration study comparing Oraxol (15-mg HM30181A + paclitaxel 205 mg/m² daily x 3 days QW) to IV paclitaxel 175 mg/m² over 3 hours every third week, in female patients with histologically- or cytologically-confirmed MBC for whom treatment with IV paclitaxel monotherapy has been recommended. The study is powered to demonstrate the superiority of Oraxol on confirmed tumor response rate vs IV Paclitaxel 1795mg/m² q3weeks. The primary efficacy endpoint is confirmed tumor response according to a blinded central radiologist using RECIST 1.1 criteria. The study is designed to enroll approximately 360 evaluable subjects. Two interim DSMB reviews were conducted at approximately 90 and 180 evaluable subjects for safety, futility, and efficacy. Enrollment was initiated Dec 2015 at 45 sites in Central and South America and enrollment has been completed. At final analysis, if there is an approximate difference of ≥10% favoring Oraxol, a p-value of 0.045 (2-tailed) will be achieved. Secondary endpoints are PFS and OS. Clinical trial information: NCT02994371.

TPS1117 Poster Session (Board #189b), Sun, 8:00 AM-11:00 AM

NRG-BR002: A phase IIIR/III trial of standard of care therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical ablation for newly oligometastatic breast cancer (NCT02364557). First Author: Steven J. Chmura, The University of Chicago Medicine, Chicago, IL

Background: This is a randomized Phase II/III trial to evaluate if stereotactic body radiotherapy (SBRT) and/or surgical resection (SR) of all metastatic sites in newly oligo-metastatic breast cancer who have received up to 12 months of first line systemic therapy without progression will significantly improve median progression free survival (PFS). If this aim is met the trial continues as a phase III to evaluate if SBRT/SR improves 5 year overall survival. Secondary aims include local control in the metastatic site, new distant metastatic rate, and technical quality. Translational primary endpoint is to determine whether < 5 CTCs is an independent prognostic marker for improved PFS and OS. Methods: Women with pathologically confirmed metastatic breast cancer to ≤ 4 sites who have been diagnosed within 365 days with metastatic disease and the primary tumor site disease is controlled. CNS metastases are ineligible. ER/PR and HER-2 neu status is required. Site radiation credentialing with a facility questionnaire and pre-treatment review of first case is required. Randomization is to standard systemic therapy with local radiotherapy/surgery for palliation when necessary versus ablative therapy of all metastases with SBRT and/or SR. For the phase IIIR portion to detect a signal for improved median PFS from 10.5 months to 19 months with 95% power and a 1-sided alpha of 0.15 and accounting for ineligible/lost patients, 128 patients will be required. For the Phase III, an additional 232 patients will be required to definitively determine if ablative therapy improves 5-year overall survival from 28% to 42.5% (HR=0.67), with 85% power and a one-sided type I error of 0.025. For the translational research assuming a two-sided probability of type I error of 0.05, the number of patients accrued in the Phase II-R and Phase III portions will provide sufficient power of at least 91% and 93% to detect whether < 5 CTC’s is prognostic for PFS and OS, respectively. Present accrual (1-31-2019): 105. Contact Information: Protocol: CTSU member web site https://www.ctsu.org. Enrollment: OPEN at https://open.ctsu.org. Support: This project is supported by NRG Oncology grants U10CA180868 and U10CA180822 from the National Cancer Institute (NCI). Translational science is supported by the Ludwig Foundation for Cancer Research. Clinical trial information: NCT02364557.
1502 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Effect modifiers in a randomized phase III trial of low-dose tamoxifen in breast preinvasive disease. First Author: Andrea De Censi, Division of Medical Oncology, E. O. Attanasio Hospital, Salerno, Italy

Background: Low-dose tamoxifen (babymam) at 5 mg/day for 3 years decreases local or contralateral recurrence by 52% in women with hormone sensitive breast pre-invasive neoplasia after surgery (DeCensi et al JCO 2019). Here we report the results of exploratory analyses to assess whether the benefit of babymam varies among subgroups of patients defined by individual characteristics. Methods: Post-hoc subgroup analyses were performed according to a mixed approach based on stratification, biomarker, and biological plausibility. Incidence of invasive breast cancer or DCIS was the primary endpoint. HRs were estimated using Cox proportional-hazards modeling. Results: Age at menopause, smoking status and Ki-67 exhibited a significant interaction with treatment. Specifically, the effect of babymam was greater in women aged ≥ 50y (n = 293, HR = 0.27, 95%CI: 0.10-0.73) than in women aged < 50y (n = 207, HR = 0.86, 0.35-2.07), p-interaction = .09. Never smokers (n = 307) had a greater benefit than former (n = 68) or current smokers (n = 97): HR = 0.28, 0.11-0.50 vs HR = 0.57, 0.39-0.78 vs HR = 1.51, 1.04-2.24, respectively (p < .05). Tumors with Ki-67 above the median level of 10% (n = 133) had a greater effect (HR = 0.27, 0.09-0.81) than Ki-67 ≤ 10% (n = 145, HR = 1.58, 0.54-5.60, p = .04). Weaker statistical interactions (p > .1) were also found for waist circumference and hot flashes (HF) at baseline. Women with waist circumference ≥89 cm (metabolic syndrome, n = 208) had a greater effect (HR = 0.22, 0.07-0.78) than women < 89 cm (n = 162, HR = 0.57, 0.30-1.08; p = .04). Additional subgroups according to obesity, family history of breast cancer, hormone use, alcohol use, extent of surgery, radiotherapy, PRS were less inclined, and HER2 expression, positive margins and treatment compliance showed no significant heterogeneity of treatment. Conclusions: Exploratory analyses showed a trend to a higher effect of babymam in women aged 50 or older, never smokers, women with hot flashes or abdominal obesity and tumours with Ki-67 above the median. Our results provide insight into the efficacy of babymam towards a personalized preventive approach. Clinical trial information: NCT01357772.

1501 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Impact of a breast cancer (BC) polygenic risk score (PRS) on the decision to take preventive endocrine therapy (ET). The Genetic Risk Estimate (GENRE) trial. First Author: Julian Hertrampf, Dept of Radiation Oncology, CancerCare Manitoba, Winnipeg, MB, Canada

Background: Despite BC risk reduction of 50-65% by preventive endocrine therapy (ET), very few at-risk women choose to take them. A woman’s perceived BC risk correlates with uptake of ET. A PRS comprised of 77 BC genetic susceptibility loci (Single Nucleotide Polymorphisms (SNP)) improves the accuracy of risk prediction for BC. We examined the impact of the addition of risk individualized for for standard risk calculator estimates on intent to take BC prevention medication. Methods: Eligible women had ≥5% 10y BC Tyrer-Cuzick risk (IBIS) or 5 year Gail score ≥3%, with no history of BC or hereditary BC syndrome. Standard BC risk estimates (IBIS or Gail) were incorporated into the counselling on BC preventive ET. A self-reported questionnaire at baseline quantified intention to take ET and explored factors associated with this decision. Blood samples were obtained and genotyped for 77 SNPs, individualized PRS were calculated then incorporated into IBIS and Gail predictions for 5y, 10y, & lifetime BC risk. At a second visit, PRS risk & prevention recommendations were revisited. Post-hoc questionnaire assessed change in intent to take ET. Multivariable linear regression was performed to assess impact of baseline variables on change in intent to take medication. Results: From 2016 to 2017, 151 women in Canada & USA were enrolled, median age: 56.1 (range 36-74, 6.5% were non-white). PRS increased BC risk estimates in 84 (55.6%) and reduced BC risk estimates in 67 (44%) women. After PRS risk counselling, intention to take ET significantly changed (p < .0001): 41.9% of those with increased PRS were more inclined, and 46.7% of women with decreased PRS were less inclined to take ET. PRS increased BC risk estimates in 85 (55.6%) and less concern about ET side effects (p < .0001) were associated with greater intent to take ET. Conclusions: In high-risk women, PRS significantly changed BC risk estimates & intent to take preventive ET. Further assessments of the impact of PRS scores on compliance with ET are warranted. Clinical trial information: NCT02517953.

1503 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Risk of subsequent cancer diagnosis in patients treated with 3D conformal, intensity modulated, or proton beam radiation therapy. First Author: Michael H. Xiang, Department of Radiation Oncology, Stanford University, Stanford, CA

Background: Approximately half of cancer patients receive radiation therapy (RT). Modern RT modalities (3D conformal [3DCRT], intensity modulated [IMRT], proton beam [PBRT]) have been theorized to pose different risks of second cancers, but the relationship between RT modality and subsequent cancers has been unclear due to their rarity. Methods: Pediatric and adult patients with a first cancer diagnosis who received 3DCRT, IMRT, or PBRT were identified in the National Cancer Database. To analyze a more uniform population, cases were required to be non-metastatic and have at least 2 years of follow-up time. Ten cancer types were included: head/neck, upper gastrointestinal (GI), lower GI, gynecological, lymphoma, non-small cell lung, prostate, breast, bone/soft tissue, and brain/central nervous system. Diagnosis of a subsequent cancer was determined using a variable denoting the sequence of malignant neoplasms over the lifetime of the patient. The risk of subsequent cancer diagnosis was modeled using multivariable logistic regression adjusting for age, follow-up time, cancer type, RT dose, chemotherapy, and other factors. Propensity score matching was additionally used to balance baseline characteristics. Results: In total, 430,866 patients were included (33.4% 3DCRT, 65.1% IMRT, 1.5% PBRT) with median follow-up of 5.0 years and total follow-up period of 2.35 million person-years. In the comparison of IMRT relative to 3DCRT, there was no difference in the risk of subsequent cancer diagnosis (adjusted odds ratio [OR] 1.01; 95% confidence interval [CI] 0.98-1.03; p = 0.62). In contrast, recipients of PBRT had significantly lower risk of subsequent cancer diagnosis relative to IMRT (adjusted OR 0.31; 95% CI 0.26-0.37; p < 0.0001). The benefit associated with PBRT persisted in sensitivity analyses that excluded patients with prostate cancer (71.6% of the PBRT cases), receipt of chemotherapy, and/or follow-up time less than 5 years. Conclusions: Risk of subsequent cancer diagnosis was similar between IMRT and 3DCRT and significantly lower for PBRT. PBRT may be preferred in situations where avoidance of second cancers is paramount, such as pediatrics and young adults.
Breast radiotherapy among ATM-mutation carriers. First Author: Leslie A. Modlin, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** Syndromes of DNA repair deficiency may confer both cancer predisposition and increased sensitivity to DNA damaging agents, such as ionizing radiation. Whereas homologous deficiency of ATM causes ataxia telangiectasia syndrome, heterozygous ATM mutation carriers exhibit increased rates of breast, pancreas and prostate cancers. ATM repairs DNA double-strand breaks; consequently, mutation carriers may exhibit excessive radiotherapeutic (RT) toxicity. We evaluated the tolerability of adjuvant breast radiation in ATM mutation carriers. **Methods:** We identified 167 ATM mutation carriers presenting to our institution with breast cancer; of these, 91 received RT and records were reviewed for RT-related morbidity. Toxicities were graded per CTCAE v5. Associations of clinicopathologic features with toxicity were evaluated by multivariate regression. **Results:** Of 91 ATM mutation carriers receiving breast RT, 31% (n = 28) harbored a pathogenic mutation whereas 69% (n = 63) harbored variants of uncertain significance (VUS). 71% (n = 65) underwent lumpectomy and adjuvant whole-breast RT; 29% (n = 26) had mastectomy and PMRT. Nine patients underwent bilateral RT for a total of 100 RT courses. 86% of RT courses comprised whole-breast/chest-wall tangents; 14% were VMAT or CMS. Median tangent dose was 50Gy; 62% included an additional boost (median 100Gy) and 48% used a bolus (median thickness 0.3cm). Lymph nodes were treated in 43% (n = 39). At last on-treatment visit, 31% had grade 2 dermatitis, 4% had other grade 2 events (fatigue, seroma, decreased range of motion, or pain), and 1% had grade 3 dermatitis. At last follow-up, 13% grade 1, 13% grade 2A lymphedema (n = 3), and grade 2 (n = 1) or 3 (n = 2) capsular contracture. At last follow-up, 4 PMRT patients had capsular contracture (3 with grade 2, 1 with grade 3); 1 patient had grade 2b lymphedema. Overall, no patients had significant (grade ≥2) telangiectasias, fibrosis, or fat necrosis; no grade 4 or 5 toxicities occurred. Sixteen toxicities were associated with acute or late RT toxicities. **Conclusions:** We found no evidence of excess breast radiation toxicity among ATM mutation carriers, either pathogenic or VUS. Breast conserving therapy can be safely considered in this population.

Ten-fold increase in genetic testing in pancreatic and metastatic prostate cancer with implementation of genomics testing. First Author: Heather Symecko, Basser Center for BRCA, University of Pennsylvania, Philadelphia, PA

**Background:** Germline genetic testing (GT) for cancer susceptibility is recommended for pancreatic and advanced prostate cancer patients, due to potential implications for targeted therapies and risk assessment of family members. Traditional cancer GT programs may create barriers for certain patient populations. To more effectively integrate testing into standard oncology care POC GT was introduced in early 2018 in a joint protocol with Memorial Sloan Kettering Cancer Center. Here we report pre and post POC referral and testing numbers at the University of Pennsylvania. **Methods:** Patients with metastatic prostate or pancreatic cancer were ascertained through their GU/GI oncologist onto an IRB approved protocol and shown an educational video about GT by research staff who obtained informed consent and facilitated biospecimen collection. Genetic counselors returned results and provided post-test counseling by phone. To evaluate the impact of this model on the uptake of GT services, the number of patients who were referred to and proceeded with GT was compared before and after study initiation. **Results:** In 2017, 77 patients were referred to genetics of which 45 underwent genetic counseling and testing. Twenty-nine (38%) did not complete genetic counseling or testing, and 3 later underwent testing through the POC study. Since the study launched in 2018, 407 patients were referred and underwent testing through the study. This represents a ten-fold increase in patients who underwent GT. **Conclusions:** Comparing uptake of GT services before and after study initiation suggests that a POC model with abbreviated pre-test education and post-test genetic counseling by phone is a possible solution to barriers of traditional genetic counseling, increasing physician referrals and uptake of testing by patients. This approach allows for more timely access to genetic information that may impact treatment strategies and medical management of family members. Clinical trial information: pending.

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Inherited DNA repair and cell cycle gene defects in chronic lymphocytic leukemia. First Author: Nicholas S. Moore, Dana-Farber Cancer Institute, Boston, MA

Background: Chronic lymphocytic leukemia (CLL) is among the most heritable cancers, with 60% of disease risk genetically determined. However, most of the genetic heritability of CLL remains unexplained. Previously, we identified ATM as the first CLL risk gene. Here, we leverage a deep-learning-based germline variant calling algorithm to evaluate the role of germline enrichment in DNA repair and cell cycle genes in CLL. Methods: A two-stage case-control analysis was conducted using gene-based mutational enrichment analysis of 50 established cancer predisposition DNA repair and cell cycle genes. In the discovery phase, a total of 285 Spanish patients and 5,608 ancestry-matched controls were evaluated. In the validation stage, an independent cohort of 514 European patients and 27,173 ancestry-matched controls were analyzed. An FDR correction was applied to both datasets and genes with a q-value < 0.2 in both cohorts were considered significant. Results: Our joint analysis of 799 CLL patients from 2 genetically distinct cohorts and 32,781 ancestry-matched cancer-free controls identified ATM and CHEK2 as significantly enriched in both CLL datasets. First, our analysis recapitulated the previously reported finding of ATM variant enrichment in CLL patients. Carriers of pathogenic ATM mutations in our cohorts (n = 9 patients, discovery: 1.05%, validation: 1.17%) were 2.8–3.7 times more likely to harbor ATM germline mutations compared to CLL controls (discovery: OR = 2.8, 95%CI = 0.7–9.0, q-value = 0.181; validation: OR = 3.7, 95%CI = 1.6–8.3, q-value = 0.0454). In addition, our analysis identified 21 CLL patients carrying pathogenic CHEK2 alterations (discovery: 1.40%, validation: 3.31%), making CHEK2 a potentially novel CLL predisposition gene. CHEK2 alterations were more frequent in cases compared to controls (discovery: 8.0, 95%CI = 2.3–27.0, q-value = 0.026; validation: OR = 4.4, 95%CI = 2.5–7.3, q-value < 0.001). Conclusions: Our analysis of genetically distinct CLL cohorts, using a high-sensitivity variant calling algorithm, supports CHEK2 as a potentially novel and cell cycle regulation pathways as a potential driver of CLL susceptibility.

Antiviral therapy to reduce hepatocellular carcinoma recurrence in patients with low HBV-DNA levels: A randomized controlled trial. First Author: Gang Huang, Eastern Hepatobiliary Surgery Hospital, National Innovation Alliance for Hepatitis and Liver Cancer, Shanghai, China

Background: Despite antiviral treatment has been shown to reduce hepatocellular carcinoma (HCC) recurrence after curative treatment for hepatitis B virus (HBV) related HCC, its effect on patients with high baseline HBV-DNA levels is still unclear. This study aimed to assess the effect of antiviral therapy on HCC recurrence in patients with low preoperative HBV-DNA levels. Methods: In this randomized controlled trial, 200 patients who underwent curative resection for HCC with low baseline HBV-DNA levels were randomly assigned to receive preemptive antiviral therapy or not. The primary endpoints were recurrence-free survival. The study was censored on March 31, 2015 when all surviving patients had a minimum follow-up of 60 months. The analysis was done on an intention-to-treat basis. Results: The baseline clinical, laboratory, and tumor characteristics of the 2 groups were comparable. The 1-, 3-, and 5-year recurrence-free survival rates for the antiviral group and the control group were 85.9%, 55.2%, and 52.0% and 80.6%, 40.9%, and 32.3%, respectively. The corresponding overall survival rates for the 2 groups were 94.0%, 75.7%, and 64.1% and 90.0%, 62.4%, and 43.7%, respectively. The recurrence-free survival and overall survival for the antiviral group were significantly better than the control group (P = 0.016, P = 0.004, respectively). After adjusting for confounding prognostic factors in a Cox model, the relative risks of recurrence and death for antiviral treatment were 0.601 (95% confidence interval (CI), 0.409–0.884; P = 0.001) and 0.509 (95% CI, 0.333–0.778, P = 0.002), respectively. Antiviral therapy was an independent protective factor of late tumor recur- rence (hazard ratio = 0.601). In patients with low preoperative HBV-DNA levels, antiviral therapy significantly reduced HCC recurrence after R0 hepatic resection. Clinical trial information: ChiCTR-IPR-15069587

Effect of germline ATM mutations on clonal hematopoiesis. First Author: Thomas Paul Slavin, City of Hope, Duarte, CA

Background: Clonal hematopoiesis (CH) in myeloid-related genes is associated with development of primary and secondary leukemia and athero- sclerotic disease, as well as, decreased overall survival. Identification of factors beyond age and cytotoxic exposures that predispose to CH may be useful to both recognize individuals at increased risk for CH and to better understand how CH develops. We have previously shown that germline mutations in the DNA repair gene ATM may predispose to CH. We hypothesized here that heterozygous ATM germline mutation carriers would have higher rates of CH in myeloid genes compared to controls. Methods: Germline DNA samples from 34 heterozygous ATM germline mutation carriers (cases) and 22 controls without ATM germline mutations were sequenced on an Illumina 2500 using a custom 79-gene-myeloid-CH-coding-exon-amplicon-based Qseq panel. Read depth averaged 130x. Pathogenic and likely pathogenic CH variants (PV) above an allele fraction of 2% were used for analyses. Cases and controls were compared using a rank-sum test. Results: Cases had a higher median age (56 years, range 30–82) than controls (48 years, range 5–72). Cases and controls were similar in solid tumor cancer history and known exposure to cancer cytotoxic therapy: 73.5% vs 86.4%, and 18.1 vs 20.6%, respectively. The number of CH PV was similarly associated with age in both cases and controls (cor = 0.31, p = 0.01). Cases had significantly higher CH PVs than control cases (discovery: 2 PVs vs 0, p = 10^-6). Of note, cases frequently had a concomitant second (n = 10; 29% of cases) or third (n = 4; 11.8% of cases) unique ATM CH PV, whereas no ATM CH PVs were seen in controls. Even after excluding ATM CH PVs, CH PVs were more frequent in cases (p = 0.00003). After ATMCH PVs, the most frequent CH PVs were in DNA repair genes such as CHEK2 (5 PVs), BCORL1 (5 PVs), and DMNT3A (4 PVs). Conclusions: Our study supports ATM as a strong predisposition locus for myeloid gene CH. CH in ATM germline mutation carriers frequently involved unique low allele fraction PVs in ATM, suggesting ATM CH PVs are driving production of likely bi-allelic ATM inactivation in white blood cells, potentially contributing to late age onset of late age ATM loss. Complete ATM loss may be a nusus particularly for lymphocytic leukemia, as bi-allelic ATM inactivation is a frequent somatic finding.

Characterization and clinical outcomes of mismatch repair deficient (dMMR) small bowel adenocarcinoma (SBA). First Author: Alicia Latham, Memorial Sloan Kettering Cancer Center, New York, NY

Background: SBA is a rare cancer known to be associated with Lynch syndrome (LS). The prevalence, tumor characteristics, and clinical course of SBAs in the setting of LS is not well understood. We sought to characterize SBAs in SBA with LS and assess its association with LS phenotype and clinical outcomes. Methods: A retrospective review of SBAs at a single institution identified 74 SBAs that were assessed for dMMR either via immunohistochemical staining (IHC) or microsatellite instability status (MSI) using NGS. Germline DNA was analyzed for mutations in LS-associated mismatch repair genes (MLH1, MSH2, MSH6, PMS2, EPAC1) and when available, clinical records were reviewed. Results: Of 74 individuals with SBA, 28.4% (21/74) of tumors exhibited dMMR and/or high-frequency MSI (MSI-H). The overall prevalence of LS in SBA was 9.5% (7/74), with all LS patients having dMMR/MSI-H tumors. 33.3% (7/21) of dMMR/MSI-H SBA patients had LS. The distribution of germline mutations among LS patients was 57.1% (4/7) in MLH1, 28.6% (2/7) in MSH2, and 14.3% (1/7) in PMS2. One patient with an dMMR/MSI-H tumor was found to have a high-penetrance APC mutation, diagnostic of familial adenomatous polyposis (FAP). In the 38 patients with available clinical follow-up, median age of onset was similar in the dMMR/MSI-H vs the pMMR/MS group (62 vs 57, p = 0.8). The prevalence of synchronous/metachronous cancers (5.9% (1/17) in the pMMR/MS group and 38% (8/21) in the dMMR/MSI-H group (p = 0.02), with 62.5% (5/8) of these in LS (p = 0.001; synchronous/ metachronous in LS (5/7) vs. non-LS (4/31)). In the pMMR/MS group, 5/8 (62.5%) of patients relapsed with metastatic disease at diagnosis, compared to 19% (4/21) in the dMMR/MSI-H group (p = 0.01). In dMMR/MSI-H SBA patients with early-stage disease, 11.8% (2/17) recurred, compared to 71.4% (5/7) in the pMMR/MS group (p = 0.009). Conclusions: This preliminary evaluation suggests that SBA exhibiting dMMR/MSI-H status is associated with increased early clinical stage and lower recurrence rates, similar to prior observations in colon cancer. LS was found in 9.5% of all SBA and in 33.3% of dMMR/MSI-H tumors, suggesting that germline assessment for LS in SBA is warranted.
New onset diabetes as a predictive factor of focal lesions in the pancreas in a high-risk screening program. First Author: Maria Fernanda Montiel, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Genetic evolution studies have suggested the existence of a window of opportunity to improve clinical outcomes by intercepting pre-malignant lesions. This study reports the outcomes of Pancreatic Cancer (PC) surveillance in a high-risk (HR) cohort for 4 years. The University of Texas MD Anderson Cancer Center (MDA) between 2014 and 2018. Methods: The MDA PC High-Risk Clinic (MDA-PCHRC) performs surveillance based on risk stratification. This study reports 54 months of surveillance. The patients were stratified based on PC family history, personal history of other cancers, and germline mutations in known breast cancer predisposition genes. Results: A total of 206 patients were referred by our clinic during this time period. From this group, 126 (61%) patients completed at least one cycle of baseline surveillance, for the purposes of the analysis we only focus in the high risk (n=71) and moderate risk group (n=38). We have identified de novo pancreatic focal lesions in 22 patients, 20 from the high-risk group (28%) and 2 from the moderate risk group (5%). Of these focal lesions included 7 patients with simple cysts, 9 with side-branch IPMN, 3 with main duct IPMN, 1 with pseudocyst, 1 with mucinous cyst and 1 with a solid nodule (pancreatic neuroendocrine tumor). We compared demographic information (age, gender, and ethnicity) as well as family and personal history between patients with focal pancreatic lesions vs negative or diffuse findings. We found that new onset diabetes was significantly correlated with presence of focal pancreatic lesions (5.22%) of patients with focal lesions versus patients without focal lesion 2 (2%) (P<0.003). Conclusions: Screening at the MDA-PCHRC detect pancreatic premalignant lesions in 20% of the patients in our cohort. We validated our risk stratification methodology and found that new-onset diabetes is predictive of pancreatic lesions, thus suggesting that this factor could be an important biomarker of focal lesions in a HR population.

1514 Poster Discussion Session: Displayed in Poster Session (Board #8), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Racial and ethnic differences in the results of mutigene panel testing of inherited cancer predisposition genes in breast cancer patients. First Author: Siddhartha Yadav, Mayo Clinic, Rochester, MN

Background: The prevalence of germline mutations in non-white patients with breast cancer and the germline genetic drivers of breast cancer risk in non-white populations are largely unknown. Methods: The study population included 1,400 patients with breast cancer. These patients were selected from Black: 6,722; Asian: 4,183; Hispanic: 5,194; Ashkenazi-Jewish: 4,798) who underwent germline mutigene panel testing of genetic predisposition genes from March 2012 to December 2016. The prevalence of predisposition gene mutations in racial and ethnic populations relative to non-Hispanic Whites was assessed while accounting for age at diagnosis of breast cancer, family history of breast and ovarian cancer, and estrogen receptor status of breast tumors. Associations between mutations in each gene and breast cancer risk were evaluated using reference controls. Results: The overall frequency of pathogenic mutations in known breast cancer predisposition genes was 9.1% for non-Hispanic White, 8.9% for African American, 7.9% for Ashkenazi-Jewish, and 7.5% for Asians. BRCA1 mutations were enriched (p < 0.05) and CHEK2 mutations were under-represented in all racial and ethnic populations relative to non-Hispanic Whites. BRCA2 and BARD1 mutations were enriched in African Americans and Hispanics relative to non-Hispanic White. While BRCA2 and RAD51C mutations were enriched in Hispanics. Among genes with mutation counts large enough for assessment, mutations in BARD1, BRCA1, BRCA2, PALB2 and TP53 were significantly associated with clinically relevant increased risks (odds ratio (OR) = 2) of breast cancer across all ethnicities and races. Rates of variants of unknown significance (VUS) was highest among Africans followed by blacks (27%), Hispanics (21%), non-Hispanic whites (16%) and Ashkenazi-Jews (14%). Conclusions: While there is some similarity across ethnic groups, substantial heterogeneity exists in the prevalence of mutations in breast cancer predisposition genes across major racial and ethnic groups in the US population. These results contribute to HR population risk and have significant implications for genetic testing, screening, and management of patients with an inherited predisposition to breast cancer, with a need for continued analysis with increased cohort size in ethnic minority groups.

1515 Poster Discussion Session: Displayed in Poster Session (Board #9), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Adequacy of self-reported family history in electronic health record for genetic risk assessment for Lynch syndrome. First Author: Mala Pande, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Self-reported family history of Lynch syndrome (FSH) is one of the key indicators of hereditary cancer risk. Studies have shown that accurate FSH documentation by healthcare providers is suboptimal, but data regarding population-provided FSH are not available. Methods: We retrospectively reviewed the medical record of patients evaluated by the patient into the electronic health record (EHR) to determine its adequacy for Lynch syndrome (LS) risk assessment. Methods: At our tertiary referral cancer center, FSH is self-reported via an online questionnaire sent prior to appointment, which is reviewed/updated by clinic nurse during initial visit and then imported into EHR review of systems. Records of all new patients from September 2016 to August 2017 were retrospectively reviewed and analyzed. FSH quality was estimated by calculating rates of reporting of 3 FSH variables required for PREMM5, a risk-prediction model for LS. Parameters required for the model were sex, personal history of cancer, and for FSH, degree of kinship (first/second degree), cancer site/ type, and age at diagnosis. Results: Of 47,647 unique patients, 47.5% reported FSH for 1 or more relative (46.1% were first degree, 64.8% second degree, 3.0% other, and 2.4% missing). A cancer type/site was specified for 88.8% reporting FSH. Age at diagnosis was listed for 21.7% of the relatives’ cancers. Overall, only 20.9% provided all 3 FSH data elements required for running PREMM5 (9.9% of the total sample, n=4738). Fewer men (9.5%) than women (28.1%) provided all 3 FSH elements. Furthermore, 46.7% of breast cancer patients, 21.9% of gastrointestinal cancer patients, 47.2% and 23.1% of patients seen for cancer prevention screening and endoscopy respectively. Lower rates were observed for other cancers. Conclusions: Patient self-reported FSH is suboptimal for estimation of LS risk and genetic counseling referral. Future steps to optimize online patient-facing FCH collection to enable routine automated risk-assessment in an essentially provider-free setting may include, patient education regarding importance of FCH, optimized data collection, and implementation of algorithms in EHRs using FCH to identify patients at risk for hereditary cancer predisposition syndromes.
1516 Poster Discussion Session; Displayed in Poster Session (Board #10), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Genome-wide association study using whole-genome sequencing to identify a novel locus associated with cardiomyopathy risk in adult survivors of childhood cancer: Utility of a two-stage analytic approach. First Author: Yadav Sapkota, St. Jude Children’s Research Hospital, Memphis, TN

Background: Survivors of childhood cancer are at increased risk of treatment-related cardiomyopathy, found to be modified by genetic factors. To further investigate genetic risks of cardiomyopathy, we utilized whole-genome sequencing (WGS) in a clinically phenotyped cohort of long-term survivors of pediatric cancer. Methods: Utilizing a novel 2-stage analytic approach, we first performed association analysis for ejection fraction (EF) using WGS data in European-descent childhood cancer survivors from the St. Jude Lifeline Cohort (SJ/LIFE). EF was analyzed as a continuous variable to increase statistical power for genetic discovery. Common variants (minor allele frequency (MAF) > 0.05) were analyzed using linear regression, adjusting for age at diagnosis, sex, age at follow-up, doses of anthracycline and average radiation dose to the heart, and eigenvectors. Rare/low-frequency variants were aggregated by different functional annotations and diagnostic 4-bp sliding windows, testing jointly using Burden/SKAT test. In the second stage, only the variant showing genome-wide significance with EF was tested for its association with cardiomyopathy risk. Results: Among the 2,015 SJ/LIFE survivors with WGS data, a locus on 6p21.2 near KCNK1 achieved genome-wide significance with EF (rs2815063; MAF = 0.13; per allele beta = -0.016; p = 2.60 x 10^-6). The 6p21.2 region is enriched for cardiomyopathy risk. In SJ/LIFE Europeans, 282 had a CTCAE Grade 2-5 cardiomyopathy. rs2815063 was significantly associated with increased risk of cardiomyopathy (per allele odds ratio (OR) = 1.38; P = 0.02), which replicated in 3,957 European survivors from the Childhood Cancer Survivor Study (CCSS). The OR was 1.40 (95% CI 1.05-1.86) for CCSS cases; per OR = 1.39; P = 0.038). rs2815063 alters DNA binding motif of EWSR1-FLI1, whose expression was found to lead to cardiomyopathy and death due to chronic cardiac failure in mice. Conclusions: Using a 2-stage approach, we report a novel locus for cardiomyopathy in childhood cancer survivors, which warrants additional work to gain mechanistic insights.

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1517 Poster Discussion Session; Displayed in Poster Session (Board #11), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Gliomas in the context of Li-Fraumeni syndrome: An international cohort. First Author: Orli Michaeli, Hospital for Sick Children, Toronto, ON, Canada

Background: Li–Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated with germline mutation in the TP53 tumor suppressor gene. As a result of increased awareness and surveillance imaging, more asymptomatic low-grade brain lesions are being identified, raising important questions regarding the management of those patients. Sporadic low-grade gliomas (LGG) in the pediatric age rarely transform to malignant lesions, whereas the prognosis of high-grade gliomas (HGG) is grim in all age groups. Although HGG is a hallmark of LFS, little is known of the natural history of these lesions in this syndrome. Methods: For this multi-institutional retrospective study, anonymized clinicopathologic data from TP53 mutation carriers with gliomas were collected and analysed. Results: Our cohort included 61 patients, of whom 71% (n = 45) were children or young adults (age < 25 years). 39% of patients with known family history of cancer had a close relative with a brain tumor. Of 31 patients with low grade lesions at presentation, 83% (n = 26) were identified through surveillance. Five-year progression-free survival (PFS) for these patients was 48%, though two patients progressed later. Furthermore, at 5 years 25% of these patients had biopsy proven malignant transformation to HGG. This “transformation free survival” rate did not plateau, as at 7 years 56% of patients transformed. When considering death from a brain tumor, the 5- and 10-year overall survival (OS) for the LGG group was 100% and 93%, respectively. Using a 2-stage approach, additional patients succumbed to other LFS related malignancies. For the HGG group, consisting of 30 patients, the 5 year OS was 35% (median follow-up 19.5 months), comparing favorably with the sporadic HGG population as reported in the literature. Almost all of these patients presented with clinical symptoms. Notably, 12 (40%) of them had a prior malignancy. Conclusions: Our analysis suggests that the risk of transformation of LGG in the setting of LFS is high and warrants ongoing surveillance. Interestingly, there are a considerable number of long-term survivors in our HGG group, although the median follow up is still short. Further study to examine potential genotype-phenotype correlations in germline TP53 mutation carriers will inform strategies to identify those patients at highest risk of glioma progression.

1518 Poster Session (Board #12), Mon, 1:15 PM-4:15 PM

Germline mutations and onset of lung adenocarcinoma in smokers and non-smokers. First Author: Karen L. Reckamp, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Eligibility for lung cancer screening is based largely on pack-years of smoking, missing many cases. To propose additional groups for screening, this observational study evaluated whether germline mutations associated with cancer risk accelerate onset of lung adenocarcinoma (LA) in ever- and never-smokers. Methods: Patients with LA and family history of cancer were recruited from our oncology clinic and the Clinical Cancer Genomics Community Research Network. With consent, blood samples were screened by large multi-gene panel for 4 categories of germline mutation [lung cancer-associated genes (TP53, EGFR, BRCA2); other genes in Fanconi anemia (FA) pathway; other DNA repair genes]. Accelerated failure-time models of age at LA diagnosis, adjusted for sex, ethnicity, and packs per day, were constructed for never-smokers and ever-smokers. Statistical significance, at p<0.05 limited the False Discovery Rate to 5% across 8 hypotheses. Results: In never-smokers with LA (n=104), mutated BRCA2, TP53 or EGFR were associated with younger age at diagnosis, while mutation in other FA or DNA repair gene was not. In ever-smokers with LA (n=65), mutated BRCA2 and other FA gene were associated with younger age at diagnosis, while other mutation categories were not (Table). Conclusions: Regardless of smoking history, BRCA2 mutation carriers experience accelerated onset of LA, as do never-smokers carrying TP53 or EGFR mutation and ever-smokers with mutation in FA gene other than BRCA2. With the exception of TP53 carriers (who inactivate whole body MRI), lung cancer screening with low-dose computed tomography, starting earlier in adulthood than usual, may be warranted for individuals with germline mutations in these genes. Age at Diagnosis of Lung Adenocarcinoma, by Germline Mutation and Smoking History, Adjusted for Sex, Ethnicity, and Packs per Day.

Conclusions: Three previously unreported variants are predicted to be protein truncating and, in addition to c.4866C>T p.(Ser1629*) result from a single nucleotide mutation in c.4874A>T p.(Lys1615Argfs*5) and c.4886C>G p.(Ser1629*) result from a single nucleotide mutation in c.4894A>T p.(Glu1631Aspfs*5) and c.4886C>G p.(Ser1629*) result from a single nucleotide mutation in c.4894A>T p.(Glu1631Aspfs*5).

1519 Poster Session (Board #13), Mon, 1:15 PM-4:15 PM

Gaining insights into the DICER1 syndrome: An early report from the Italian DiCeR1 registry. First Author: Marcella De Nicolò, Cancer Genomics Program, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

Background: DICER1 is a keyendonuclease in the microRNA pathway that modulates gene expression. Germline loss of function variants in DICER1, first found in pleuropulmonary blastoma, have been subsequently linked to a variety of cancers and (non) conditions referred to as DICER1 syndrome. In 2018, the Italian Society of Human Genetics launched an national familial oncological registry of DICER1 germline sequence variants. Methods: Centers involved in genetic testing for cancer predisposition were asked to report any identified DICER1 germline variants and related clinical information. Five University and/or research institutes filled-in the electronic survey. Informed consent was obtained from patients or their legal guardians prior to DNA testing by NGS and/or Sanger sequencing. Results: Six DICER1 sequence variants were identified in 11 individuals. Three missense variants are secondary results of NGS panels for cancer predisposition and lack definitive categorization in online databases. Three previously unreported variants are predicted to be protein truncating and, hence, likely pathogenic. Of these, DICER1 c.4944delA p.(Lys1615Argfs*5) and c.4886C>G p.(Ser1629*) result from ad hoc testing offered to probands based on a history of early onset follicular thyroid carcinoma and botryoid-type embryonal rhabdomyosarcoma of the cervix and of pleuropulmonary blastoma 2nd type, respectively. DICER1 c.4643T>G p.(Lys1614*), instead, results from whole exome sequencing in two siblings with malignant melanoma who tested non informative for alterations in the CDKN2A and CDK4 melanoma predisposing genes. Further investigation unearths thyroid disease in the family and identified two other young carrier individuals, one unaffected and one thyroidectomized due to multinodular goiter. A DICER1 somatic hot spot sequence variant was detected in goitre specimen. Additionally, a newly established national registry we uncovered novel DICER1 germline sequence variants and uncommon genotype-phenotype associations. Our joint effort will help us to refine our knowledge of the rare DICER1 syndrome, to inform research studies, and to improve testing and clinical management strategies.
Genetic identification and characterization of Lynch syndrome in a multi-ethnic biobank. First Author: Rachel Rosenblum, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Lynch syndrome (LS), caused by germline pathogenic variants in mismatch repair (MMR) genes, results in increased risk of colorectal, endometrial, and other cancers. LS has a prevalence of ~1 in 440 in European ancestry populations; prevalence data in other populations are limited. We identified and characterized carriers of pathogenic MMR gene variants in the multi-ethnic BioMe Biobank in New York City. Methods: Exome sequence data from ~31,000 BioMe participants were evaluated for known (per ClinVar) and predicted (loss-of-function) pathogenic variants in MMR genes. Population groups were defined by genetic ancestry. Participant questionnaires and electronic health records (EHRs) of carriers were reviewed for personal or family history of malignancy. Results: We identified 48 carriers of 33 distinct pathogenic variants in PMS2 (48%), MLH1 (27%), MSH6 (15%), and MSH2 (10%), for an estimated prevalence of ~1/640 in the BioMe Biobank. Prevalence was higher among individuals of Non-Jewish European (N = 14; 1/400) and African (N = 14; 1/490) ancestries, compared to Puerto Rican (N = 8; 1/640), Ashkenazi Jewish (N = 6; 1/690), and other/mixed (N = 6) ancestries. Carriers had a median age of 56 years (range 27 to 77) years and were 50% female. Overall rate of malignancy among carriers was 38%, with the lowest rate in PMS2 (26%) and the highest rate in MSH6 (57%) variant carriers. We found a high prevalence of endometrial cancer (21% of female carriers) and a lower prevalence of colorectal cancer (14% of all carriers). Only 2 carriers (4%) had a diagnosis of LS at the time of EHR abstraction, and 41% had self-reported LS as a history.

Conclusions: These data show that ~0.15% of participants in a multi-ethnic biobank are carriers of pathogenic MMR gene variants and suggest that the prevalence is higher in European and lower in non-European ancestry populations. Notably, most carriers do not have a clinical diagnosis of LS and do not meet diagnostic criteria for LS. Our results demonstrate variable rates of cancer, which may contribute to under-diagnosis of LS. Genomic screening for pathogenic MMR variants may lead to earlier diagnosis of LS and improved outcomes.

Risk of cancer in first-degree relatives of childhood cancer patients: A linked longitudinal population-based registry study. First Author: Laura Canas Madanat-Harjuoja, Radcliffe Institute for Advanced Studies, Harvard University, Boston, MA

Background: Population based data on risk of cancer in relatives of childhood cancer patients are sparse. Using linked population-based registries, we set out to evaluate risk of early onset cancer in first-degree relatives of childhood cancer patients. Methods: We queried the Finnish Cancer Registry and ascertained a cohort of 9135 individuals diagnosed with at least one cancer under the age of 21 between 1970 and 2012. We then went on to identify a total of 58,211 unique first- and second-degree relatives by linking to the Central Population Registry. Relatives were then linked back to the annually updated Finnish Cancer Registry to identify cancer diagnoses in siblings, offspring and parents of childhood cancer patients, restricting to cancers occurring under the age of 40. Risk of cancer in relatives of the index case was estimated using standardized incidence ratios (SIRs) comparing cancer age and period specific incidence in relatives to that of the general population. Results: A total of 288 cancers were diagnosed in relatives during the 900,907 years of follow-up, while 266 cancers were expected. The overall risk of cancer in siblings of childhood cancer patients was elevated (SIR 1.18 95% CI 1.00-1.39). 144 of the childhood cancer patients were identified as having a sibling additional to index case with a diagnosis of cancer at age < 40; 44 of these 144 also had a parent with early onset cancer. The risk of early onset cancer was elevated in offspring overall (SIR 1.79 95% CI 1.05-2.81) and in offspring of retinoblastoma, malignant bone tumor and neuroblastoma patients. Siblings of lymphoma patients were at elevated risk of early cancer, and the mothers of 11 of 27 sibling pairs (lymphoma + cancer < 40 yo) also had cancer at age < 40. Conclusions: Linked registries allow family history of cancer to be evaluated across multiple relatives and to be longitudinally updated. Results are generally reassuring with regard to risk of cancer in relatives of childhood cancer patients. Elevated risk in relatives of retinoblastoma and malignant bone tumor patients are in line with the known cancer syndromes associated with these tumor types, and lymphoma and neuroblastoma families need further analysis.
Tumor mutation burden and PD-L1 expression in SDH/FH mutated solid tumors. First Author: Leylah Druszosky, NantHealth, Culver City, CA

Background: Succinate Dehydrogenases and Fumarate Hydratase (SDH/FH) deficient tumors are characterized by succinate/fumarate accumulation and resultant pseudohypoxia that drives malignant transformation. This state of pseudohypoxia leads to dysregulation of PD-1 receptor-ligand signaling. In this study, we explored tumor mutation burden (TMB), gene expression of PD-L1, and expression of other immune checkpoint- associated genes in a diverse cohort of human tumors harboring SDH A, B, C, D and FH mutations.

Methods: Retrospective analysis was performed on whole exome sequencing (WES; > 150x coverage) and whole transcriptome RNAseq (~200x106 reads per tumor) data from NantHealth to identify tumors harboring SDHx and/or FH mutations. WES was performed on tumor tissue and matched normal tissues for each patient to assess TMB. TMB was measured by counting all somatic-specific non-synonymous exonic mutations, with > 200 mutations qualified as TMB-high. Immune checkpoint therapy-related gene expression was evaluated for PD1, CTLA4, IDO, LAG3, FOXP3, PD-L2, TIM2, TIM3, and OX40. Results: Among tumor samples from 3377 patients analyzed, 42 patients were found to harbor potentially-pathogenic & pathogenic mutations, with > 200 mutations qualified as TMB-high. Immune checkpoint therapy-related gene expression was evaluated for PD1, CTLA4, IDO, LAG3, FOXP3, PD-L2, TIM2, TIM3, and OX40. Results: Among tumor samples from 3377 patients analyzed, 42 patients were found to harbor potentially-pathogenic & pathogenic mutations, with > 200 mutations qualified as TMB-high. Immune checkpoint therapy-related gene expression was evaluated for PD1, CTLA4, IDO, LAG3, FOXP3, PD-L2, TIM2, TIM3, and OX40.

Conclusions: For the first time an association between increased TMB and increased PD-L1 expression in a variety of SDH/FH mutated tumors. These key parameters, imply that a higher TMB may drive the evolutionary pressure to select clones with a PD1 high phenotype. This observation supports a potential therapeutic role for inhibition of PD-1/PD-L1 pathway in these tumors.

Preimplantation genetic diagnosis: What do BRCA mutation carriers think? First Author: Olivia R Khouri, NYU School of Medicine, New York, NY

Background: The use of pre-implantation genetic diagnosis (PGD) to select against BRCA mutated embryos for in-vitro fertilization (IVF), introduces complex choices for patients with pathogenic BRCA mutations. We sought to describe the uptake of and attitudes toward this technology in this patient population. Methods: We conducted a prospective survey study at a single institution in New York City affiliated with both a Cancer Center and Fertility Center, to assess attitudes and utilization of PGD. Cancer Center staff distributed surveys to patients with known BRCA mutations between April and August 2018. Survey participation was voluntary and anonymous. Survey data were analyzed using descriptive statistics and two-tailed t tests. Results: 80 survey responses were collected. A majority of the patient population identified as Caucasian (87.5%), 70 and Jewish (52.5%, 42). The survey was distributed to all age groups; however 81% (65) were between 26 and 45 years of age. 63.8% (51) had heard of PGD prior to completing the survey, while 36.3% (29) had not. Only 40% of respondents (32) felt sufficiently educated regarding PGD. 35% (28) patients met with an REI, of whom 6.3% (5) utilized IVF with PGD, and 21.3% (17) plan to use IVF with PGD in the future. 11.3% (9) wish they had known about this technology prior to starting a family. 20% (16) would not have used PGD had they known about it prior to childbearing. Reasons respondents were unlikely to pursue PGD included: cost (38.8%, 31), completed childbearing (25%, 20), medical risk (18.8%, 15), and ethical concerns (16.2%, 13). Patients gave cost estimates for PGD ranging from $500 - $120,000. There was no statistically significant correlation between likelihood of pursing PGD and parity (p = 0.45), religion (p = 0.78), education level (p = 0.13), number of family members affected by BRCA mutation (p = 0.20) or by cancer (p = 0.11).

Conclusions: Overall, a small number of patients with pathogenic BRCA mutations utilize PGD. A minority of survey respondents felt adequately educated about PGD. Reported barriers to uptake were varied, and there was a wide range of cost estimates reported. Our results suggest that increased patient education regarding PGD in BRCA mutation carriers is warranted.

Preventive surgery after multiplex genetic panel testing (MGPT). First Author: Gregory Idos, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA

Background: Guidelines recommend consideration of prophylactic surgery for patients with a germline pathogenic variant in some cancer predisposition genes. We assessed surgery utilization in a prospective, multi-institutional cohort study of MGPT. Methods: 2000 patients had MGPT and completed questionnaires at 3, 6, and 12 months. Patients reported surgical utilization and indication (treatment or prevention). Surgery utilization was assessed among those testing positive to cancer risk and pretest MGPT test results: Positive, pathogenic variant; VUS, variant of uncertain significance; Negative, benign variants.

Results: Overall, 12.9% (198/1537) of patients reported surgery after MGPT (median follow-up 13 months). Only 31.3% (62/198) of patients specified that their surgery was preventive. Preventive surgery utilization was significantly higher among patients who tested positive (n=30, 14.9%) compared to those testing negative (n=20, 2.3%, p<0.001) or VUS (n=12, 2.2%, p<0.001). Preventive surgery was very low among patients testing negative or VUS who had no personal history of cancer in the relevant organ (Table). For example, mastectomy was not reported among any patients testing negative or VUS who had no personal history of breast cancer (Table).

Conclusions: More than one year after MGPT, prophylactic surgery use was low among patients with VUS or negative results, especially among those with no personal history of cancer at the relevant site. Surgery utilization.

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Germline variants in urothelial carcinoma: Analysis of pathogenic and likely pathogenic variants in 645 subjects. First Author: Sarah Abou Alaiwi, Dana-Farber Cancer Institute, Boston, MA

Background: While small studies have supported a genetic cancer predisposition among subjects with urothelial carcinoma (UC), systematic germline evaluation of this population is lacking. Here, we report the prevalence of germline variants among subjects with UC from multiple centers completing panel-based testing at a large, commercial laboratory.

Methods: 1149 UC subjects underwent germline testing of 1 to 126 genes using massively parallel sequencing with customized capture bait-sets to analyze exonic regions, flanking intronic sequences, and copy number alterations. Pathogenic (P) and likely pathogenic (LP) were confirmed using orthogonal technology in accordance with Invitae standard operating practices. Analysis was limited to 645 subjects who completed testing of a shared set of 42 genes, P/LP variants including single nucleotide variants/indels/copy number variants are reported. De-identified personal and family cancer histories were evaluated. Fisher’s Exact test and the Mann-Whitney test were used to analyze categorical and continuous variables respectively.

Results: Among the 645 UC subjects with 42-gene testing for any indication, median age at testing was 60 years (6-88) and 326 (51%) were female. P/LP variants were identified in 21 (50%) of the 42 genes in 98 (15%) of subjects, including Lynch syndrome genes (n = 26 (4%)), BRCA1/2 (n = 16 (2.5%), CHEK2 (n = 15 (2.3%)), and heterozygous MUTYH (n = 12 (1.9%). Among 18 DNA damage repair (DDR) genes assessed, 90 P/LP variants were detected in 88 subjects (12.2%). There was no significant association between potential DDR variant and age at diagnosis, gender or reported family history of UC in a first degree relative (n = 48). Among subjects with documented history of UC only without other cancers (n = 195), 24 (12.3%) had P/LP variants, of which 23 (11.8%) were in a DDR gene.

Conclusions: Germline P/LP variants were identified in 15% of UC subjects, most of which (92%) were in DDR genes, including 27% in Lynch syndrome genes. PARP and T-cell checkpoint inhibitors may warrant evaluation in subjects with germline DDR mutations. Further validation in unscreened UC pts is warranted to propose examining germline P/LP variants in all UC patients.

Test of InheRET, an online tool to facilitate NCCN Guideline compliant referrals for cancer genetic counseling. First Author: Lynn McCain, University of Michigan, Ann Arbor, MI

Background: Identifying the ∼60 million unaffected persons in the US at risk for inherited cancers has the potential to reduce their cancer risk by up to 95%. However, most of these individuals are not identified currently because of multifactorial deficits in the 3-generation pedigree collection in clinical settings.

Methods: Here we evaluated the impact InheRET, an online family history gathering and risk assessment reporting tool, has on facilitating National Comprehensive Cancer Network (NCCN) Guideline-compliant referrals for cancer genetic counseling/genetic evaluation by decreasing and/or removing the barriers of 1) in-clinic 3-generation family history collection, and 2) interpretation of the family and personal history in light of current NCCN Guidelines. Patients enrolled from primary care and specialty clinics completed the family health history from a web-enabled devices using InheRET Inherited Risk Evaluation Tool. Results: Of 255 enrolled patients, 78.4% completed the history form and, of these, 86.5% completed the feedback survey. 39.2% of primary care and 79.9% of specialty cancer clinics completed the feedback survey.

Conclusions: In a prospective cohort of early triple-negative breast cancer patients, First Author: Elsa Curtit, University Hospital - Medical Oncology Department, Besançon, France

Background: Triple-negative breast cancers (TNBC) are a heterogeneous group of tumors with poor outcome. In this study, the association between germline variants and invasive disease-free survival (iDFS) was analyzed in TNBC patients.

Methods: A genome-wide association study (GWAS) aimed to identify variants (single nucleotide polymorphisms, SNPs) associated with prognosis in 1121 patients with TNBC in the SIGNAL prospective cohort. Associations between gene variants and iDFS were assessed in univariate Cox regression models. Variants were combined in a score to identify risk categories. A prognostic model based on breast cancer stage and genetic variants was estimated using a multivariate Cox regression. Interaction between stage and genetic score was tested. Discrimination of the model was assessed by the Harrell’s C statistic and internal validity by bootstrap method.

Results: The characteristics of the 1121 patients were representative of a population with early TNBC. Four SNPs on chromosomes 9 and 2 were found significantly associated to iDFS in univariate Cox models. Homozygous status for the most frequent allele was associated with poorer iDFS for both SNPs and this status was present in 50% and 57% of the population. For the two SNPs, the most frequent allele was associated with more favorable iDFS. Three prognostic categories were derived from the genetic score. The following table presents the results from the multivariate Cox model including genetic score and disease stage. Clinical trial information: RECFL098. Conclusions: In a prospective cohort of 1121 patients with early TNBC, 4 genetic variants (SNPs) were associated with iDFS. A score involving SNPs provided similar prognostic indications as breast cancer stages. A cross-sectional assessment of the function and the role of the involved genes is ongoing.

Prognosis value of a genetic score based on germline genetic variants in a prospective cohort of early triple-negative breast cancer patients. First Author: Malin, Sachdev Dhawan, University of California San Francisco, San Francisco, CA

Background: There is considerable uncertainty on cancer risk and recommendations for genetic testing in various populations. The purpose of this study is to test types and frequencies of cancer risk mutations in large, unaffected multiethnic populations, as well as feasibility and acceptance of general population germline testing. Methods: After consent, germline genetic testing via Color Genomics 30-gene Cancer Risk panel with personal and family cancer history assessment was offered to 500 participants residing in the San Francisco Bay Area. Participants were older than 21 and without a known family history of a cancer risk mutation. Recruitment occurred at random and through various, non-cancer related community events. Genetic counseling through a genetic counselor at UCSF was offered to all participants. Post-participation surveys were sent out to those who completed testing with 195 responses to assess attitudes towards genetic testing. Results: 500 participants completed testing; 35 were found to have a cancer risk mutation (7.0%). The majority of these have been in moderate risk cancer mutations including CHEK2 (1.0%), APC (0.8%), MUTYH (1.4%) and NBN (0.4%); higher risk mutations were found in BRCA1 (0.4%), BRCA2 (0.6%), BRIPI (0.4%), PMS2 (0.2%) and PALB2 (0.2%). Data via self-reporting and SNP testing via the Color Genomics platform was collected to contextualize the racial, ethnic, and geographic association of these results. Rates of VUS (variants of uncertain significance) differed among the various ethnic groups (p=0.027) with the lowest rates in Europeans vs. all other ethnicities (16.6% vs. 29%, p=0.001). 37 (19.8%) out of 187 respondents reported that their genetic testing influenced testing in family members. In those 37 families, 8 additional people were positive for genetic mutations. One of the biggest barriers to accessing genetic testing according to most individuals (20% of respondents); others were too busy (12%) or did not feel genetic testing was medically recommended (9%). Conclusions: The PHACT study demonstrates that large population screening of cancer risk mutations is feasible. The number of participants found to have mutations was greater than expected although the majority of these were in moderate risk genes. We found high rates of VUS in non-Europeans, which points to the complexity of population-based genetic testing.

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1532 Poster Session (Board #26), Mon, 1:15 PM-4:15 PM
Characterization of Lynch syndrome (LS) associated cancers in patients with immune dysfunction. First Author: Shahla Bari, Moffit Cancer Center, Tampa, FL

Background: LS is caused by a germline mutation in one of several DNA mismatch repair (MMR) genes: MLH1, MSH2, MSH6 or PMS2. Inappropriate immune responses as seen in chronic inflammatory conditions as well as immunodeficiency states confer increased risk of developing cancer. This aim of this study was to evaluate the effect of immune dysfunction on the characteristics of LS associated cancers. Methods: This was a retrospective analysis of LS patients and carriers at two institutions listed above. We evaluated mutational profiles, immune status, age of onset of first and subsequent cancers in this cohort. Results: 106 patients with mutations consistent with LS were included. 72 patients had at least one cancer while 34 were carriers. 44% patients were Caucasian female, 18% white males, 14% African American males, 11% African American females and 10% Hispanic females. Colon cancer (CRC) was the most common cancer (44%) and PMS2 was the most common mutation, noted in 35 patients (33%). Of the 72 patients with LS associated cancer, 18 patients were either immunosuppressed or had an autoimmune condition. Of the 10 patients who had an autoimmune condition, 7 had multiple cancers. Of the 9 patients who were immunosuppressed, 5 had multiple cancers. Out of a total of 18 out of 72 patients who had multiple cancers, 12 (66%) had either an autoimmune condition or were immunosuppressed. CRC was the index cancer in 42% and breast in 33% of patients with multiple cancers. Patients with MSH2 were most likely to have an immune related condition (32%) and accounted for 41% of patients with multiple cancers. The median age of first cancer in this group was 46 years while it was 48.5 years in the population without immune dysfunction (p = 0.2). There was a high prevalence of breast cancer (24%) as a LS associated cancer in our study population. 66% of the patients with PMS2 mutation had breast cancer with a median age of onset of 48 years (62 years for sporadic cancer). Conclusions: Our study is the first to look at the effect of immune dysfunction in LS patients. Immune dysfunction was associated with a higher rate of multiple cancers and was more commonly associated with the MSH2 mutation. It also highlights importance of aggressive screening for breast cancer in LS patients (especially with PMS2 mutation).

1534 Poster Session (Board #28), Mon, 1:15 PM-4:15 PM
Role of vitamin D supplementation for primary prevention of cancer: Meta-analysis of randomized controlled trials. First Author: Varun Samji, Hurley Medical Center/ Michigan State University, Flint, MI

Background: In the United States cancer is the second leading cause of mortality, as such, primary prevention of cancer is a major public health concern. Vitamin D supplementation has been studied as a primary prevention method for multiple diseases including cardiovascular disease, osteoporosis, diabetes mellitus and cancer. The role of aspirin as primary prevention of cancer is still controversial. With fast emergence of large randomized controlled trials (RCTs) in that regards, we aimed to evaluate the efficacy of Vitamin D supplementation as primary prophylaxis for cancer. Methods: A comprehensive electronic database search was conducted for all RCTs where comparison of Vitamin D supplementation versus placebo for the prevention of any type of disease with at least 3 years of Vitamin D supplementation was used and where cancer incidence or mortality was reported. The primary outcome was cancer-related mortality and cancer incidence. We calculated risk ratios (RRs) and 95% confidence intervals (CIs) using a random-effects model at the longest follow-up period. Results: We included 16 RCTs with 104,018 total patients, mean age of 60.51 years, mean follow-up of 5.48 years, and a male percentage of 38.72%. We found that asparin was not associated with a significant reduction of cancer-related mortality compared with placebo (RR 0.99; 95% CI: 0.87-1.12; P = 0.85; I² = 41%). Compared with placebo, aspirin was not associated with significant reductions of all-cause mortality (RR 0.97; 95% CI: 0.92-1.02; P = 0.49; I² = 13%) or cancer incidence (RR: 0.98; 95% CI: 0.92-1.04; P = 0.43; I² = 16%). However, aspirin treatment was associated with significantly increased risks of any bleeding (RR 1.63; 95% CI: 1.31-2.03; P < 0.01), major bleeding (RR 1.41; 95% CI: 1.26-1.57; P < 0.01), and GI bleeding (RR 1.85; 95% CI: 1.38-2.46; P < 0.01) compared with placebo. Conclusions: Our study did not find any significant reductions in cancer-related mortality or cancer incidence when compared with placebo. Our study also highlights the dangers of aspirin for primary prevention of cancer as aspirin was found to cause higher rates of bleeding (any bleeding, major bleeding, and GI bleeding) compared to placebo at the longest follow-up period with no significant benefit in cancer primary prevention.

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1536 Poster Session (Board #30), Mon, 1:15 PM-4:15 PM
Management of high, moderate, and low penetrance ovarian cancer susceptibility gene mutations: An assessment of current practice patterns. First Author: Catherine S. West, Duke University, Durham, NC
Background: Limited information exists regarding appropriate risk-reduction strategies for women with moderate and low penetrance ovarian cancer (OVCA) susceptibility mutations. We sought to assess current practice patterns for women with these genetic changes through a survey of members of the Society of Gynecologic Oncology (SGO). Methods: All full SGO members were e-mailed a survey consisting of two vignettes: 1) a 35-year-old premenopausal woman who desires pregnancy and is associated with a reduced risk of developing triple negative/basal-like breast cancer if she chooses to breastfeed; and 2) a 40-year-old postmenopausal woman with multiple comorbidities. Each vignette contained sub-scenarios in which the patient had either a BRCA1 (RR = 30-60), RAD51C (RR = 5.0) or ATM (RR 1.5-2.0) OVCA susceptibility mutation. Respondents were queried about their preferred management approach. Chi-square test was used for statistical analysis. Results: 193 (15%) of 1284 SGO members responded. 58% were in academic practice. For the premenopausal woman, 52%, 13% and 6% would perform an RRSO prior to age 40 in the setting of a BRCA1, RAD51C and ATM mutation respectively; 2%, 8% and 39% would observe (with/without screening) and 0%, 7% and 19% would do further research prior to proceeding. Distribution of responses for carrying RAD51C and ATM mutations in the postmenopausal women was similar. Conclusions: Our findings suggest that different strategies for women with low penetrance mutations are needed.

1537 Poster Session (Board #31), Mon, 1:15 PM-4:15 PM
Implementation of a low-dose computed tomography (LDCT) lung cancer screening program (LCSP) across a large integrated health system. First Author: Maria J Blagovich-Weidman, Aurora Health Care/Aurora Cancer Care, Milwaukee, WI
Background: The LDCT LCSP was launched as a critical component of our Cancer Program to support tobacco cessation efforts and increase early detection. Initially it was offered as a self-referral low cost screening. The program was expanded when the Affordable Care Act and Center for Medicare/Medicaid Services covered it as a preventative services benefit in January 2015. Methods: Data from all LDCT LCSP locations were implemented between 2014-September 2016. Program data are submitted to the American College of Radiology Lung Cancer Data Registry since 2016. In 2017, a Best Practice Alert was created within our electronic health record (EHR) to alert the primary care clinician if his/her patient met criteria for a LDCT. Each of the sites managed their own programs up until September 2018 when a dedicated team (Team) of two nurses and one data support specialist was justified. The Team focuses is to increase awareness of the LDCT LCSP and criteria for eligibility, improve tobacco history taking and pack year documentation in the EHR, increase smoking cessation counseling and referral, and facilitate presentation of our LDCT LCSP to external stakeholders. Results: 1536 Poster Session (Board #30), Mon, 1:15 PM-4:15 PM
Management of high, moderate, and low penetrance ovarian cancer susceptibility gene mutations: An assessment of current practice patterns. First Author: Catherine S. West, Duke University, Durham, NC
Background: Limited information exists regarding appropriate risk-reduction strategies for women with moderate and low penetrance ovarian cancer (OVCA) susceptibility mutations. We sought to assess current practice patterns for women with these genetic changes through a survey of members of the Society of Gynecologic Oncology (SGO). Methods: All full SGO members were e-mailed a survey consisting of two vignettes: 1) a 35-year-old premenopausal woman who desires pregnancy and is associated with a reduced risk of developing triple negative/basal-like breast cancer if she chooses to breastfeed; and 2) a 40-year-old postmenopausal woman with multiple comorbidities. Each vignette contained sub-scenarios in which the patient had either a BRCA1 (RR = 30-60), RAD51C (RR = 5.0) or ATM (RR 1.5-2.0) OVCA susceptibility mutation. Respondents were queried about their preferred management approach. Chi-square test was used for statistical analysis. Results: 193 (15%) of 1284 SGO members responded. 58% were in academic practice. For the premenopausal woman, 52%, 13% and 6% would perform an RRSO prior to age 40 in the setting of a BRCA1, RAD51C and ATM mutation respectively; 2%, 8% and 39% would observe (with/without screening) and 0%, 7% and 19% would do further research prior to proceeding. Distribution of responses for carrying RAD51C and ATM mutations in the postmenopausal women was similar. Conclusions: Our findings suggest that different strategies for women with low penetrance mutations are needed.

1538 Poster Session (Board #32), Mon, 1:15 PM-4:15 PM
Analysis of healthy breast tissue from Komen Tissue Bank shows distinct histology, decreased proliferation, and lower periductal collagen deposition in women with prolonged history of breastfeeding. First Author: Mustafa Basree, University of Pikeville Kentucky College of Osteopathic Medicine, Pikeville, KY
Background: Epidemiological studies have shown that prolonged breastfeeding is associated with a reduced risk of developing triple negative/basal-like breast cancer (TN/BLBC). We have modeled abrupt interruption (AI) following short breastfeeding (SB) and gradual reduction (GR) of the mammary gland that occurs over time upon prolonged breastfeeding in wild-type FVB/N mice and discovered prominent histological and molecular changes in the AI glands over time. Further, we demonstrated that breast tissue from healthy women who breastfed ≤6 months showed enrichment in stem-cell and cell renewal pathways. Here, we corroborate these studies using normal human breast tissue obtained from Susan G. Komen for the Cure Tissue Bank (KTB). Methods: FFPE breast tissue sections obtained from KTB (Protocol #2017CO184). Donors were parous women, aged 18 to 45, without history of breast cancer and for whom breastfeeding history was available. H&E sections and TDLU, the primary anatomical source of most breast cancers, of women who breastfed for >6 months (GI, n=49) vs. those who breastfed for ≤3 months (AI, n=20) were evaluated by a blinded pathologist. Masson Trichrome stain was used to measure collagen deposition. Ki67 immunohistochemistry was utilized to determine proliferation. Statistical significance was assessed using Fisher’s exact t-test and two-sample t-test with a p-value of <0.05. Results: H&E analysis revealed that breast tissue obtained from women in the AI cohort exhibited histological features of inflammation (p-value=0.025), using Ki67 IHC (AI, n=15; GI, n=32) and Masson Trichrome stain (AI, n=3; GI, n=4), sections in the AI cohort showed 2-fold increase in proliferation of lobular epithelium (p-value=0.048) and 1.4-fold increase in periductal collagen deposition (p-value=0.027) when compared to GI cohort. Age, race, and BMI were not statistically different between AI and GI cohorts. Conclusions: Breast tissue from parous women who breastfed ≤3 months is histologically different than tissue of women with ≥6 months history of breastfeeding. We are currently staining more breast tissue samples obtained from KTB. Experiments are underway to assess the long-term effect of breastfeeding on breast epithelial cell lineage and biomarkers of inflammation. Understanding this mechanistic link will help in developing prevention strategies, particularly for African-American women who have lower prevalence of breastfeeding and higher incidence of TN/BLBC.

1539 Poster Session (Board #33), Mon, 1:15 PM-4:15 PM
Low-fat dietary pattern and breast cancer mortality by metabolic syndrome definition: Secondary analyses of the Women's Health Initiative (WHI) Dietary Modification randomized trial. First Author: Kathy Pan, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA
Background: The WHI Diet Modification (DM) trial randomized 48,835 postmenopausal women with no prior breast cancer to a low-fat dietary intervention or comparison group. After 16.1 years follow-up, the intervention was associated with an 18% reduction in risk of death after breast cancer (P =0.01), with greater reduction (29%) in those with waist circumference ≥88 cm (DeCensi et al. Oncol 2017). To extend these findings, we examined the influence of the dietary intervention on breast cancer mortality in subgroups defined by number of metabolic syndrome (MS) components with 19.6 years median cumulative follow-up. Methods: WHI DM has been previously described. Four MS components were determined at entry: 1) waist circumference ≥88 cm, 2) high blood pressure or anti-hypertensive use, 3) high cholesterol history and 4) diabetes history, with women categorized as having 0 (n=10,639), 1-2 (n=30,948), or 3-4 (n=4,246) MS components. Forest plots of hazard ratios (HRs) were generated with P-values for interaction between randomized group assignment and number of MS components. Results: Women with 3-4 MS components were more likely to be Black, obese (BMI ≥30), and have diabetes (P<0.001). Breast cancers in women with 3-4 MS components were less likely to be local stage (P=0.005) or well differentiated (P = 0.03). The magnitude of reduction in deaths from breast cancer in the dietary intervention vs comparison group increased as the number of MS components increased (interaction P = 0.01). Hazard ratios (HR) and 95% confidence intervals (CI) for death from breast cancer for intervention vs comparison groups for women with 0 MS components was 1.09 95% CI, 0.63-1.87, with risk low and MS components, HR 0.80 95% CI, 0.62-1.02; and for women with 3-4 MS components, HR 0.31 95% CI, 0.14-0.69, with risk in the intervention group reduced to 0.026. Conclusions: Adoption of a low-fat dietary pattern had a greater effect on reducing deaths from breast cancer in women with more MS components, suggesting that this is a high risk group more likely to benefit from the dietary intervention. Clinical trial information: NCT00000611.
The impact of smoking cessation on breast cancer patients’ survival. **First Author:** Mazen Jazmi, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Breast cancer remains to be one of the highest causes of cancer mortality amongst females globally, second only to lung cancer. Smoking is strongly associated with increased all-cause mortality, including breast cancer related death. It has also shown to have a negative influence on quality of life and long-term survival after successful breast cancer treatment. Prior studies have shown that smoking cessation may delay advanced-stage diagnosis and lead to better outcomes. **Methods:** This is a retrospective cohort study of breast cancer patients who were identified as smokers, some of who were referred to the tobacco treatment program (TTP) located at MD Anderson Cancer Center. We complemented the original data collected by conducting in-depth chart reviews to extract data including patient demographics, date of diagnosis, stage of cancer, smoking status, duration of abstinence and dates of follow-up or death. We then examined associations between smoking status and survival status using multivariable regression models adjusting for bio-markers of disease and personal characteristics. **Results:** Among all breast cancer patients (N = 31069), we identified those who were smokers (n = 2320) by matching the TTP database with smoking status from our institutional database. Using logistic regression we selected the most significant variants between both cohorts and correlated them with KRAS mutation status of LUAD patients. **Results:** Mean ages for the cancer and cancer free cohorts were 50 (range 34-55) and 78 years (72-90). Mean tobacco consumptions were 44 (range 6-72) and 55 pack-years (20-124). Median coverage was 96% at >10K, median depth was 97X. Table shows the most significant variants: rs7240666 (ALPK2) achieved top significance (p=8.14x10^-5, OR 1.18), rs78898229 (ANKRD36C) and rs74866537 (PTPN4) were predominantly represented in patients with KRAS+ tumors, OR: 16 (3.5-78) and 11.9 (3.3-43); and rs12426243 (CCDC41) in KRAS tumors: OR: 13 (5.3-85). **Conclusions:** Our study characterizes for the first time the genotypes of individuals presenting extreme phenotypes of high and low risk to develop tobacco-induced LUAD according to KRAS status. Our results warrants further study to assess their value to screen these clinically relevant phenotypes; and to identify mechanisms of high susceptibility and resistance to carcinogens.

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**First Author:** Yinghong Wang, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** In our clinical practice at a tertiary cancer center, we have observed increased colon adenoma detection rate (ADR) in patients with breast cancer. Here, we describe ADR in patients with breast cancer and define the窗 optimal timing to initiate colonoscopy screening in these patients. **Methods:** We conducted a retrospective study of patients with breast cancer who underwent a colonoscopy after their diagnosis of breast cancer between 2000 and 2017. A control group (n = 3295) comprised patients without any type of cancer who underwent their first screening colonoscopy between 2008 and 2017 and was used in the logistic regression. **Results:** Of the 62,820 patients who had a diagnosis of breast cancer, 3304 were included. The mean age was 59 years. Regarding ADR, 1803 patients (55%) had adenomas. High-grade dysplasia was evident in 28% of polyps and invasive adenocarcinoma in 172 (5%). The median time from breast cancer diagnosis to adenoma detection was 3 years (IQR 1-6). The ADR was 21% in patients younger than 40 years (n=63), 39% in patients between 40 and 50 years (n=314), 54% in patients between 50 and 60 years (n=1420), and 60% in patients over 60 years (n=1507). ADR in patients younger than 50 years of age who do not have a family history of colorectal cancer, or a body mass index (BMI) higher than 30 kg/m² was 26%. A subsequent colonoscopy was performed in 831 patients who had colonic adenoma in the initial colonoscopy. The ADR was 40% in patients who had a repeat colonoscopy within 3 years, 50% within 3-5 years, and 53% > 5 years. Multivariate logistic regression analyses revealed an increased risk of colon adenoma with older age, BMI, higher BMI and a family history of colon cancer (P<0.05). **Conclusions:** In patients with breast cancer, ADR was higher than that of patients without history of cancer. Notably, breast cancer was an independent risk factor for colon adenoma. In patients who are younger than 40 years of age, screening colonoscopy should be considered within five years of breast cancer diagnosis. Multivariate logistic regression: risk factors of adenoma.

**First Author:** Jason Aboudi Mouabbi, Ascension St John Hospital and Medical Center, Detroit, MI

**Background:** Lung cancer is the leading cause of cancer death in the United States (US) and worldwide. Chest X-ray (CXR) is ineffective in reducing lung cancer mortality. National Lung Cancer Screening Trial (NLST) reported 20% reduction in mortality with the use of low-dose computed tomography (LDCT) scan for high risk individuals. Therefore, major organizations including US Preventive Services Task Force has adopted LDCT for lung cancer screening in high risk populations. However, The generalizability of this approach in community setting is yet to be confirmed. Our objective is to assess the ability of LDCT in detection of lung nodules in the community setting and to compare the results to those reported in the NLST. **Methods:** Charts of subjects who underwent LDCT screening between 2013 and 2016 at SJHMC were retrospectively reviewed. Demographic data, the results of the LDCT scans, interventions performed, complications of procedures and pathology findings were collected. All cancer cases found by LDCT and the stage of cancers were documented. The results of our study were statistically compared to the results of both arms of the NLST (CT and CXR arms). Since CXR is ineffective for lung cancer screening, CXR arm serves equivalently to no screening. Results: The baseline characteristics of the subjects are significantly different between this study and NLST. In our study detected significantly higher positive findings. There are more cancers detected in this study compared to NLST CT and CXR arms, which could reflect higher incidence of cancer in this community or higher proportion of current smokers in our study. In this study, LDCT detected cancers at higher stages compared to that of the NLST CT arm but similar stages to NLST CXR arm. This may indicate that LDCT when performed in the community is less effective in detecting cancer at early stages. **Conclusions:** The community population have different characteristics compared to those enrolled in clinical trials. This may also affect the generalizability of the results. Population-based studies are needed to confirm the results of the NLST.

**First Author:** Kamran Aboumousavi, AJMC, Ascension St John Hospital and Medical Center, Detroit, MI

**Background:** Among all breast cancer patients, the relationship varied among disease stage, the direction of the relationship remained consistent. Conclusions: Our results show that smoking cessation is associated with improved survival status amongst breast cancer survivors across all stages. Comprehensive smoking cessation services may improve survivorship when started as early as the time of diagnosis. Further analysis of the association between smoking cessation and other associated medical outcomes will be conducted to further determine the specific impact of cessation programs.
1544 Poster Session (Board #38), Mon, 1:15 PM-4:15 PM
Improving risk assessment of obesity-associated breast cancer. First Author: Neil M. Iyengar, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Elevated body mass index (BMI) is associated with increased risk of estrogen receptor (ER)-positive postmenopausal breast cancer. The risk is also elevated in women with a normal BMI (BMI 18-24) but excess body fat. These risks may be driven by breast white adipose tissue inflammation (WATi), which is associated with elevated aromatase levels and systemic metabolic dysfunction (e.g., hyperinsulinemia). We hypothesized that body fat assessment is superior to BMI for detecting the pathophysiology that promotes obesity-related breast cancer, particularly among normal BMI women.

Methods: Non-tumorous breast tissue was collected from women undergoing mastectomy for breast cancer treatment or prevention. Breast WATi was detected by the presence of crown-like structures in the breast, which are pathognomonic of WATi. Exercise behavior was also assessed prior to surgery using the Godin Leisure Time Exercise Questionnaire. Associations among categorical variables were examined using χ² or Fisher’s exact test. Relationships between continuous variables were examined using the Spearman correlation.

Results: From April 5, 2016 to August 31, 2018, 100 patients were enrolled; median age 49 (range 29–82) years. Breast WATi was present in 56/100 (56%) women and was associated with elevated BMI and body fat levels, breast adipocyte hypertrophy, postmenopausal status, metabolic syndrome and decreased physical activity (P < 0.05). Among 39 women with normal BMI, breast WATi was present in 14 (36%) and was associated with elevated body fat levels, breast adipocyte hypertrophy, dyslipidemia, and decreased physical activity (P < 0.05). There was no statistically significant association between BMI and breast WATi in the normal BMI group. Multinomial logistic regression analysis was performed to control for other covariates. The model was significant (χ² 14.36, df 2, p < 0.001) and was significant in all subgroups. Of these findings is ongoing in an independent cohort of ~5,000 cancer pts from CCGA using an optimized assay; updated performance results will be reported.

Conclusions: Measurement of body fat is superior to BMI for predicting breast inflammation, which has been shown to promote obesity-related breast cancer.

1546 Poster Session (Board #40), Mon, 1:15 PM-4:15 PM
A comparison of risk factors for cigarette and e-cigarette use in the United States adult population. First Author: Leo Chen, University of British Columbia, Vancouver, BC, Canada

Background: The US CDC and public health agencies have reported alarming increases in e-cigarette (ecig) use among youth, even as cigarette (cig) use among youth declined. In this study, other risk factors for cig and ecig use are compared. Methods: This study used data from the Health Information National Trends Survey 5 Cycle 1 survey, and was associated in 2017. Univariate survey-weighted logistic regression analysis responses as a nationally representative US population. Results: Inverted trends included being 35 or older (cig: OR=1.18, p<0.01; ecig: OR=0.97, p<0.01) and being a student (cig: OR=1.07, p<0.01; ecig: OR=0.99, p<0.01) compared to being employed, and being single (cig: OR=1.09, p<0.03; ecig: OR=1.12, p<0.01). Having considered quitting smoking was not significantly associated with ecig use. Conclusions: Segments of the US adult population educated with anti-tobacco campaigns may remain at increased risk for ecig use.

Survey-Weighted Univariate Logistic Regression Analysis of Cigarette and eCigarette Use:

<table>
<thead>
<tr>
<th>cigs</th>
<th>ecigs</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age 18-34</td>
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<td>0.88 0.17</td>
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<tr>
<td>40-44</td>
<td>1.18 0.01</td>
<td>0.92 0.01</td>
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<tr>
<td>Gender Male</td>
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<td>0.79 0.01</td>
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<tr>
<td>Female</td>
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<td>1.00 0.92</td>
</tr>
<tr>
<td>Race White</td>
<td>1.00 0.95</td>
<td>1.13 0.18</td>
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<tr>
<td>More than High School</td>
<td>1.01 0.70</td>
<td>1.21 0.01</td>
</tr>
<tr>
<td>Marital Status Married</td>
<td>1.03 0.29</td>
<td>1.06 0.52</td>
</tr>
<tr>
<td>Occupation Status Not employed</td>
<td>1.10 0.17</td>
<td>1.08 0.22</td>
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</tbody>
</table>
| BMI | 0.843 vs. 0.779, respectively). For the detection of breast WATi compared to a BMI-based model (AUC 0.843 vs. 0.779, respectively).

1545 Poster Session (Board #39), Mon, 1:15 PM-4:15 PM
Prognostic significance of blood-based cancer detection in plasma cell-free DNA (cfdNA): Evaluating risk of overdiagnosis. First Author: Geoffrey R. Gondar, Dana-Farber Cancer Institute, Boston, MA

Background: Screening tests for early cancer detection are often criticized due to risk of overdiagnosis—detection of good prognosis cancers which may not require immediate treatment. We recently reported development of cfdNA sequencing approaches for cancer detection; longitudinal follow-up (F/U) data were utilized here to evaluate prognostic significance of cancer detection using cfdNA. Methods: Plasma cfdNA samples were subjected to whole-genome bisulfite sequencing (WGBS, 30X) as part of a previously-reported circulating Cell-free Genome Atlas (CCGA, NCT02889978) sub-study. This exploratory analysis evaluated the overall survival (OS) of training and test set participants (pts) with cancer (20 cancer types, any stage I-IV). Combining train and test set pts, univariate and multivariate analyses (Cox proportional hazards) assessed OS association with WGBS result (cancer detected vs not detected, set at 98% specificity), clinical stage (IV vs II-III), diagnostic method (symptom- vs screen-detected), sex, age, and histologic grade. Results: Of 827 pts from the training set with F/U (median 12.2 mo), 334 (40.4%) had WGBS-detected cancer. Among 127 (15.4%) pts with cancer that died during F/U, cancer was detected in 104 (81.9%). Results were similar in the test set. In univariate analyses all variables were associated with prognosis, including WGBS result (HR 7.7 p<0.001). In multivariate analyses accounting for other covariates, the three variables that most significantly remained prognostic were WGBS (HR 3.0, p<0.001), clinical stage (HR 1.3, p=0.001), and diagnostic method (HR 1.6, p=0.001). Validation of these findings is ongoing in an independent cohort of ~5,000 cancer pts from CCGA using an optimized assay; updated performance results will be reported.

Conclusions: Cancers detected using WGBS of cfdNA had a worse prognosis than cancers not detected. WGBS cancer detection carried comparable prognostic significance as clinical stage. By preferentially detecting high risk cancers, cancer detection using plasma cfdNA may avoid some of the over-detection that has been seen with some existing cancer screening methods. Clinical trial information: NCT02889978.

1547 Poster Session (Board #41), Mon, 1:15 PM-4:15 PM
Comparison of risk-reducing surgery in women with BRCA and non-BRCA ovarian cancer susceptibility genes. First Author: Zachary Phillip Schwartz, Cedars Sinai Medical Center, Los Angeles, CA

Background: Risk reducing gynecologic surgery (RRSO) is standard of care for women with BRCA mutations. The optimal management for women with non-BRCA ovarian cancer susceptibility mutations remains unclear. We sought to characterize the practice patterns for these women at our two institutions. Methods: Women with germline ovarian cancer susceptibility genes who had a RRSO were identified from 1/2000-1/2019 in an IRB approved study. All patients were asymptomatic with no suspicion for malignancy at time of RRSO. Clinico-pathologic characteristics were extracted from the medical records. Continuous variables were analyzed with Kruskal-Wallis and categorical variables analyzed with chi square and t-tests. Results: 152 BRCA1, 95 BRCA2, and 63 Non-BRCA mutation carriers were identified. Of 827 pts from the training set with F/U (median 12.2 mo), 334 (40.4%) had WGBS-detected cancer. Among 127 (15.4%) pts with cancer that died during F/U, cancer was detected in 104 (81.9%). Results were similar in the test set. In univariate analyses all variables were associated with prognosis, including WGBS result (HR 7.7 p<0.001). In multivariate analyses accounting for other covariates, the three variables that most significantly remained prognostic were WGBS (HR 3.0, p<0.001), clinical stage (HR 1.3, p=0.001), and diagnostic method (HR 1.6, p=0.001). Validation of these findings is ongoing in an independent cohort of ~5,000 cancer pts from CCGA using an optimized assay; updated performance results will be reported.

Conclusions: Cancers detected using WGBS of cfdNA had a worse prognosis than cancers not detected. WGBS cancer detection carried comparable prognostic significance as clinical stage. By preferentially detecting high risk cancers, cancer detection using plasma cfdNA may avoid some of the over-detection that has been seen with some existing cancer screening methods. Clinical trial information: NCT02889978.
Poster Session (Board #42), Mon, 1:15 PM–4:15 PM

Association between breast cancer mortality-to-incidence ratios and state health disparities in the United States. First Author: Yu-Che Lee, University of Miami, Miami, FL.

Background: Breast cancer is the most commonly diagnosed cancer and second leading cause of cancer deaths among women in the United States. The cancer mortality-to-incidence ratio (MIR) provides a population-based indicator of cancer survival and has been established previously to evaluate healthcare variations among different countries. We aim to evaluate the association between state MIRs and other state health variables, which have not been investigated before, between MIR of breast cancer and state-level health disparities in the United States. Methods: We used United States Cancer Statistics (USCS) database to calculate 6-year average of MIRs for breast cancer from 2010 to 2015. America’s Health Rankings (AHR) is a platform used weighted measures in 5 different categories (Behaviors, Community & Environment, Policy, Clinical Care and Outcomes) to determine annual state health rankings. Six-year average (2010-2015) of health uninsured rate by state was obtained from the U.S. Census Bureau and 5-year average (2010-2014) of health spending per capita by state was obtained from Centers for Medicare & Medicaid Services. The correlations between breast cancer MIRs and state health variables were calculated by linear regression analyses. Results: From 2010 through 2015, 1,390,357 females were diagnosed with breast cancer and 246,671 females died from breast cancer in the United States. The 6-year average of age-adjusted incidence rate, mortality rate and MIRs were 124.2 ± 1.3 per 100,000 population, 21.1 ± 0.6 per 100,000 and 1.107 ± 0.007, respectively. Among 50 states we included for analyses, Hawaii had the lowest MIR (0.116 ± 0.014) and Nevada had the highest MIR (2.024 ± 0.004). AHR showed Hawaii had the highest health ranking (No. 1) whereas Louisiana had the lowest health ranking (No. 50) in 2015. In our analysis, states with better health rankings, lower health uninsured rates and higher health spending per capita were significantly correlated with lower MIRs (R2 = 0.695, 0.453 and 0.253, respectively; all P < 0.001). Conclusions: The difference of MIRs for breast cancer was strongly associated with state health diversities. These findings suggest that MIR of breast cancer can be an applicable measure to evaluate and reflect the state-level health disparities in the United States.

Poster Session (Board #44), Mon, 1:15 PM–4:15 PM

Epidemiology and survival in patients with urethral clear cell carcinoma. First Author: Mauzam Patel, University of Arkansas for Medical Sciences, Little Rock, AR.

Background: Clear cell carcinoma (CCC) of the urethra is a very rare histologic variant of urethral adenocarcinoma. The majority of studies have been case reports and case series with no large population based studies. A retrospective analysis was performed with the National Cancer Institute’s (NCI) Surveillance, Epidemiology, and End Results (SEER) database to establish the epidemiology of urethral CCC and determine the clinical factors associated with survival. Methods: All cases of clear cell carcinoma of the urethra diagnosed from January 1, 1973 to December 31, 2014 were extracted from SEER. Age at diagnosis, sex, marital status, race, grade, stage, surgery, radiation, chemotherapy, overall survival (OS), disease specific survival (DSS), and survival months were extracted for analysis. Descriptive statistics were calculated for all variables. Univariable analysis to assess for differences in survival with respect to covariates was performed using the log rank test. Multivariable analysis was performed with Cox proportional hazards regression models to determine the predictive performance of covariates with respect to OS and DSS, reported as hazard ratio (HR) with 95% CIs. Comparisons were considered statistically significant at P < 0.05. Results: Sixty one cases were extracted for analysis. The mean ± SD was 63.0 ± 13.9 years. Fifty eight (95.1%) patients were female with 53 (86.8%) locoregional cases at presentation. There were 50 (82%), 18 (29.5%), and 12 (23.0%) patients who underwent surgery, radiation therapy, respectively. On univariable analysis, the following covariates were associated with both OS and DSS: age, stage, and surgery (all p < 0.001; log rank test). On multivariable analysis, surgery was a predictor for improved OS and DSS (HR, 0.178; 95% CI [0.068; 0.464]) and HR, 0.166; 95% CI (0.196; 2.132), respectively). Additionally, both increasing age and distant disease were associated with worse OS and DSS. Radiation therapy was not significantly associated with OS or DSS. Conclusions: Surgery improves OS and DSS in patients with urethral CCC. While neither radiation nor chemotherapy were significantly associated with survival, additional studies are necessary to determine how these therapeutic interventions may impact prognosis.

Poster Session (Board #43), Mon, 1:15 PM-4:15 PM

Contralateral breast cancer risk according to first breast cancer characteristics among United States women from 1992 to 2015. First Author: Cody Ramin, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD.

Background: After recent advances in breast cancer treatment and increasing uptake of contralateral prophylactic mastectomies, estimates of contralateral breast cancer (CBC) risk by year of diagnosis and other patient characteristics are needed to help inform decision making. Methods: We estimated CBC risk in 399,032 1-year survivors of a first primary breast cancer (stage I-II) in the US Surveillance, Epidemiology, and End Results Database (1992-2015). CBC was defined as an invasive second breast cancer diagnosed in the opposite breast 12+ months after the first breast cancer diagnosis. We estimated standardized incidence ratios (SIRs) and 5-year cumulative incidence of CBC by calendar period, age, breast cancer subtype, and receipt of hormonal therapy for the initial breast cancer. SIRs were calculated as the observed number of CBCs among survivors compared to the expected number of first breast cancers in the general population. Cumulative incidence was estimated in women without contralateral prophylactic mastectomies and accounted for competing risks. Results: Among 399,032 breast cancer survivors, 11,365 cases of CBC were diagnosed in 2015. Risk of CBC was elevated over the entire study period (SIR = 2.23, 95% CI = 2.19-2.27). SIRs for CBC declined over calendar period and this decreasing trend was observed irrespective of age, estrogen receptor (ER) status, and hormonal therapy. Survivors had an overall 5-year cumulative incidence of CBC of 1.49% (95% CI = 1.44%-1.54%), which decreased over time, to 1.31% (95% CI = 1.29%-1.34%) in 1992-1996, 0.99% (95% CI = 0.96%-1.01%) in 2001-2005, and 0.81% (95% CI = 0.79%-0.83%) in 2010-2015. Conclusions: Although CBC incidence is declining in the US from 1992-2015, survivors have approximately twice the risk of an incident breast cancer (in the contralateral breast) compared to the general population. The 5-year cumulative risk of CBC is highest after ER-negative/triple negative tumors highlighting the need for medical surveillance and targeted interventions among these patients.

Poster Session (Board #45), Mon, 1:15 PM-4:15 PM

Association of geographic clustering of cutaneous T-cell lymphoma in the state of Georgia with environmental carcinogenic exposure. First Author: Pamela Blair Allen, Emory University, Winship Cancer Institute, Atlanta, GA.

Background: Geographic clustering of CTCL has been recently reported in large registries, but its association with environmental factors is unknown. Benzene and trichloroethylene (TCE) are two common carcinogenic environmental toxins associated with hematological cancers. We investigated associations between geographic clustering of CTCL incidence in the state of Georgia with benzene and TCE exposure. Methods: We obtained county-level incidence of CTCL within Georgia from the Georgia Cancer Registry between 1999-2015. To account for the demographic structure in each county, standardized incidence ratios (SIR) were calculated by dividing the observed number of cases of CTCL in Georgia by the expected number of cases using national incidence rates by age, sex, and race. Using spatial analyses, we assessed for population-adjusted county-level clustering of SIRs. We also recorded county-level exposure concentration of benzene and TCE between 1996-2014 from the EPA’s National Air Toxics Assessment database. Linear regression analyses on CTCL incidence were performed comparing SIRs to exposure levels of benzene and TCE by county. Results: Our analyses demonstrated significant geographic clustering of CTCL in Georgia (Moran’s I statistic 0.0991, p-value = 0.022). Local spatial tests revealed several statistically significant hot spots of CTCL in Georgia, particularly around Atlanta. This clustering was strongly correlated with benzene (R² = 0.8284, p-value 0.0006) and TCE (R² = 0.0614, p-value 0.0016) exposure concentration. Among the most populous counties in Georgia (Cobb, Dekalb, Fulton, and Gwinnett) CTCL incidence was 1.7 to 2.7 times higher than the average county, and benzene and TCE exposure concentration was 3.0 to 6.3 times higher. Conclusions: These results demonstrate non-random geographic clustering of CTCL incidence in Georgia. This is the first analysis to correlate geographic clustering of CTCL with environmental toxic exposures, demonstrating a statistically significant correlation between environmental exposure to benzene and TCE and CTCL incidence within Georgia.
Insulin resistance measured by the triglyceride-glucose index and risk of obesity-related cancers: An epidemiological investigation in more than 500,000 individuals. First Author: Josef Fritz, University of Colorado, Boulder, CO

Background: The role of insulin resistance as a mediator in the association of body mass index (BMI) with site-specific cancer risk has, to our knowledge, never been systematically quantified. We aimed to determine to what extent insulin resistance measured as the logarithmized triglyceride glucose product (TyG index) mediates the effect of BMI on risk of obesity-related cancers.

Methods: A total of 510,471 individuals from six European cohorts with a mean age of 43.1 years were included in the study. We fitted Cox models, adjusted for relevant confounders, to investigate associations of TyG index with ten common obesity-related cancer sites, and quantified the proportion of the effect of BMI mediated through TyG index.

Results: During a median follow-up of 17.2 years, 16,052 individuals developed obesity-related cancers. TyG index was associated with the risk of cancers of the kidney (hazard ratio (HR) per one standard deviation increase 1.13, 95% confidence interval: 1.07-1.20), liver (1.13, 1.04-1.23), pancreas (1.12, 1.06-1.19), colon (1.07, 1.03-1.10), and rectum (1.09, 1.04-1.14). Substantial proportions of the effect of BMI were mediated by TyG index for cancers of the pancreas (42%), rectum (34%), and colon (20%); smaller proportions for kidney (15%) and liver (11%); none for endometrium, ovary and breast (postmenopausal).

Conclusions: In this pooled cohort study including more than 500,000 individuals, insulin resistance measured as the logarithmized triglyceride glucose product significantly mediated the effect of overweight and obesity on risk of cancers of the kidney, liver, pancreas, colon, and rectum. In contrast, insulin resistance did not mediate the risk for cancers of the endometrium, ovary and breast. Our results confirm a promoting role of insulin resistance in the pathogenesis of gastrointestinal cancers. Although often claimed, insulin resistance does not appear to connect excess body weight with cancers of the female reproductive organs.

Comorbidity and racial differences in risk of mortality of men with breast cancer. First Author: Carol Parisie, Sutter Institute for Medical Research, Sacramento, CA

Background: Black men with breast cancer have more comorbid disease and worse survival than white men. Less is known about comorbid conditions. A score of 0 indicates no significant comorbidity and scores of 2 (CCI). The CCI is a weighted index based on the presence of certain comorbid conditions. A total of 510,471 individuals from six European cohorts with a mean age of 43.1 years were included in the study. We fitted Cox models, adjusted for relevant confounders, to investigate associations of TyG index with ten common obesity-related cancer sites, and quantified the proportion of the effect of BMI mediated through TyG index.

Methods: A total of 510,471 individuals from six European cohorts with a mean age of 43.1 years were included in the study. We fitted Cox models, adjusted for relevant confounders, to investigate associations of TyG index with ten common obesity-related cancer sites, and quantified the proportion of the effect of BMI mediated through TyG index.

Results: During a median follow-up of 17.2 years, 16,052 individuals developed obesity-related cancers. TyG index was associated with the risk of cancers of the kidney (hazard ratio (HR) per one standard deviation increase 1.13, 95% confidence interval: 1.07-1.20), liver (1.13, 1.04-1.23), pancreas (1.12, 1.06-1.19), colon (1.07, 1.03-1.10), and rectum (1.09, 1.04-1.14). Substantial proportions of the effect of BMI were mediated by TyG index for cancers of the pancreas (42%), rectum (34%), and colon (20%); smaller proportions for kidney (15%) and liver (11%); none for endometrium, ovary and breast (postmenopausal).

Conclusions: In this pooled cohort study including more than 500,000 individuals, insulin resistance measured as the logarithmized triglyceride glucose product significantly mediated the effect of overweight and obesity on risk of cancers of the kidney, liver, pancreas, colon, and rectum. In contrast, insulin resistance did not mediate the risk for cancers of the endometrium, ovary and breast. Our results confirm a promoting role of insulin resistance in the pathogenesis of gastrointestinal cancers. Although often claimed, insulin resistance does not appear to connect excess body weight with cancers of the female reproductive organs.

Burden of thrombocytopenia in adult cancer patients receiving chemotherapy. First Author: Gerald A. Soff, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Thrombocytopenia is a common toxicity of chemotherapy, yet there are limited data on its occurrence in routine clinical practice. Methods: Using structured patient-level data from the Flatiron Health EHR-derived database, we assessed risk (3-month cumulative incidence) of chemotherapy-induced thrombocytopenia (CIT) in adult patients (2012-2017) based on platelet counts, overall and by each grade of CIT, cancer type, and chemotherapy regimen (Table); and the co-occurrence of other hematologic abnormalities. Results: Of 15,521 solid tumor patients who initiated chemotherapy, 13% had evidence of CIT within 3 months (platelet count <100x10^9/L), 4% had grade 3 (25 to <50x10^9/L) and 2% had grade 4 (<25x10^9/L) CIT. Of the solid tumors examined, incidence was highest in melanoma patients. In hematologic malignancies (N = 2,537), 3-month risk was even higher with nearly 30%, 16%, and 12% having any grade, grade 3 and 4 CIT, respectively; and the greatest risk being in multiple myeloma patients. Anthracycline-based regimens were associated with the highest risk of CIT (7% grade 3; 4% grade 4), followed by gemcitabine- and platinum-based regimens. Anemia often accompanied first evidence of CIT (49%); isolated thrombocytopenia occurred in 15%. Conclusions: This study provides a current snapshot of CIT risk in a large sample of adult patients undergoing chemotherapy in routine clinical practice, highlighting patients at highest risk for CIT and underscoring the complexity of managing cancer treatment.

Select chemotherapies and cancer types, N

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<tr>
<th>Chemotherapy</th>
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<th>Grade 4</th>
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<tr>
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<td>Platinum, 8,058</td>
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<td>Tauxane, 2,116</td>
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<td>Non-Hodgkin's Lymphoma, 1,321</td>
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<td>Melanoma, 58</td>
<td>21.4 (14.7, 31.3)</td>
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<td>All Solid Tumors, 15,521</td>
<td>12.8 (12.3, 13.4)</td>
<td>4.2 (3.9, 4.6)</td>
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</table>

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Cardiometabolic risk factors and survival after cancer in the women’s health initiative. First Author: Michael S. Simon, Barbara Ann Kamanos Cancer Institute, Wayne State University, Detroit, MI

Background: Features associated with metabolic syndrome have been connected to both risk and poor outcomes for certain cancers. Methods: We used data on 12,107 women enrolled in the Women’s Health Initiative diagnosed prospectively with either local or regional stage cancer to evaluate the association between cardiometabolic risk factors identified at study entry, (elevated waist circumference (WC), hypertension, high cholesterol, and presence of type 2 diabetes), with death from either cancer, cardiovascular disease (CVD), or other causes. Results: Cancer sites included those previously linked in the published literature to metabolic syndrome and cancer risk: breast, colorectal, endometrial, non-Hodgkin’s lymphoma, kidney, pancreatic, ovarian, stomach and liver. Multiple imputation methods were used to account for missing data (6.9%). Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI), adjusted for other significant predictors of survival. Results: After a median follow-up of 10.0 years, there were 3,612 total deaths with 1,547 (43%) due to cancer. Most participants (60.3%) had at least 2 cardiometabolic risk factors, and 5.8% had 3 or 4. Having 3-4 risk factors, was associated with mortality due to cancer (HR: 1.39, 95% CI: 1.12, 1.71), CVD (HR: 2.62, 95% CI: 1.91, 3.59), and other causes (HR: 1.97, 95% CI: 1.57-2.47) compared with no risk factors. High WC was associated with higher mortality due to cancer and other causes, and history of diabetes, and hypertension were associated with higher mortality due to CVD, and other causes. Conclusions: Women diagnosed with early or regional stage cancer, the presence of 3-4 cardiometabolic risk factors which is consistent with a diagnosis of metabolic syndrome, are significantly associated with death due to cancer, CVD, and other causes. Attention to primary prevention focused on weight control, physical activity and diet after cancer diagnosis and treatment, can have an important positive influence on survivorship after cancer.

Characteristics of cancer patients with a history of solid organ transplantation: Analyses of a patient cohort reporting to a large cancer center. First Author: Susen Burock, Charité Comprehensive Cancer Center, Berlin, Germany

Background: Solid organ transplant recipients have a 2-4-fold elevated risk of developing cancer compared to the general population due to immunosuppressive therapy. Cancer patients with a history of organ transplantation (TPx) may or may not have a cancer attributed to immunosuppression. Here we report on a cohort of cancer patients of the Charité, diagnosed with the first occurrence of a solid cancer in 2010-2014 and a history of TPx. Methods: The cancer registry database of the Charité Comprehensive Cancer Center was queried for patients diagnosed with the first occurrence of solid cancer between 2010 and 2014 and a previous solid organ transplantation. General tumor and patient characteristics as well as outcome were analyzed. Results: A total of 226 patients (151 male, 75 female) were identified and included in the analysis. Transplanted organs included kidney in 148 patients, liver in 63, and heart, lung or a combination of both in 15. The median age at transplantation and initial tumor diagnosis was 54.7 years and 63.4 years respectively. Median interval between organ transplantation and diagnosis of the cancer was 8.1 years, range 0 - 39 years. 60.6% of cancers developed > 10 years after TPx. The interval between TPx and development of cancer inversely correlated to patient age at TPx, with a median of 17.9 years (age group 18-34), 13.0 years (35-49), 6.7 years (50-64), and 5.3 years, (65+ years). The majority of cancers occurred within the first 10 years after TPx, however especially for the age group 35-49 cancer diagnoses peaked 20-25 years after transplantation. The most common cancer types where non-melanoma skin cancer (34%), followed by kidney (15%), lung (13%) prostate (8.61% of all male patients) and colorectal (4.87%). Median survival of all patients after tumor diagnosis was 4.6 years, with 1.0 years for lung cancer, 6 years for colorectal cancer, 5.7 years for prostate cancer respectively. The median OS was not yet reached for non-melanoma skin cancer and kidney cancer. Conclusions: Our data support the necessity of long-term follow up and cancer screening in patients after organ transplantation beyond the commonly practiced 10 years post transplantation screening.

Breast cancer screening adherence at multiple timepoints over eight years among women in a familial cohort. First Author: Nancy L. Schaeffer, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Background: Since 2007, U.S. guidelines recommend cancer-free women with ≥20% lifetime breast cancer (BC) risk undergo BC screening with mammogram and breast MRI. There is limited long-term data on BC screening adherence among young, high-risk women. To address this knowledge gap, we examined utilization of multiple BC screening modalities over time. Methods: Eligible women were ≥30 years old, had no history of BC ovarian cancer, an intact breast, were enrolled in the Breast and Ovarian Surveillance Service (BOSS) Cohort, and visited the Johns Hopkins Cancer Genetics Clinic for risk assessment within 2 months of cohort enrollment (N = 374). All screening was self-reported at baseline, 4, and 8 years. A subset has been validated. We categorized women by BC risk (Tyner-Cuzick version) obtained at the clinic. We examined frequency of screening over follow-up, and defined adherence to annual mammography and breast MRI based on age- and risk-based guidelines. We modeled the association between BC risk and adherence at 4 and 8 years using logistic regression. Results: At baseline, the median age was 47 years, 31% had lifetime risk < 20%, and 69% had risk ≥20%. Frequency of mammography and clinical breast exam over follow-up was > 60%, while frequency of breast MRI and breast ultrasound was < 40%. Twenty-five percent of high-risk women at 4 years and 40% at 8 years did not report any mammography, breast MRI, or breast ultrasound. At 4 years, high-risk women were 85% less adherent (multivariable adjusted OR = 0.15, 95%CI = 0.05, 0.45) to mammography compared to women with a risk of < 20% due to low uptake of breast MRI, while at 8 years, high-risk women were also less adherent to mammography (multivariable adjusted OR = 0.42; 95%CI = 0.18, 0.95). We observed similar associations among women at high-risk at 5- and 10-year follow-up, and predicted adherence at any given time for women who did not uptake MRI complied with other health screening including for colorectal cancer. Conclusions: High-risk women were not adherent to risk-appropriate BC screening, and adherence did not improve over time. Low adherence appears specific to BC screening. New approaches to BC screening are urgently needed for this high-risk group.
1560 Poster Session (Board #54), Mon, 1:15 PM-4:15 PM
Health insurance literacy, financial hardship and financial sacrifices among cancer survivors in the United States. First Author: Jingxuan Zhao, American Cancer Society, Atlanta, GA

Background: Rising costs of cancer care have imposed substantial financial burden on cancer survivors. To date, little is known about the associations between potentially modifiable patient characteristics, including health insurance literacy (HIL), on financial burden among cancer survivors. This study aimed to evaluate the associations between HIL and financial hardship and financial sacrifices among adult cancer survivors in the United States.

Methods: We identified 914 adult cancer survivors from the 2016 Medical Expenditure Panel Survey Experiences with Cancer Questionnaire. HIL was measured based on the question "Did you ever have a problem understanding health insurance or medical bills related to your cancer, its treatment, or the lasting effects of that treatment?" Medical financial hardship was measured in three domains—1) material (e.g. problems paying medical bills); 2) psychological (e.g. worry about large medical bills); and 3) behavioral (e.g. delay or forego healthcare because of cost). Financial sacrifices were based on questions related to changes in spending on vacation or leisure activities. We used multivariable logistic regression modeling to separately evaluate the associations between HIL and 1) financial hardship and 2) financial sacrifices.

Results: 18.9% cancer survivors aged 18-64 years and 14.6% survivors ≥65 years reported HIL problems. Regardless of age groups, cancer survivors with HIL problems were more likely to report any material (OR =3.2; 95% CI:1.9-5.2) or psychological (OR=7.2; 95% CI: 4.1-12.7) financial hardship than those without the problems, as well as more likely to delay or forgo multiple medical care due to cost, including prescription medicine (OR=3.6; 95% CI: 1.8-7.1), specialist visit (OR=2.6; 95% CI: 1.2-5.8), and follow-up care (OR=2.1; 95% CI 1.2-4.0). Higher likelihood of reporting all measures of financial sacrifices were observed among those with HIL problems in both age groups (all <p<0.05).

Conclusions: Cancer survivors with HIL problems were more likely to report financial hardship and financial sacrifices than those without the problems. Improving HIL may help mitigate financial hardship.

1562 Poster Session (Board #56), Mon, 1:15 PM-4:15 PM
Does ethnicity affect the relationship between body mass index (BMI) and overall survival (OS) in non-smoking cell lung cancer (NSCLC)? First Author: Aline Fusco Fares, Princess Margaret Hospital, Toronto, ON, Canada

Background: In Caucasian-predominant populations, overweight or obese NSCLC pts (BMI≥25-kg/m²) have better prognosis while underweight (BMI<18.5-kg/m²) pts have a worse prognosis. A large pooled sample allowed us to evaluate the role of ethnicity in this BMI-NSCLC OS relationship.

Methods: Using individual data, survival analysis was performed on 15 ILCCO studies, assessing the interactions between ethnicity and BMI on overall survival (OS). Adjusted Hazard Ratios (aHR) from Cox models and adjusted penalized smoothing spline plots were generated.

Results: In Caucasian-predominant populations, overweight or obese (BMI≥25-kg/m²) have better prognosis while underweight (BMI<18.5-kg/m²) pts have a worse prognosis. Differences likely reflect genetically-informed muscle/adipose tissue distributions, where Black pts may have less sarcopenic obesity than other ethnicities. In future prognostic studies, BMI relationships must account for ethnic differences.

1565 Poster Session (Board #55), Mon, 1:15 PM-4:15 PM
Incidental atypical hyperplasia/LCIS in mammoplasty specimens and subsequent risk of breast cancer. First Author: Francisco Acevedo, Pontificia Universidad Católica de Chile, Santiago, Chile

Background: Proliferative breast lesions with atypia (atypical hyperplasia and lobular carcinoma in-situ (LCIS)) increase the risk of breast cancer (BC). Most cases are diagnosed in the context of an abnormal mammogram. Little is known about BC risk for patients with these lesions who are asymptomatic. Mammoplasty specimens allow us to study breast tissue in asymptomatic healthy women. We previously published the rate of atypia in the largest reported mammoplasty cohort. The aim of this study is to examine the risk of BC in the atypia cohort.

Methods: Breast pathology reports were retrospectively reviewed for evidence of atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH) or LCIS in bilateral reduction mammoplasty specimens from five institutions within a single healthcare system between 1990 to 2017. Patients with prior or concurrent BC or prior atypia were excluded. Data was extracted from electronic medical records using natural language processing and manual review to assess subsequent risk of BC.

Results: From our mammoplasty cohort of 4771 patients, 295 patients were found to have atypia (6.2%) at baseline. 40 of these patients were lost to follow-up and excluded from the study. For the remaining 255 patients, 13 had severe ADH bordering on ductal carcinoma in situ, 52 had LCIS, 119 had ALH, and 71 had ADH at baseline. The median age at baseline was 52.1 (range 17.9 – 74.3). With a median follow-up of 7.7 years, of the 255 patients 9 patients developed BC (8 invasive carcinomas, 1 ductal carcinoma in situ). 81.3% of the cohort did not receive chemoprevention. Only one patient out of the nine who developed BC received chemoprevention. The risk of developing BC among women with atypia at baseline was 0.5%, 2.9% and 4.1%, at 3, 5 and 10 years respectively. Conclusions: Patients with asymptomatic atypias found in reduction mammoplasty specimens appear to be at lower risk of developing BC than those diagnosed with atypia in the context of an abnormal mammogram. These results may provide guidance on how to manage this group of patients related to future screening and/or chemoprevention.
Background: Breast cancer survivors are the largest group of cancer survivors in the United Kingdom (UK). Having had a breast cancer diagnosis may adversely affect the patient’s mental health. We aimed to estimate the long-term risk of anxiety and depression in women with history of breast cancer compared to those who have never had cancer. Methods: We conducted a matched population-based cohort study using data from the Clinical Practice Research Datalink (CPRD) GOLD primary care database. The exposed cohort included all adult women diagnosed with breast cancer between 1987 and 2018; the unexposed group included women with no cancer history, matched to exposed women in a 4:1 ratio on primary care practice and age. Cox regression models stratified on matched set were used to estimate hazard ratios of the association between breast cancer survivorship and anxiety and depression. Results: 59,972 women (mean 62 years; standard deviation (SD) 14.0) had history of breast cancer. The median follow-up time was 3.0 years (SD 4.4), which amounted to 256,186 person-years under observation. The comparison group included 240,387 women followed up over 3.5 years (SD 4.5) (1,163,819 person-years). The incidence of anxiety in breast cancer survivors was 0.08 (95% confidence interval (95% CI) 0.07-0.08) per 1000 person-years, and the incidence of depression was 70 (95%CI 68-71) per 1000 person-years. The risks of both depression and anxiety were raised in breast cancer survivors compared with controls, and this appeared to be driven by the first 3 years following diagnosis (Table). Conclusions: Breast cancer survivors in the UK had significantly higher risk anxiety and depression diagnosed in primary care for three years following diagnosis than women who never had cancer. Risk of anxiety and depression in breast cancer survivors compared to women who did not have cancer by time since diagnosis.

### Table: Anxiety and Depression in Breast Cancer Survivors

<table>
<thead>
<tr>
<th>Time since diagnosis (years)</th>
<th>Anxiety HR 95% CI</th>
<th>Depression HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>1.01</td>
<td>2.84</td>
</tr>
<tr>
<td>1-3</td>
<td>1.04</td>
<td>3.06</td>
</tr>
<tr>
<td>3-5</td>
<td>1.04</td>
<td>3.06</td>
</tr>
<tr>
<td>&gt;5</td>
<td>1.04</td>
<td>3.06</td>
</tr>
<tr>
<td>Overall</td>
<td>1.00</td>
<td>2.84</td>
</tr>
</tbody>
</table>

HR: hazard ratio; 95% CI: 95% confidence interval

Factors associated with breast cancer mortality-per-incident case in low-to-middle-income countries (LMICs)

Background: Reducing breast cancer mortality is a key healthcare challenge worldwide. We sought to determine the impact of macro-socioeconomic factors on breast cancer age-standardized incidence (ASI) and mortality-per-incidence case in LMICs. Methods: Data regarding breast cancer ASI and mortality in 78 LMICs were obtained from IARCWHO. MPI was defined as the age standardized mortality ratio divided by the ASI. Further economic data were obtained from World Bank, UN Development Project, and WHO data sources. Results: In 2018, the median ASI for breast cancer was 26.5 (range; 5-67.3) per 100,000 population in LMICs, with a median MPI of 50.6% (range 27-70%). ASI and MPI were inversely correlated (Spearman rho = -0.236, p = 0.044). Factors associated with ASI and MPI are shown in the table below. We found no factor could discriminate between the highest and lowest quartile in terms of ASI. However, all (except health expenditure as a % of GDP) were significantly different between the highest and lowest quartile in terms of MPI. Conclusions: Results suggest considerable variation in terms of breast cancer MPI within LMICs. Improved rates are seen with increasing GDP, literacy, contraceptive use, and provision of doctors and mammography, but overall % GDP expended on public health does not seem to significantly influence breast cancer MPI.

### Table: Factors Associated with Breast Cancer Mortality

<table>
<thead>
<tr>
<th>Factor</th>
<th>ASI Rho value</th>
<th>ASI p-value</th>
<th>MPI Rho value</th>
<th>MPI p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography machines per pop. (2014)</td>
<td>0.11</td>
<td>0.44</td>
<td>0.35</td>
<td>0.01</td>
</tr>
<tr>
<td>% adult women with BMI&lt;30 (2016)</td>
<td>0.30</td>
<td>0.06</td>
<td>0.49</td>
<td>0.005</td>
</tr>
<tr>
<td>Incidence inequality (GINI coefficient), 2017</td>
<td>0.09</td>
<td>0.43</td>
<td>0.78</td>
<td>0.004</td>
</tr>
<tr>
<td>GDP per capita (2017)</td>
<td>0.13</td>
<td>0.02</td>
<td>0.67</td>
<td>0.001</td>
</tr>
<tr>
<td>Avg fertility rate per woman (2000-2005)</td>
<td>0.12</td>
<td>0.03</td>
<td>0.54</td>
<td>0.001</td>
</tr>
<tr>
<td>Contraceptive prevalence rate, 1995-2005</td>
<td>0.12</td>
<td>0.03</td>
<td>0.54</td>
<td>0.001</td>
</tr>
<tr>
<td>Doctors per 100,000 pop (1993)</td>
<td>0.11</td>
<td>0.42</td>
<td>0.58</td>
<td>0.001</td>
</tr>
<tr>
<td>Adult literacy rate (2004)</td>
<td>0.09</td>
<td>0.41</td>
<td>0.58</td>
<td>0.001</td>
</tr>
<tr>
<td>Public health expenditure (% GDP, 2001)</td>
<td>0.05</td>
<td>0.66</td>
<td>0.14</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Factor: Mammography machines per pop. (2014); % adult women with BMI<30 (2016); Incidence inequality (GINI coefficient), 2017; GDP per capita (2017); Avg fertility rate per woman (2000-2005); Contraceptive prevalence rate, 1995-2005; Doctors per 100,000 pop (1993); Adult literacy rate (2004); Public health expenditure (% GDP, 2001)

Conclusions: Risk of anxiety and depression in breast cancer survivors compared to women who have never had cancer: A population-based cohort study in the United Kingdom. First Author: Helena Carrière, London School of Hygiene and Tropical Medicine, London, United Kingdom
Adverse effects of early bilateral oophorectomy on body composition: Results from a nationally representative sample of United States women. First Author: Priyash S Varia, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Background: Prior studies suggest that bilateral oophorectomy (BO), a common cancer prevention strategy, may be associated with adiposity. However, the impact of BO on lean mass, a potential marker of healthy aging, and whole-body composition is not known. Declines in lean mass have been linked to physical disability and mortality. We examined the association between BO and total and regional distribution of fat and lean mass in a cross-sectional study.

Methods: The study population included women 35-70 years who underwent dual-energy x-ray absorptiometry (DXA) scans at enrollment as part of the National Health and Nutrition Examination Survey 1999-2006 (N = 3,764). Multinomial logistic regression models were used to examine the relationship between prior BO and tertiles of fat and lean mass. Models were adjusted for age, race, education, BMI at age 25, physical activity, smoking, alcohol use, parity, oral contraceptive use and hormone replacement therapy use.

Results: Women with prior BO (< 45 years (n = 346) had 2.9-times higher odds compared to women without BO (n = 3,418) of being in the highest compared to the lowest tertile of total fat mass (OR, 2.91; 95% CI, 1.93-4.38) and 2.7-times higher odds of being in the lowest compared to the highest tertile of total lean mass (OR, 2.67; 95% CI, 1.81-3.95). Results were similar when stratified by age at enrollment (< 45, 45-54, and ≥55). Similarly, among women with normal BMI at enrollment, those with prior BO < 45 years (n = 741 had higher odds of being in the highest tertile of total fat mass (OR, 9.88; 95% CI, 2.21-44.00) and the lowest tertile of total lean mass (OR, 10.09; 95% CI, 2.72-37.46). These differences in body composition were most pronounced in the trunk region. No difference was observed in women with BO ≥45 years compared to women without BO. Conclusions: Women with a history of early BO experience significant changes in body composition, including increased fat mass and decreased lean mass, even while maintaining a normal BMI. If validated in future prospective studies, our results suggest that a comprehensive evaluation of body composition may be warranted in young women who undergo BO.

“Early impact” of the lung cancer screening in United States population in the SEER REGistries. First Author: Isabel M Emmerick, University of Massachusetts, Worcester, MA

Background: The Lung Cancer Screening Trial (NLST) demonstrated improved overall survival (OS) and lung cancer specific survival (LCSS), likely due to finding early-stage NSCLC. Our study investigates the impact of the NLST publication in 2011 on the lung cancer outcomes in the general US Population by assessing the incidence rates, ratio of early/late stage, and lung cancer mortality in the years immediately prior to and following this publication. Methods: Rate sessions from the SEER18 database were accessed during the years 2008-2015. We analyzed overall lung cancer incidence and mortality rates. The ratio of early/late stage was obtained by dividing the number of stage I and II cases by the number of stage III and IV diagnosed by year. We investigate changes in level and trend using interrupted time series in STATA12, considering 2011 as the intervention. In addition, we performed a T-test for averages ratios comparing the years 2007-2010 to the years 2012-2015 for the entire lung cancer population and for subgroups by median family, ethnicity, Sex, Age and SEER Registry. Results: Although the overall lung cancer rates remained stable during the study period, a significant increase in the ratio of early/late stage was observed following the release of NLST for the overall lung cancer population (p=0.006) and for the screening age group (p= 0.014). The effects of ratio of early/late stage as noted in the overall group persisted for all patient subgroups, except for patients associated with a median income <$40,000, for those there were while it and for the following regions Detroit Metro, Iowa, Greater and Rural Georgia and Louisiana where no association was found between the release of NLST changes in the ratios of early detection even more, in some cases there was a decrease in late stage detection. There was no impact on lung cancer mortality in the general lung cancer population or in any patient subgroups. Conclusions: Since the publication of the NLST in 2011, there has been no impact on lung cancer mortality or incidence of lung cancer in the general US population. However, favorable increase in the proportion of early stage lung cancers, depending upon median family income, race and location. We expected a greater impact of lung cancer screening after 2015 since CT-screening for lung cancer was adopted by CMS and other insurances during that year.

Sex-specific mortality trends in adolescents and young adults with cancer from 2007 to 2016. First Author: Allison Close, UPMC Children’s Hospital of Pittsburgh, Pittsburgh, PA

Background: Adolescents and young adults (AYA) aged 15-39 years make up approximately 70,000 new oncology cases in the USA. Historically, mortality from cancer has smaller incremental improvements in AYA patients when compared to children and older adults, and not much is known about current sex-specific trends. We assessed overall and sex specific AYA mortality for the last 10 years (2007-2016). Methods: Trends in age-adjusted mortality rates per 100,000 (1972-2016) were obtained from the CDC’s National Center for Health Statistics (NCHS). Average annual percent changes (AAPCs) in relative survival were analyzed using NCI’s JPSurv webtool and mortality AAPCs were quantified using Joinpoint regression analysis. Results: Overall declines in mortality are similar in AYA men and women from 1972-2016, with 54% and 51% decline, respectively. In the most recent 10 years of data (2007 to 2016), combined sex AYA mortality AAPC’s declined by about 0.8% per year, slightly slower than declines in children <15 years (1.3% per year) and adults ages >40 years (1.5% per year). Among AYA males there have been 10 year AAPC mortality declines in leukemia (-1.8%), Hodgkin lymphoma (HL) (-5.1%), Non-Hodgkin lymphoma (NHL) (-4.1%) and melanoma of the skin (-3.4%). For AYA females, 10 year AAPC mortality declines occurred in leukemia (-1.9%), ovarian (-1.5%), HL (-10%), NHL (-4.9%) and melanoma (-2.8%). These declines have been offset by stable or increasing mortality rates for several common AYA cancers, including colorectal cancer (CRC) (1.1%) and bone and joint cancer (0.6%) in AYA males. AYA females have experienced mortality increases for CRC (0.6%), bone and joint cancer (0.5%) and uterine corpus cancer (2.8%). Conclusions: In general, mortality rates for both AYA men and women have declined over the past 10 years due to decreased mortality in hematologic malignancies and melanoma. Despite overall improvement, tumor categories in both AYA males and female such as CRC, bone and joint cancer, and uterine corpus cancers show increasing mortality. These diseases require specific investigations by both pediatric and adult researchers.

Race disparities in cancer survival: A trend analysis based on SEER data (1973-2010). First Author: Seyed Navid Alavi, Howard University Hospital, Washington, DC

Background: African Americans have higher incidence of cancer and lower survival rates compared to other ethnicities. We studied the 5-year relative survival between black and white races for the most common cancers in the United States. Methods: Data was obtained from the SEER database, the largest population-based cancer database including 28% of US population. Data containing 5-year relative survival from the patients who were diagnosed from 1973 to 2010. We included data for cancers of colorectal, lung, prostate, breast, and melanoma, the most common cancers in the United States. Results: For colorectal cancer average 5-year relative survival from 1973 to 2010 is 59.9% for whites and 51.5% for blacks. Same results for lung cancer are 14.6% for whites and 12.2% for blacks, for breast cancer is 84.5% for whites and 71.6% for blacks, for prostate cancer is 86.9% for whites and 80.5% for blacks, and for melanoma is 87.9% for whites and 66.4% for blacks. The average black to white 5-year relative survival ratio is 0.86, 0.84, 0.85, 0.92, and 0.76 for cancers of colorectal, lung, breast, prostate, and melanoma, respectively. This ratio has decreased from 0.89 to 0.86 and from 0.87 to 0.81 for colorectal and lung cancer, respectively and for cancers of breast, prostate and melanoma this ratio has decreased. Better understanding of the factors contributing to racial differences in cancer survival has potential applicability in policymaking for a better and equal health care delivery.
Tumor mutation burden (TMB) levels were calculated for LS patients in MLH1 and PMS2. Approximately, 50% of patients had CNAs. One patient had no mutation detected from this panel. Except for 2 patients, 1 with HER2 amplification and another with KRAS mutation, no other classic NSCLC driver genes were detected. The most frequently mutated genes were CCND1, TP53, DAXX and NRAS, occurring in 30%, 26%, 22% and 19% of patients, respectively. Interestingly, 78% (21/27) patients had mutations in epigenetic regulators. Of the 184 mutations identified, 51 occurred in epigenetics-related genes. Pathway analysis also revealed an enrichment of genes participating in chromatin remodeling and organization. Next, we compared the genomic profile of PLELC with lung adenocarcinomas and EBV positive nasopharyngeal carcinomas. Our results indicated that LRP1B or TP53 mutation was a poor prognostic factor for lung cancer. In this study, we elucidated a distinct genomic landscape associated with PLELC with no classic NSCLC driver mutation but an enrichment of mutations in epigenetic regulators. The observation of high expression of PD-L1 and lack of canonical druggable driver mutation raises the potential of immunotherapy blockade therapy for PLEC.

Characterization of genomic alterations in Chinese LCNEC and SCLC via comprehensive genomic profiling. First Author: Lin Wu, Department of Thoracic Medicine, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University (Hunan Cancer Hospital), Changsha, China

Background: LCNEC and SCLC are aggressive neuroendocrine carcinomas with overlap in clinical, histopathologic, morphologic and genomic features. Differential molecular features between the two subtypes have not been well established. We aimed to contribute to the advancement of optimal clinical strategies for each subtype. Here we interrogated the genomic characteristics in LCNEC as compared to SCLC along with their histologically related subtypes: carcinoids and atypical carcinoids via comprehensive genomic profiling. Methods: FFPE samples from 31 LCNECs, 35 SCLCs, 14 carcinoids and 22 atypical carcinoids were sequenced in a CLIA-certified sequencing laboratory using 520 cancer-related genes. Results: Comparative mutational analysis revealed that LRP1B or TP53 mutation was a poor prognostic factor for lung cancer. In this study, we elucidated a distinct genomic landscape associated with PLELC with no classic NSCLC driver mutation but an enrichment of mutations in epigenetic regulators. The observation of high expression of PD-L1 and lack of canonical druggable driver mutation raises the potential of immunotherapy blockade therapy for PLEC.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Blood-based genomic profiling of circulating tumor DNA from patients with advanced biliary tract cancer. First Author: Junying Wang, Zhongda Hospital, Soochow University, China

Background: Biliary tract cancer (BTC) is a highly lethal malignancy as diagnosed occurring at late stages and marginally sensitive to chemotherapy. Increasing evidence indicates targeted therapeutics may provide new hope for improving clinical response in BTC, hence better comprehending the genomic profile is particularly important. However, tissue of BTC is highly wide tumor heterogeneity and often inadequate for molecular characterization, a proper method is urgently needed. Circulating tumor DNA (ctDNA) may be regarded as a reliable tool to reveal genomic signature. Methods: Next-generation sequencing (NGS) targeted 150 cancer-related genes was used to detect blood-based ctDNA from 154 Chinese patients with BTC. The mean sequencing depth was more than 3000×. Somatic genomic alterations (GA) including single nucleotide variation (SNV), copy number variation (CNV) and fusion were analyzed and compared with an internal tissue genomic database (545 Chinese patients with BTC) tested by NGS and TCGA database (n = 227) tested by the whole exome sequencing (WES). Allele frequency (AF) represented the percentage of mutant allele reads relative to total reads (mutant plus wild type). Maximum somatic allele frequency (MSAF) was defined as the maximum AF (0.1% < AF < 35%) of all the somatic alterations identified per sample. Results: Among ctDNA database, at least one GA was found in 95% (147/154) of samples (a median of 4 GA per patient). The median MSAF across all cases was 6.47% (range, 0%–34.8%). Pathologic type (P < 0.01) and stage (P = 0.001) were significantly related with MSAF, respectively. Frequencies of SNV in commonly mutated genes from ctDNA were similar to those observed among tissue samples, like TP53 (35.1% vs 40.4%) and KRAS (20.1% vs 22.6%), however, a little lower in TCGA database (TP53 24.2%; KRAS 10.1%). Besides the consistency of SNV detected from ctDNA and tissue samples was poor, and tumor heterogeneity might be in charge of this phenomenon. Among the highly frequent mutations (AF > 5%) in ctDNA, 45% of genes was considered as druggable targets, such as EGFR/RAS/RAF pathway and AKT/mTOR/PI3K pathway. Conclusions: These findings demonstrated that ctDNA testing by NGS was feasible in revealing somatic genomic profiles and identifying potential therapeutic targets. Noninvasive ctDNA could be used as a complementary approach to tissue testing in patients with metastatic BTC.

Outcomes associated with rapid genetic testing for BRCA1 and BRCA2 at time of breast cancer diagnosis. First Author: Kelly A. Metcalf, University of Toronto, Toronto, ON, Canada

Background: Bilateral mastectomy improves survival for women with BRCA-associated breast cancer. Most women do not know their BRCA status at the time of BC diagnosis when making surgical decisions. Rapid genetic testing (RGT) allows a woman to have genetic test results prior to treatment decision making, but it is unclear if RGT has an impact on treatment choices. It is also unclear if there are psychosocial implications associated with genetic testing at the time of breast cancer diagnosis. The objective of the current study was to assess the impact of RGT at the time of BC diagnosis on surgical decision-making and psychosocial functioning. Methods: Eligible women were referred from participating surgeons at BC diagnosis. Women completed baseline questionnaires assessing treatment preferences, cancer related distress, anxiety, and depression. All participants received in-person pre-test genetic counselling and genetic test results were given within 10 days. Participants completed surveys at 1 week and 1 year post-genetic testing to assess treatments and psychosocial functioning. Results: 1010 women consented to participate and 60 (5.9%) were identified with a BRCA mutation. 15% of those identified with a BRCA mutation did not meet provincial eligibility criteria for genetic testing, and 20% were eligible prior to a breast cancer diagnosis but had not received testing. Mean levels of cancer-related distress, anxiety and depression declined significantly from baseline to 1 year for all women (all p < .05), and there were no differences at any time point between those with and without a BRCA mutation. Of those identified with a BRCA mutation, 67.3% reported that their surgery choice changed. 73.7% of BRCA carriers had a bilateral mastectomy, compared to 20.2% of BRCA negative (p < 0.001). Most women used genetic testing results for surgical decision making (96.1% of BRCA positive and 86.4% for negative). Conclusions: RGT for BRCA1 and BRCA2 at the time of BC diagnosis does not have a negative impact on psychosocial functioning. There are no differences in cancer-related distress, anxiety or depression between women who receive a positive result compare to a negative genetic test result. Furthermore, surgical choice changed for many women identified with a BRCA mutation, with the majority electing for bilateral mastectomy.
Comprehensive germline multigene panel testing changes clinical care for patients with breast cancer. 99% of patients harbored at least one variant. 72% P/LP variants were identified in 19 cancer predisposition genes with BRCA2 being the most common. 63 patients (10.8%) carried a P/LP variant in a gene that would be recommended by the ACMG to be reported due to clinical actionability with the most common being ATM (n = 17), BRCA2 (n = 13), MUTYH (n = 8), and APC (n = 5). We observed a higher frequency of patients who carried autosomal recessive non-cancer pathogenic mutations of varying penetrance. Notable mutated genes included CFTR (cystic fibrosis, n = 16), BTD (bietidase deficiency, n = 43), and CBS (homocystinuria, n = 90). Of 209 mutated genes, 173 genes had mutations present in 1% or less of our population, demonstrating significant genetic heterogeneity. Conclusions: The majority of patients undergoing clinical cancer WES harbors pathogenic germline variation. Identification of clinically actionable germline findings will create additional burden on oncology clinics as broader WES becomes commonplace.

Comprehensive germline multigene panel testing changes clinical care for patients with breast cancer. 99% of patients harbored at least one variant. 72% P/LP variants were identified in 19 cancer predisposition genes with BRCA2 being the most common. 63 patients (10.8%) carried a P/LP variant in a gene that would be recommended by the ACMG to be reported due to clinical actionability with the most common being ATM (n = 17), BRCA2 (n = 13), MUTYH (n = 8), and APC (n = 5). We observed a higher frequency of patients who carried autosomal recessive non-cancer pathogenic mutations of varying penetrance. Notable mutated genes included CFTR (cystic fibrosis, n = 16), BTD (bietidase deficiency, n = 43), and CBS (homocystinuria, n = 90). Of 209 mutated genes, 173 genes had mutations present in 1% or less of our population, demonstrating significant genetic heterogeneity. Conclusions: The majority of patients undergoing clinical cancer WES harbors pathogenic germline variation. Identification of clinically actionable germline findings will create additional burden on oncology clinics as broader WES becomes commonplace.

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Germline mutation profile among Hispanic women with epithelial ovarian cancer (EOC). First Author: Yanin Chavarrí Guerra, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

Background: Hospital-based studies have reported a 15% prevalence of BRCA1/2 mutations, with a slightly higher yield of other pre-disposition genes on multigene panel testing (MGPT) among women with EOC, and National Comprehensive Cancer Network guidelines recommend genetic cancer risk assessment for women with EOC. However, there is limited data about the genetic epidemiology of EOC among underrepresented populations, such as Hispanics. Therefore, we determined the germline mutation profile of Hispanics with EOC, and compared them with non-Hispanics.

Methods: We included all women with a personal history of EOC from the U.S. and Latin America (LatAm; Mexico, Colombia, and Peru), enrolled in the Clinical Cancer Genomics Community Research Network registry. We assessed the prevalence of pathogenic variants (PV) in BRCA1/BRCA2/BRCA3 and other genes, contrasting the germline mutation profile between Hispanics living in LatAm, U.S. Hispanics, women of Ashkenazi Jewish (AJ) ancestry in the US, and other U.S. non-Hispanics.

Results: Among 1186 women with EOC (209 from LatAm, 254 U.S. Hispanics, 78 AJ, and 649 other non-Hispanics), 10% were of LatAm origin, and 5% were Hispanic. Hispanics from LatAm and the U.S. had a similar frequency of BRCA mutations to AJ (30.6%, 29.9%, and 38.4%, respectively; p = 0.14); while non-Hispanics showed a significantly lower frequency of BRCA mutations (14.2%, p = 0.03). The most frequently mutated gene was BRCA1 (n = 197, 74.6%), followed by BRCA2 and BRCA3. For BRCA-negative cases (n = 924), 59% (n = 545) were evaluated by MGPT and PVS were identified in 2.9% (6 Hispanics (1.2%), 3 AJ (3.8%) and 26 Non-Hispanics (4%)), of which 66% (n = 23) were in mismatch repair genes (MSH2, MLH1, MSH6, PMS2). And 34% (n = 12) in other EOC-associated genes (APC, PALB2, RAD51C, and RAD51D). Clinically actionable PVS in ATM (n = 4; 0.3%) and CHEK2 (n = 6; 0.5%) were also observed.

Conclusions: Hispanics with EOC have an elevated frequency of PV, similar to that of classic founder populations such as AJ, and significantly higher than other non-Hispanics. This is partially explained by a high prevalence of recessive EOC in LatAm, highlighting the importance of conducting genetic studies in underrepresented populations. There was modest incremental benefit of MGPT.

Incidence of second primary neoplasms among cancer survivors in the United States. 2000 through 2015. First Author: Jesse Erick Atiya Baydoun, Saint Louis University Center for Health Outcomes Research, St. Louis, MO

Background: The number of cancer survivors in the United States is projected to exceed 20 million by 2024. Survivors are at risk of developing a second primary neoplasm (SPN) – a leading cause of survivor death. We described the risk of developing a SPN among survivors of common cancers (smoking-related vs non-smoking-related) in the United States. Methods: We identified patients aged >15 years with a history of cancer treated within 2 years from the date of diagnosis with a survival time to date of 2 months after first cancer diagnosis. Excess SPN risk was quantified using standardized incidence ratios (SIRs) stratified by sex. Results: A cohort of 2,908,349 patients (50.1% female) was identified and 260,267 (9.0%) developed a SPN. The SIR for females and males of 10.3% of males. All index cancer sites were associated with a significant increase in SPN risk for females and males except prostate cancer. Index smoking-related cancers (SIR range 1.20 – 1.27 for females and 1.12 – 1.91 for males) had higher increased risk of SPN than non-smoking-related cancers (SIR range 1.08 – 1.39 for females and 0.55 – 1.38 for males) relative to the general population.

Conclusions: Nearly 10% of cancer survivors developed an SPN, and those with smoking-related cancers had higher risk. Given the increasing number of cancer survivors and importance of SPN as a cause of cancer death, these findings can improve secondary prevention and surveillance guidelines.

Cancer Prevention, Hereditary Genetics, and Epidemiology

Poster Session (Board #79), Mon, 1:15 PM–4:15 PM

Genomic testing and treatment landscape in patients with advanced non-small cell lung cancer (aNSCLC) using real-world data from community oncology practices. First Author: Hincio Jasper Giemna, Integra Connect, West Palm Beach, FL

Background: While aNSCLC is a leading cause of US cancer deaths, targeted therapies and immune checkpoint inhibitors (ICI) have emerged as important new treatment options for these pts. NCCN guidelines recommend testing of eight genes in aNSCLC patients at diagnosis. Targetable alterations (TA) in four genes, EGFR, ALK, ROS1, and BRAF, are associated with FDA-approved targeted therapies. The labels for ICPs indicate that pts with TAs in EGFR and ALK are not candidates for first line treatment with ICP.

Methods: The Integra Connect database, which includes electronic medical record (EMR) and claims data on approximately 600,000 cancer patients, was queried across five community oncology practices (289 oncologists) to identify aNSCLC patients (stage 3B or 4) treated since January 2017. Manual review of charts was done to abstract tumor type/stage, drug regimens, and evidence of somatic genetic testing. A Wilcoxon rank sum test was used to test difference in time to results (TTR) for blood- vs tissue-based tests.

Results: A total of 1,203 aNSCLC patients were identified. Testing rates varied from 54% for EGFR to 22% for ALK. 31% of patients had a TA in EGFR, ALK, ROS1, or BRAF, and 55% of these pts did not receive targeted therapy. 84 pts with TAs in EGFR or ALK had no evidence of progression on targeted therapy, yet 31 (37%) received an ICP; 24% had the TA test result prior to ICI use and 13% received the TA result after starting ICI. Median TTR for blood-based somatic testing was shorter than tissue-based tests (4 vs 14 days, p-value= 3.5-e07).

Conclusions: Our analysis in the community oncology setting for aNSCLC pts finds evidence of underutilization of genomic testing, underutilization of targeted therapies, and ICP use outside of label. Further research is needed to identify strategies to increase testing in aNSCLC pts to provide physicians with the information needed to make optimal treatment decisions.

TPS1585 Poster Session (Board #81a), Mon, 1:15 PM–4:15 PM

A phase II study of PD-1 inhibition for the prevention of colon adenomas in patients with Lynch syndrome (LS) and a history of partial colectomy. First Author: Joanne M. Jeter, The Ohio State University, Columbus, OH

Background: Colon cancer and adenomas that are associated with Lynch syndrome (LS) often display microsatellite instability (MSI), a characteristic that is associated with increased response to treatment with PD-1 inhibitors. Because LS patients have a history of colon cancer, we are increased risk of having a second primary colon cancer or high-risk adenoma, preventive measures are of particular interest in this population. We hypothesize that a maintenance schedule of nivolumab can be safely administered to LS patients with a history of treated colon cancer with remaining colon at risk in order to decrease the incidence of adenomas, advanced adenomas and second primary colon cancers.

Methods: OSI 17198 is a phase II multi-center, single-arm study of nivolumab in patients with germline MLH1 or MSH2 mutations and a history of hemicolectomy for colon cancer at least one year prior to study entry. Subjects must have completed any adjuvant therapy at least 6 months prior to study participation and may not have received prior therapy with a PD-1 inhibitor. Nivolumab is given at 240mg IV every 3 months for two years, and colonoscopies will be performed prior to study entry, after the fourth dose, after the eighth dose, and one year after the eighth dose. Subjects will be monitored for auto-immune adverse effects. The primary endpoint is incidence of adenomas at three years, and secondary endpoints are safety, incidence of advanced adenomas, and incidence of colon and non-colon cancers at three years. Approximately 104 subjects will be enrolled to obtain 94 evaluable subjects. This study is currently open for enrollment at the Ohio State University and at various stages of activation at seven additional sites in the United States. Enrollment of this study is anticipated to be completed in 2020, and data collection is anticipated to be completed in 2023. This study has undergone safety review by the FDA and the Ohio State University Institutional Review Board.
TPS1588  Poster Session (Board #81b), Mon, 1:15 PM-4:15 PM
Phase I trial of endoxifen gel versus placebo gel in women undergoing breast surgery. First Author: Katrina Alber, Northwestern University, Chicago, IL

**Background:** Despite large Phase III clinical trials that have established the success of selective estrogen receptor modulators (SERMs) for breast cancer prevention and therapy of duct carcinoma in situ (DCIS), acceptance by women likely to benefit has been low, primarily because of toxicity related to systemic exposure. Local drug delivery to the breast in gel form is an attractive alternative since low systemic levels could minimize toxicity. Endoxifen (ENX) is an active metabolite of tamoxifen, that has unique activity compared with 4-hydroxytamoxifen (4-OHT). It is smaller and more polar than 4-OHT making it potentially more suitable for transdermal delivery. The NCI PREVENT program has developed ENX transdermal alcoholic gel products. **Methods:** We are conducting a randomized, double-blinded, placebo-controlled, Phase I trial to establish the dermal tolerability and safety of endoxifen (ENX) gel. 38 women planning unilateral or bilateral mastectomy will be enrolled across 3 institutions in 3 cohorts: (a) ENX gel 10mg (N = 8) vs. placebo gel (N = 4) daily; (b) ENX gel 20mg (N = 8) vs. placebo gel (N = 4) daily; (c) the maximum tolerated dose (N = 8) with last dose 72 hours prior to surgery. Treatment duration will be 4 ± 1 weeks. All participants will be evaluated for toxicity and skin tolerability. Secondary endpoints include TAM metabolite measurements in breast tissue and plasma; serum hormone concentrations, serum estrogen response, changes in coagulation parameters, gene expression changes reflective of therapeutic effects, and experienced symptoms. 65 potential participants have been pre-screened for eligibility, 33 were ineligible prior to contact, most commonly due to the use of neoadjuvant chemotherapy. Of 32 potential participants who have been eligible to be contacted, 21 did not consent for screening, most commonly because they were too overwhelmed with their recent diagnosis. 7 have consented, 4 are pending consent, and 6 have started study intervention. No adverse events have been reported to date. This pre-surgical trial testing transdermal ENX for breast cancer prevention is accruing as projected. The results will establish the skin safety of this agent, provide data on skin permeability, and the duration of drug retention in the breast. Clinical trial information: NCT03317405.

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Second interim and first molecular analysis of the EORTC randomized phase III intergroup CATNON trial on concurrent and adjuvant temozolomide in Second interim and first molecular analysis of the EORTC randomized phase III intergroup CATNON trial on concurrent and adjuvant temozolomide in

Conclusive about concurrent (conc) TMZ. A 2nd interim analysis was planned after 356 events.

Van Den Bent, Erasmus MC Cancer Centre, Rotterdam, Netherlands

With a median follow-up of 56 months and 356 events, the hazard ratio (HR) for OS adjusted for stratification factors after conc TMZ was 0.96 (99.1% CI 0.73, 1.28). 5-year OS was 50.2% with and 52.7% without conc TMZ (95% CI [44.4, 55.7] and [46.9, 58.1]). An IDH mut status was found in 33% of 480 assessed cases (70%). Median OS was 19 mo (95% CI 16.3, 22.3) in IDH mt tumors and 116 mo (95% CI 08.2, 116.6) in IDH wt tumors. HR for OS after conc TMZ in patients with known IDH status. Clinical trial information: NCT00626990. IDH mut was predictive of benefit from adj TMZ (IDH mut HR: 0.41, 95% CI 0.27, 0.64; IDH wt HR: 1.05, 95% CI 0.73, 1.52) interaction test (p = 0.001). In IDs patients that received adj TMZ, the HR for OS after conc TMZ was 0.71 (95% CI 0.35, 1.42, p = 0.32). MGMT status was found in 288 of 410 assessed cases (70%), interaction test for conc TMZ (p = 0.092) and adj TMZ (p = 0.166) did not reach statistical significance. Conclusions: In the phase I study cohort, conc TMZ did not increase OS. However, in IDH mut tumors a trend towards benefit of conc TMZ is present. Adj TMZ increased OS in IDH mut but not in IDH wt tumors. The ongoing molecular analyses and further follow-up will allow full assessment of efficacy in the molecular subgroups.

IDH wt IDH mt

Patients n events HR (95% CI) interaction test

145 120 1.27 (0.89, 1.82) p = 0.19 0.016

335 92 0.67 (0.44, 1.03) p = 0.06

2002 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Updated predictive analysis of the WHO-defined molecular subgroups of low-grade gliomas within the high-risk treatment arms of NRG Oncology RTOG 9802. First Author: Erica Haivin Bell, The Ohio State University, Columbus, OH

Background: This study sought to update the predictive significance of the three WHO-defined molecular glioma subgroups (IDHwt, IDHmut/nonco-deleted, and IDHmut/codel) in the subset of specimens available for analysis in NRG Oncology RTOG 9802, a phase III trial of high-risk low-grade gliomas (LGGs) treated with radiation (RT) with and without PCV after biopsies/surgical resection. Notably, this is the first phase III study to evaluate the predictive value of the WHO subgroups in LGGs using prospectively-collected, well-annotated long-term overall survival data, in a post-hoc analysis. Methods: IDH1/2 mutation status was determined by immunohistochemistry and/or next-generation sequencing. 1p/19q status was determined by Oncoscan and/or 450K methylation data. Treatment effects on overall survival (OS) and progression-free survival (PFS) by marker status were determined by the Cox proportional hazard model and tested using the log-rank test in a secondary and exploratory analysis. Results: Of all the randomized eligible high-risk G2 patients (N = 251) in NRG Oncology RTOG 9802, 106(42%) patients had tissue available with sufficient quality DNA for profiling. Of these, 80(75%) were IDHmut; 43(41%) were IDHmut/non-co-deleted, 37(35%) were IDHmut/co-deleted, and 26(24%) were IDHwt. Upon univariate analyses, no significant difference in either PFS or OS was observed with the addition of PCV in the IDHwt subgroup. Both the IDHmut/non-co-deleted and IDHmut/co-deleted subgroups were significantly correlated with longer PFS (HR = 0.32; p = 0.003; HR = 0.13; p < 0.001) and OS (HR = 0.38; p = 0.013; HR = 0.21; p = 0.029) in the RT plus PCV arm, respectively. Conclusions: Our analyses suggest that both IDHmut/non-co-deleted and IDHmut/co-deleted subgroups received benefit from treatment with PCV although sample size is limited and analyses are post-hoc. Our results also support the notion that IDHwt high-risk LGG patients do not benefit from the addition of PCV to RT. Funding: U10CA180868, U10CA180822, and U24CA196067. Also, RO1CA108633, R01CA169368, R2CAIA189190, U10CA190850-01, BTF, OSU-CCC (all to AC). Clinical trial information: NCT0003375.

2003 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

A phase 1/2a open-label, periprojective study of AG-120 and AG-881 in recurrent IDH1 mutant, low-grade glioma: Results from cohort 1. First Author: Ingo K. Melinghoff, Memorial Sloan Kettering Cancer Center, New York, NY

Background: AG-120 (ivosidenib [IVO]) is a first-in-class oral inhibitor of mutant isocitrate dehydrogenase 1 (mIDH1) evaluated in 66 glioma patients (pts) in an ongoing phase 1 study. AG-881 (vorasidenib [VOR]) is an oral, potent, brain-penetrant inhibitor of mIDH1/2 evaluated in 52 glioma pts in an ongoing phase 1 study. In an orthotopic glioma model, IVO and VOR reduced 2-hydroxyglutarate (2-HG) by 85% and 98%, respectively, despite different brain:plasma ratios (<0.04 vs 1.33). Methods: Primary endpoint: brain tumor 2-HG concentration with IVO or VOR treatment in mIDH1 low-grade glioma. Pts with recurrent non-enhancing WHO-2016 Grade (Gr) 2 or mIDH1-R132H oligodendroglioma or astrocytoma undergoing craniootomy were randomized 2:2:1 to IVO 500mg QD, VOR 50mg QD or no treatment for 4 wks preoperatively in Cohort 1. Post-operatively, pts continued to receive IVO or VOR and control pts were randomized 1:1 to IVO or VOR. Tumors were assessed for mIDH1 status, cellularity, 2-HG, and drug concentration. Treated samples were compared to control pts and mIDH1 and wild type (WT) banked reference (ref) samples. Plasma and CSF 2-HG were assessed. Pts with non-evaluable tissue were replaced. Results: As of 29 Nov 2018, 26 pts (17M, 9F; 25 Gr 2, 1 Gr 3) were randomized preoperatively (IVO 10, VOR 11, control 5), 25 received drug (IVO 12, VOR 13). At the data cut, 19 tumors were analyzed with 16 evaluable. Common (>10%) TEAs (all grade 1/2): diarrhea (36%), hypocalcemia and constipation (each 20%), anemia, hyperglycemia, pruritus, headache and nausea (each 16%), and hypokalemia and fatigue (each 12%). Mean brain:plasma ratio: 0.16 for IVO, 2.4 for VOR. Tumor 2-HG results are shown in Table. Updated data from Cohort 1 will be presented. Conclusions: In Cohort 1 of this PCV 1 periprojective study, IVO and VOR were CNS penetrant and lowered 2-HG compared to untreated samples. Cohort 2 is open and will evaluate IVO 250mg BID and VOR 10mg QD. Brain tumor 2-HG concentration. Clinical trial information: NCT03343197.

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2004 Oral Abstract Session, Mon, 1:15 PM-4:15 PM
Phase I study of a brain penetrant mutant IDH1 inhibitor DS-1001b in patients with recurrent or progressive IDH1 mutant gliomas. First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY.

Background: WHO grade II/III gliomas frequently harbor isocitrate dehydrogenase 1 (IDH1) mutations, resulting in intratumoral accumulation of oncometabolite 2-hydroxylutarate (2-HG) and subsequent clonal expansion. DS-1001b is an oral selective inhibitor of mutant IDH1 R132X that was designed to penetrate the blood-brain barrier. Methods: In this first-in-human, multicenter, phase I study (NCT03030066), eligible patients (pts) with recurrent/progressive IDH1 mutant glioma received DS-1001b twice daily (bid), continuous. A modified continual reassessment method was used for dose escalation. RANO and RANO-LGG criteria were used to assess tumor response. Pts who planned to undergo salvage surgery after developing progressive disease (PD) and who provided informed consent received DS-1001b treatment until surgery. Tumor samples were also obtained from those pts to measure the free form of DS-1001b and 2-HG levels. Results: Between Jan 2017 and Oct 2018, DS-1001b (125-1400 mg bid) had administered for 45 pts (median age 44 yrs, prior radiation therapy 100%, prior chemotheraphy 82%), and 17 pts were continuing treatment. Maximum tolerated dose (MTD) was not reached. Most AEs were Grade 1-2. Gr3 AEs were observed in 42.2% of pts. No Gr 4 or 5 AEs or serious drug-related AEs were reported. One dose limiting toxicity was Gr 3 white blood cell count decreased (1000 mg bid). Common AEs (> 20%) were skin hyperpigmentation, diarrhea, pruritus, nausea, rash, and headache. Of 29 evaluable pts with contrast enhancing gliomas, one, three and 10 achieved complete response, partial response and stable disease (SD), respectively. Of evaluable nine pts with contrast non-enhancing gliomas, two achieved minor response and seven achieved SD. Peak plasma concentration (Cmax) and area under the curve (AUC) increased dose-dependently. The brain/plasma ratio of free form of DS-1001b ranged 0.19–0.77 in 17 pts. Cmax was 100% of dose (N = 14). Conclusions: DS-1001b was well tolerated up to 1400 mg bid with favorable brain distribution, and MTD was not reached. Recurrent/progressive IDH1 mutant glioma pts responded to treatment. Investigation is ongoing to determine the recommended Phase II dose. Clinical trial information: NCT03030066.

2006 Oral Abstract Session, Mon, 1:15 PM-4:15 PM
Activity of larotrectinib in TRK fusion cancer patients with brain metastases or primary central nervous system tumors. First Author: Matthias Preusser, Medical University of Vienna, Comprehensive Cancer Center, Vienna, Austria

Background: TRK fusions are oncogenic drivers of a variety of cancers, many of which can involve the central nervous system (CNS). Larotrectinib is an FDA-approved selective TRK inhibitor for the treatment of TRK fusion cancer (Driol et al., NEJM 2018). While larotrectinib has been shown to cross the blood-brain barrier (Ziegler et al, Br J Cancer 2018), its clinical activity in a series of TRK fusion cancers with primary or metastatic intracranial disease has not been described. Methods: Patients (pts) with non-primary CNS solid tumors with brain metastases, or primary CNS tumors harboring a TRK fusion treated with larotrectinib in 2 clinical trials (NCT02637687, NCT02576431) were identified. Larotrectinib was administered until disease progression (PD), withdrawal, or unacceptable toxicity. Disease status was investigator-assessed (RANO and RECIST). Data cutoff: July 30, 2018. Results: 14 pts were identified: 5 non-primary CNS solid tumors (3 lung cancer, 2 thyroid cancer; fusion type: 2 ETv6-NTRK3, 2 SQSTM1-NTRK1, 1 EPP15-NTRK1; age range 25–79 y) and 9 primary CNS tumors (3 glioma, 2 glioblastoma, 1 astrocytoma, 3 NOS; fusion type: 3 BCR-NTRK2, 2 KANK-NTRK2; 1 each of AFAF1-NTRK1, AGTBP1-NTRK2, ETv6-NTRK3, SPEC1L1-NTRK2; age range 2–79 y). In the 5 pts with non-primary CNS tumors, the best objective response to therapy was PR in 3 (60%, 1 pending confirmation), SD in 1 (20%), and not evaluable (NE) in 1 (20%). Duration of response ranged from 9+ to 13 mo. In the 9 pts with primary CNS tumors, disease control was achieved in all evaluable pts (primary PD not observed; 1 pt required dose increase). The best objective response to therapy was PR in 1 (11%; pending confirmation), −55% tumor shrinkage, ongoing at 3.7 mo, SD in 7 (78%; tumor shrinkage range 1% to −24% for pts with measurable disease, 5 had SD ≥ 4 mo), and NE in 1 (11%). Duration of treatment ranged from 2.8–9.2+ mo. Conclusions: Larotrectinib is active in pts with TRK fusion cancers with intracranial disease. Confirmed responses and durable disease control were seen in metastatic disease and primary CNS tumors of various histologies. These results further support expanded testing for TRK fusions across all cancers, including primary CNS tumors. Clinical trial information: NCT02637687 and NCT02576431.

2005 Oral Abstract Session, Mon, 1:15 PM-4:15 PM
Efficacy and safety of selinexor in recurrent glioblastoma. First Author: Andrew B. Lassman, Columbus University Irving Medical Center, New York, NY.

Background: New treatment modalities are needed for recurrent glioblastoma (rGBM). Selinexor (SEL) is a novel, oral selective inhibitor of nuclear export which forces nuclear retention of tumor suppressor proteins including p53 and p27, leading to apoptosis. We previously reported interim results showing tolerability, preliminary efficacy, and blood-brain barrier penetration in a surgical cohort (N = 8). Here we report updated results following completion of a surgical and a medical cohorts (N = 68). Methods: This is an open-label, multicenter, phase 2 study of SEL monotherapy. Patients (pts) not undergoing surgery for measurable rGBM (per RANO) were enrolled in one of three arms comprising different dosing schedules. Treatment was continuous, although cycles were defined as 28 days and response was assessed every other cycle by MRI. Prior treatment with radiotherapy and temozolomide was required and prior bevacizumab was exclusionary. The primary endpoint was 6-month progression free survival (6mPFS) rate, calculated by the Kaplan Meier method. Results: A total of 76 pts were enrolled. Median age was 56 years (range 21–78). Median number of prior treatments was 2 (range 1–7). At the end of the 6 cycles, 30.2% patients on 80 mg QW were free from progression. The 6mPFS rate on 80 mg QW was 15.1%. Best RANO-defined responses (assessed locally) among 26 evaluable pts on 80 mg QW included 1 complete response, 2 partial responses, 7 stable disease, and 16 with progressive disease. Median duration of response was 10.8 months. The most common related adverse events in pts on ~85 mg BIW/60 mg BIW/80 mg QW were nausea (42%/64%/60%), leucopenia (38%/7%/43%), fatigue (71%/14%/43%), neutropenia (29%/14%/33%), decreased appetite (46%/71%/27%), and thrombocytopenia (67%/29%/23%). Conclusions: SEL demonstrated efficacy, with durable responses and disease stabilization in rGBM. Based on the favorable efficacy and safety profile, SEL at a dose of 80 mg QW is recommended for further development in rGBM. Clinical trial information: NCT01986348.

2007 Oral Abstract Session, Mon, 1:15 PM-4:15 PM
Trabectedin for recurrent WHO grade II or III meningioma: A randomized phase II study of the EORTC Brain Tumor Group (EORTC-1320-BTG). First Author: Matthias Preusser, Medical University of Vienna, Comprehensive Cancer Center, Vienna, Austria

Background: EORTC-1320-BTG investigated the activity, safety and quality of life of therapy with the tetrahydroisoquinolino alkaloid trabectedin (Yondelis) in patients with recurrent higher-grade meningiomas. Trabectedin was originally derived from the Caribbean sea squirt, Ecteinascidia turbinata, and is currently manufactured by total synthesis. Methods: Adult patients with histological diagnosis of WHO grade II or III meningioma and radiologically documented progression after maximal feasible surgery and radiotherapy were randomly assigned in a 2:1 ratio to receive intravenous trabectedin (1.5 mg/m² every three weeks) or local standard of care (LOC). The primary endpoint was progression-free survival (PFS). Results: Within 22.1 months, we randomized a total of 90 patients (n=29 in LOC arm, n=61 in trabectedin arm) in 35 institutions and nine countries. In the LOC arm, the following treatments were administered: hydroxyurea (n=11), bevacizumab (n=9), none (n=4), chemotherapy (n=3), somatostatin analogue (n=1), combined chemotherapy and somatostatin analogue (n=1). With 71 PFS events, median PFS was 4.17 months in the LOC and 2.43 months in the trabectedin arm (hazard ratio [HR] for progression, 1.42; 95% CI, 1.00–2.03; p=0.204) with a PFS-6 rate of 29.1% (95% CI, 11.9%–48.8%) in the LOC and 21.1% (95% CI, 11.3%–32.9%) in the trabectedin arm. Median OS was 10.61 months in the LOC and 11.37 months in the trabectedin arm (HR for death, 0.98; 95% CI, 0.54–1.76; p=0.94).Grade 3 to 5 adverse events occurred in 44.4% (18.5% related, 4 serious adverse events, 0 lethal events) of the patients in the LOC and 59% (32.8% related, 57 serious adverse events and 2 toxic deaths) of patient in the trabectedin arm. Conclusions: In this first prospective randomized trial performed in recurrent grade II or III meningioma, trabectedin did not improve PFS and OS and was associated with significantly higher toxicity as compared to LOC treatment. The data collected in this study may serve as benchmark for future clinical trials in this setting. Clinical trial information: NCT02234050.

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Methods: We performed a standard phase I escalation study in patients with non-progressive DIPG 4 to 14 weeks post-completion of radiation therapy. Seven dose levels of a single injection of 124I-8H9 (Ombutramab) (range 0.25 to 4.0 mCi) were studied. Results: 37 children were treated with 34 evaluable for primary and secondary end-points. The median age at enrollment was 6.8 years old (range 3.2 - 17.9). There was no dose limiting toxicity (DLT). Among adverse events that were at least possibly related to the treatment, there were no grade 4 or 5 events, and only 4 reversible grade 3 events in 4 patients (2 hemiparesis, 1 skin infection and 1 anxiety). Estimations of distribution volumes based on T2-weighted coverage is likely needed. There seems to be a survival benefit using this method. Median survival was 15.3 months (n=29, 95% CI 12.7 - 17.4). Median follow-up of the 5 surviving patients is 27.2 months (range 11.5 - 72.4). Overall survival rate at 12 months was 64.7% (2/34, 4 alive), and overall survival rate at 18 months 14.7% (1/34, 1 alive). Children in the brain stem of children with DIPG who were previously irradiated is a safe therapeutic strategy. An infusion volume of 4,000 mL appears to be a reasonable single dose for a target distribution volume but enhanced tumor coverage is likely needed. There seems to be a survival benefit using this therapeutic strategy and outcomes might be dependent on dosimetry and distribution patterns. Clinical trial information: NCT01502917.

A randomized phase II trial of veliparib (V), radiotherapy (RT) and temozolomide (TMZ) in patients (pts) with unmethylated MGMT (uMGMT) glioblastoma (GBM), First Author: Mustafa Khasraw, Royal North Shore Hospital/ University of Sydney, St Leonards, Australia

Background: TMZ offers minimal benefit in uMGMT GBM pts. V is synergistic with both RT and TMZ in preclinical models, safe when combined with either. While TMZ and V alone are not the triplets (V+RT+TMZ) is poorly tolerated. This study examined an novel approach to patients with uMGMT GBM. Methods: VERTU is a randomized Phase 2 trial comparing Arm A (Standard of care) = RT (60Gy/30 fractions) + V (200mg PO BID) followed by TMZ (150-200mg/m2/2d 1-5) every 28 days for 6 cycles vs Arm B (experimental arm) = RT (60Gy/30 fractions) + V (200mg PO BID) followed by TMZ (150-200mg/m2/2d 1-5) + V (40mg/m2, d1-7) every 28 days for 6 cycles in pts with newly diagnosed centrally determined uMGMT GBM. The study aims to randomize 120 pts (2:1 to the experimental arm). The primary endpoint was 6 months progression free survival (6mPFS) with multiple secondary and tertiary endpoints. Evaluation of feasibility and safety was planned after completion of RT in the first 60 pts (Stage 1). (ANZCTR ACTRN12615000407594). Tumor tissue and serial bloods were collected for translational research. Results: 125 pts were randomized (41 Arm A, 84 Arm B). Mean (range) age 58 (22-78) years, 70% male, 61% ECOG 0, 86% macroscopic resection, 14% biopsy. At Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information. 37% (22-52) in Arm A and 53% (41-63) in Arm B, and median PFS was 4.4 (95 CI 4.0-6.0) for Arm A and 6.2m (95% CI 4.9-7.1) for Arm B (HR = 0.81, 95% CI 0.54-1.21). 50% of pts in Arm A and 53% in Arm B experienced ≥3 adverse events (AEs). The most common G 3/4 AEs were decreased appetite, seizures, hyperglycemia and diabetes (each 5%) in Arm A and decreased platelets (13%) and seizures (11%) in Arm B. Conclusions: In this multicenter, randomized study, the experimental therapy was feasible and well tolerated. The observed 6mPFS appeared longer in Arm B, but at the time of submitting the abstract, this result did not meet the prespecified boundaries. Future mature results will be presented at the annual meeting. QoL in VERTU is reported separately. Central MR review, biomarker analyses, including DNA repair and methylation signature analyses are ongoing. Clinical trial information: ACTRN12615000407594.

A randomized phase II trial of veliparib (V), radiotherapy (RT) and temozolomide (TMZ) in patients (pts) with unmethylated MGMT (uMGMT) glioblastoma (GBM), First Author: Mustafa Khasraw, Royal North Shore Hospital/ University of Sydney, St Leonards, Australia

2008 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

2008 Oral Abstract Session, Mon, 1:15 PM-4:15 PM
Impact of predictive impact of MGMT promoter methylation in malignant astrocytomas depends on the methylation subgroup. First Author: Wolfgang Wick, National Center for Tumor Diseases (NCT), UKHD and German Cancer Research Center (DKFZ), Heidelberg, Germany

Background: O6-methylguanine DNA-methyl transferase (MGMT) status is predictive for alkylating chemotherapy in most series, but there are non-benefiting subgroups. Despite multiple attempts, MGMT has not been unambiguously established as a predictive biomarker for patients with malignant gliomas. Further, these tumors are to be better classified according to global methylation profiles. Methods: Long-term efficacy data of the NOA-08 trial (NCT01502241) that compared efficacy and safety of radiotherapy (RT, n = 176) to temozolomide (TMZ, n = 193) in patients > 65 years with anaplastic astrocytoma (AA) or GB as well as genome-wide DNA methylation patterns and copy number variations assessed by methylation arrays in a biomarker subset (n = 104) and an independent cohort (n = 380) have been used to assess the interaction between MGMT status and methylation subgroups. Results: In the long-term update of NOA-08 patients with MGMT methylated tumors had longer OS and EFS when treated with TMZ (18.4 [13.9-24.4] months and 8.6 [6.9-13.3] months) versus RT (9.6 [6.4-13.7] months and 4.8 [4.3-6.2] months, HR 0.44 [0.27-0.70], p < 0.001 for OS and 0.46 [0.29-0.73], p = 0.001 for EFS). These data compared favorably with recently published data from patients treated with chemotherapy (Ferry et al. NEJM 2017). Importantly, only patients with glioblastomas of the methylation class from patients treated with chemoradiation (Perry et al. NEJM 2017). Im-

long-term update of NOA-08 patients with [6.9-13.3] months) longer OS and EFS when treated with TMZ (18.4 [13.9-24.4] months and 8.5 [6.9-13.3] months) vs EFS (9.4 [6.4-13.7] months vs 4.8 [4.3-6.2] months, p = 0.001). Results: In 3257 pts, data were available from lung (n = 1621), brain (n = 180), and liver (n = 167). There were 941 1st progression, 135 2nd progression, and 99 deaths in the lung cohort. In 1163 pts, patients had liver disease (135 deaths). In 1001 pts, patients had liver only (99 deaths). With a median follow-up of 38.6 months, there were 135 1st progression, 135 2nd progression, and 61 deaths in the brain cohort. In 180 pts, patients had brain disease only (61 deaths). There were 180 1st progression, 135 2nd progression, and 61 deaths in the liver cohort. In 167 pts, patients had liver only (61 deaths). With a median follow-up of 38.6 months, there were 135 1st progression, 135 2nd progression, and 61 deaths in the brain cohort. In 180 pts, patients had brain disease only (61 deaths). The data call for embedding of MGMT tests into global methylation analyses for all patients with malignant gliomas potentially treated with alkylating chemotherapy.

2015 Poster Discussion Session; Displayed in Poster Session (Board #204), Sun, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-6:00 PM

Circulating tumor DNA analysis (ctDNA) for genomic testing in NSCLC patients with isolated CNS progression. First Author: Mihaela Aldea, Medical Oncology Department, Gustave Roussy, Villejuif, France

Background: Genomic DNA profiles are mandatory in advanced, treatment naive non-small cell lung cancer (NSCLC) patients (pts) and strongly recommended at progression (PD) on personalized treatment. In pts with PD limited to central nervous system (CNS), tissue biopsy is difficult and the performance of ctDNA is unknown. Methods: Clinical, molecular, imaging data of NSCLC pts included in 2 prospective studies from 01.2016 to 11.2018 at Gustave Roussy were collected. Inclusion criteria were: stage IV disease and any known tissue genomic alteration (GA) EGFR, ALK, BRAF, KRAS, HER2, ROS1, MET, PIK3CA, TP53. Plasma ctDNA collected at baseline/ PD were analyzed by next-generation sequencing (NGS-InVisonFirst™-Lung) in 3 groups: pts with isolated CNS (iCNS), extra-CNS only (noCNS) or both combined (cCNS) disease. iCNS was defined as any PD to CNS, while stable/absent extra-CNS metastases (mets). ctDNA was considered positive if ≥1 GA was found. ctDNA in cerebrospinal fluid (CSF) was also collected. Results: Out of 245 pts with ≥1 ctDNA; 56 had iCNS (65 samples, 97 noCNS (127 samples) and 92 cCNS (107 samples). In this cohort, 60% were female, median age 60 years, 47% smokers; 92% had adenocarcinoma. The median number of mts sites was 3 in noCNS/cCNS groups. Proportions of tissue GA at baseline were (iCNS vs noCNS/cCNS): EGFR (50% vs 44%), ALK (30% vs 11%), BRAF (4% vs 12%), KRAS (5% vs 15%), HER2 (2% vs 5%), ROS1 (5% vs 4%). Tyrosine kinase inhibitors were used in 73% iCNS vs 61% noCNS/cCNS. Local brain treatments were performed in 43% (n = 24) vs 32% (n = 29) and leptomeningeal mts (LM) detected in 34% (n = 19) vs 8% (n = 9), in iCNS and cCNS respectively. ctDNA was positive in 52% in iCNS and 84% in noCNS vs 92% in cCNS (p < 0.0001). In CNS, there was a non-significantly higher proportion of + ctDNA in pts with LM vs only brain disease (59 vs 48%, P = 0.44). 12/56 pts of iCNS group had serial ctDNA being collected also at time of ctDNA. In 25% of cases, a negative ctDNA at time of iCNS diagnosis was subsequently positive (93%) in iCNS vs 84% in noCNS. In 50% of pts, ctDNA was positive at diagnosis. Detection of a negative ctDNA at time of diagnos

2016 Poster Discussion Session; Displayed in Poster Session (Board #205), Sun, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-6:00 PM

SurVaxM with standard therapy in newly diagnosed glioblastoma: Phase II trial update. First Author: Manmeet Singh Ahluwalia, Burkhardt Brain Tumor NeuroOncology Center, Neurological Institute, Taussig Center Institute, Cleveland Clinic, Cleveland, OH

Background: SVNS3-67/M57-KLH (SurVaxM) is a novel cancer vaccine designed to stimulate an immune response targeting the tumor-specific antigen survivin. A multi-center, single-arm phase 2 clinical trial of SurVaxM in survivin-positive newly diagnosed glioblastoma (nGBM, NCT024455557) is now fully enrolled and data updated. Methods: Patients (n = 63) with nGBM were enrolled at 5 US cancer centers and followed for safety, 6-month progression-free survival (PFS6), 12-month overall survival (OS12) and immunologic response. All patients underwent craniotomy with near-total resection (< 1 cm³ residual contrast enhancement), TMZ chemoradiation, adjuvant TMZ and SurVaxM. Patients received 4 doses of SurVaxM (500 mcg) in Montanide with sargamostim (100 mcg) biweekly, followed by maintenance SurVaxM with adjuvants every 12 weeks until tumor progress-

ion. Immunogenicity of SurVaxM was assessed by detection of survivin-specific antibody (IgG) and CD8+ T-cell levels. Results: Median age was 60 yrs (range, 20-82), 53% methylated MGMT, 46% unmethylated MGMT (1 N/A) and 60% were male. Survivin expression ranged from 1-40% (median 12%) by immunohistochemistry. Median time to first immunization was 3.0 mo (1.9-4.0 mo) from diagnosis. There have been no RLT or grade ≥3 SAE attributable to SurVaxM. The most common AE was grade 1-2 immunization reaction. 30 SAE were recorded during the study. No adverse events were reported. Conclusion: SurVaxM is well tolerated with a favorable safety profile in a large pool of patients with newly diagnosed glioblastoma.
Updated phase I trial of anti-LAG-3 or anti-CD137 alone and in combination with anti-PD-1 in patients with recurrent GBM. First Author: Michael Lim, The Johns Hopkins Hospital, Baltimore, MD

Background: Preclinical GBM data targeting the checkpoint molecules Lag-3 and CD137 have shown promising anti-tumor immune response with resultant improved survival when combined with anti-PD-1. Here we report our experience from a multi-arm safety study in patients with recurrent GBM treated with anti-Lag-3 and anti-CD137. Methods: The Adult Brain Tumor Consortium (ABTC) 1501 trial is a phase I, open label, multicenter, multi-arm dose-finding/safety study of anti-LAG-3 (BMS-986016) or anti-CD137 (BMS-663513) alone and in combination with anti-PD-1 in patients at first recurrence of GBM. The primary objective is to define MTD for the mono and combination treatment. The major secondary objective is to explore for a signal in efficacy. The key inclusion criteria are adults, first recurrence of GBM following RT+TMZ, KPS>60%, stable corticosteroid regimen, measurable disease, and written informed consent. Sequential allocation was used for the treatment assignment at starting dose of 80mg for anti-LAG-3 and 8mg for anti-CD137. Anti-PD-1 was given at a flat dose of 240 mg in the combination treatment arms. The 3+3 design is used for the dose finding with a target DLT rate <33%. Results: to date 44 patients were enrolled into the trial with median age at 57, median KPS at 90. Median treatment cycle was 3 and 39% tumors were MGMT methylated. The highest safe dose of Anti-Lag-3 alone is 800 mg with 1 DLT. The safe dose of anti-CD137 alone arm is 8mg with 1 DLT, and 2 grade 3 elevated serum ALT at end of cycle 2. Combination arms of Anti-LAG-3 + anti-PD-1 (160 mg/ 240mg as the highest dose combination) had one DLT (hypertension) and no toxicities were seen in the combination arm of Anti-CD137+Anti-PD-1 (3.75mg/kg, 3mg/kg). No DLT was observed for Anti-Lag-3, and 7 months for Anti-Lag-3 + Anti-PD-1. Correlative data will be discussed. Conclusions: The trial is ongoing. The RP2D is 800mg for anti-LAG-3 as a monotherapy and 8mg for anti-CD137. For the combination arms, 160 mg of anti-Lag-3 and 240 mg of anti-PD-1 and 3 mg of anti-CD137 and 240 mg anti-PD-1 were the RP2D. Clinical trial information: NCT02658981.

First-in-human phase I trial of the combination of two adenoviral vectors expressing HSV1-TK and FLT3L for the treatment of newly diagnosed resectable malignant glioma: Initial results from the therapeutic reprograming of the brain immune system. First Author: Pedro R. Lowerstein, Univ of Michigan Medical School, Ann Arbor, MI

Background: This is the initial report on a first in human Phase I dose escalation trial of the combination of two adenoviruses expressing HSV1-TK and Flt3L for the treatment of newly diagnosed, resectable malignant gliomas. The absence of functional dendritic cells from the brain precludes anti-tumor immunity and the capacity for neoantigen recognition. Methods: The trial was approved by FDA and all institutional citites. Treatment was administered intraoperatively following complete glioma resection in newly diagnosed gliomas. The trial consisted of vector dose escalation, starting at 1x10^-9 i.u., and increasing to 1x10^-11 i.u. of each vector. Dose escalation proceeded by increasing the vector dose through a total of 6 combinations administered to 6 cohorts of 3 patients each. Two cycles of 14 days each of valacyclovir were administered to activate HSV1-TK cytotoxicity. Cycle 1 starts on Day 1-3 post surgery for 14 days, and Cycle 2 on Week 8-12. Standard radiation, i.e., 60 Gy in 2 Gy fractions over 6 weeks, with concurrent temozolomide, was followed by cyclic temozolomide. Results: Examination of tumor samples at primary resection and first recurrence show an increase in the infiltration of inflammatory cells. The experimental treatment was well tolerated, and this time the MTD has not been reached. There were approx. 248 AEs, and 26 SAEs; these have not been linked to treatment. At this time the MTD has not been reached. A secondary outcome is overall survival. Preliminary analysis of partial data may suggest that the combined viral vector therapy may provide a clinically significant survival benefit. Conclusions: Our data suggests that the combinatorial reprogramming of the host’s brain immune system to recognize gliomas reveals a new approach for the treatment of highly malignant brain tumors. Clinical trial information: NCT01811992.
Background: Proteasome inhibition sensitizes glioma cells to TMZ and RT, providing a novel therapeutic strategy for GBM. MRZ, an irreversible, brain-penetrant, pan-proteasome inhibitor with anti-glioma activity was combined with standard TMZ/RT → TMZ in newly diagnosed glioblastoma (GBM). First Author: Wolfgang Wick, National Center for Tumor Diseases (NCTD), UKHD and German Cancer Research Center (DKFZ), Heidelberg, Germany.

Methods: Patients were enrolled in separate cohorts (TMZ+RT→MRZ+TMZ, N=18) in dose-escalation (3+3 design), followed by dose-expansion (N=20) with TMZ+RT→MRZ at RD to TMZ+MRZ at RD. A separate cohort received TMZ+RT→MRZ+RT at RD with Tumor Treating Fields (Optune, N=13). MRZ was infused IV (10 min at 0.55, 0.78, 0.8, and 1.0 mg/m<sup>2</sup>) on Days 1, 8, 15, 29, 36 (42-day TMZ+RT→MRZ cycle) and Days 1, 8, 15 (28-day TMZ+MRZ cycle).

Results: 66 patients treated; median age 58 years, 68% male, 50% receiving corticosteroid at baseline, 52% unmethylated MGMT. Dose-limiting toxicities (DLTs) in dose-escalation cohorts: 1 (fatigue) at 0.7 mg/m<sup>2</sup>, MRZ, 5 (ataxia/diarrhea; ataxia/confusion; myocardial infarction, delirium/ataxia; fatiguelate 1.0 mg/m<sup>2</sup>) cohorts. MRZ demonstrated a steep dose-response with treatment-emergent adverse events (TEAEs)/DLTs predominantly CNS AEs (Grade ≥3 TEAEs in 12 of 12 patients at 1.0 mg/m<sup>2</sup> and 22 of 41 patients at <0.8 mg/m<sup>2</sup>); the RD for MRZ was determined to be 0.8 mg/m<sup>2</sup>. Most common TEAEs (all grades): fatigue, nausea (both 70%), hallucination (54%), vomiting (53%), headache (47%), confusional state (33%), ataxia, constipation, muscular weakness (all 29%).

Conclusions: CNS TEAEs were short-lasting, reversible and ameliorated by early dose reductions (29% patients dose-reduced), allowing patients to remain on treatment. For patients receiving MRZ with TMZ/RT→TMZ (N=35), the median OS was 14.8 months (17 deaths, median follow-up 14.3 months), and 7 patients remain active (Cycles 11-23). The MRZ RD + TMZ/OpTune combination was tolerated, with 4 of 13 patients treated on this arm remaining active. An international Phase 3 trial (EORTC 1709-BTO/CCCT CE.8, NCT03345095) is ongoing. Clinical trial information: NCT02903069.

2023 Poster Session (Board #211), Sun, 8:00 AM-11:00 AM

DGM1 may serve as a novel genetic biomarker of response to enzastaurin in glioblastoma. First Author: Nicholas A. Butowski, University of California, San Francisco, CA.

Background: Despite countless clinical trials being conducted, little has changed over the last decade in the chemotherapies available for glioblastoma (GBM) with survival remaining poor. Meaningful advances in treating this deadly malignancy may rely on precision medicine. We discovered a novel pharmacogenomic biomarker for enzastaurin (entz) in treating lymphoma (lymph). We evaluated if this biomarker can be used to predict entz response in GBM.

Methods: Biomarker discovery was performed by a genome-wide screen using DNA extracted from blood samples from a ph 3 entz lymph trial and a novel biomarker, Denovo Genomic Marker 1 (DGM1), a germline polymorphism on chromosome 8, was found to be highly correlated with response to entz in the two lymph trials. Using DNA extracted from blood of pts from the single-arm ph 1/2 study of newly diagnosed glioblastoma (GBM) will be further evaluated in a planned randomized phase 2b study in newly diagnosed glioblastoma (GBM) and in GBM.

Conclusions: These data are supportive of DGM1 as a potentially predictive biomarker for entz response in both lymph and GBM. There is an ongoing biomarker-driven piliot 3 study in lymph at 500 mg/day, and DGM1 in GBM will be further evaluated in a planned randomized ph 2b study in newly diagnosed GBM with 500 mg/day of entz in combination with TMZ.

2024 Poster Session (Board #212), Sun, 8:00 AM-11:00 AM

Barriers to accrual and enrollment in brain tumor trials. First Author: Eudocia Quant Lee, Dana-Farber Cancer Institute, Boston, MA.

Background: A major impediment to improving neuro-oncology outcomes is poor clinical trial accrual. Methods: We convened a multi-stakeholder group including Society for Neuro-Oncology, Response Assessment in Neuro-Oncology, patient advocacy groups, clinical trial cooperative groups, and other partners to determine how we can improve trial accrual. Results: We describe selected factors contributing to poor trial accrual and possible solutions. Conclusions: We will implement strategies with the intent to double trial accrual over the next 5 years.

Table: Challenges and Potential solutions

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Phase 1/2a study of once daily oral BAL101553, a novel tumor checkpoint controller (TCC), in adult patients with progressive or recurrent glioblastoma (GBM) or high-grade glioma. First Author: Juanita S. Siemens, NHS Foundation Trust, Sutton, United Kingdom

Background: BAL101553 (produg of BAL27862) is a novel TCC that promotes tumor cell death by modulating the spindle assembly checkpoint. BAL27862 is a lipophilic, small molecule shown in rodents to penetrate the brain (brain/plasma ratio around unity), with promising antitumor activity in orthotopic preclinical GBM models as monotherapy or in combination with radiotherapy (RT) with or without temozolomide. In this ongoing study (NCT02490800, CDI-OS-002), daily oral BAL101553 was initially examined in solid-tumor patients, with an MTD of 16 mg/d and DLTs of G4 hyponatremia and G2 hallucinations (Lopez 2018, JCO 36, 2018, suppl. TPS2601). Subsequently the study was expanded by including a separate cohort of patients with progressive or recurrent GBM or high-grade glioma (Ingles Garces 2017, JCO 35, 2018, suppl. TPS2601). Methods: Patients with histologically-confirmed GBM or high-grade glia, with progressive or recurrent disease after prior RT with/without chemotherapy, received once-daily oral BAL101553 (28-day cycles) in a 3+3 dose-escalation design to determine the maximum tolerated dose (MTD). Adverse events were assessed by CTCAE v4.03 grade (G), and tumor response by RANO every two cycles. Pharmacokinetics (PK) were evaluated on Day 1 of Cycles 1 and 2.

Results: In the ongoing study, 23 pts (13M/10F; median age 50 y), median cycles 6, were assessed by CTCAE v4.03 grade (G), and tumor response by RANO every two cycles. Pharmacokinetics (PK) were evaluated on Day 1 of Cycles 1 and 2. Overall, 1 pt (M) had positive preop mutant ctDNA. 2 pts who were negative initially developed detectable mutant ctDNA preop progression. 3/4 pts with equivocal radiographic pseudoprogession had ctDNA dynamics that correlated with eventual clinical outcome. One patient with unresectable GBM had declining mutant ctDNA in later collections during clinical stability.

Conclusions: We detected plasma TERT ctDNA in 46% of TERT mutant GBM pts before surgery, and in 100% of pts with multiple contrast enhancement. TERT mutant ctDNA levels correlated with eventual clinical progression before MRI. These data suggest that larger studies to test circulating cell-free TERT mutation as a diagnostic and pharmacodynamic biomarker in GBM are warranted.

Safety and activity of a first-in-class oral HIF2-alpha inhibitor, PT2385, in patients with first recurrent glioblastoma. First Author: Roy E. Stroud, Wake Forest School of Medicine, Winston-Salem, NC

Background: Hypoxia inducible factor-2-alpha (HIF2a) mediates cellular responses to hypoxia and is overexpressed in GBM. PT2385 is an oral HIF2a inhibitor with in vivo activity against GBM. Methods: A two-stage single-arm open-label phase II study of adults with first recurrent GBM following chemoradiation with measurable disease was conducted through the Adult Brain Tumor Consortium. PT2385 was administered at the phase II dose (800 mg b.i.d.). The primary objective was to find the maximum tolerated dose (MTD) of PT2385. The stage I enrolled 24 patients, and an MTD was established in patients with advanced solid tumors, and shows indications of clinical activity. Clinical trial information: NCT03216499.

Results: Of the 24 patients, mean age was 61 ± 11 years, median KPS 80, 42% pts with IDH2 (3.9%) or IDH 1 non-canonical mutations (p = 0.022) showed a significant role for improved survival. 0.001), 1p19q codeletion (p = 0.003) and presence of non-canonical mutations (p = 0.001) were associated with improved survival. The validated thresholds for positive detection were 1.5 (C228T) and 1.7 (C250T). Plasma cell-free circulating tumor DNA (ctDNA) detection in longitudinally followed glioblastoma patients using TERT promoter mutation-specific droplet digital PCR assays. First Author: Christine Cordova, National Institutes of Health, Bethesda, MD

Background: There is a critical need for more specific and less invasive diagnostic and pharmacodynamic biomarkers in glioblastoma (GBM) patients (pts). Previously, we detected TERT promoter hotspot mutations (C228T and C250T) in the ctDNA of IDH wildtype (IDHwt) TERT promoter mutant GBM pts with 100% specificity using mutation-specific droplet digital PCR (ddPCR) assays. Here, we explored the dynamics and clinical associations of mutant TERT ctDNA levels in GBM pts undergoing therapy. Methods: We examined 14 pts with suspected IDHwt GBM based on preoperative MRI. Plasma was isolated and frozen from ~15 mL whole blood samples collected pre- and post-op, at end of radiation (RT), and 1, 3, and 6 months after end of RT. TERT promoter mutations were identified in FFPE tumor samples using ddPCR assays for C228T and C250T. Plasma samples were analyzed using ddPCR assays specific for the corresponding tumor mutation. The validated thresholds for positive detection were 1.5 (C228T) and 1.7 copies/mL (C250T). Results: 13/14 (92.9%) IDHwt tumors had TERT mutations: 10 C228T and 3 C250T. Six of these 13 (46%) pts had positive preop mutant ctDNA. All 4 pts with multiple contrast enhancement had positive preop mutant ctDNA. 2 pts who were negative initially developed detectable mutant ctDNA preop progression. 3/4 pts with equivocal radiographic pseudoproggression had ctDNA dynamics that correlated with eventual clinical outcome. One patient with unresectable GBM had declining mutant ctDNA in later collections during clinical stability.

Conclusions: We detected plasma TERT ctDNA in 46% of TERT mutant GBM pts before surgery, and in 100% of pts with multiple contrast enhancement. TERT mutant ctDNA levels correlated with pseudoprogession or true disease progression and predicted progression before MRI. These data suggest that larger studies to test circulating cell-free TERT mutation as a diagnostic and pharmacodynamic biomarker in GBM are warranted.

Survival outcomes in glioma patients with noncanonical IDH mutations: Beyond diagnostic improvements. First Author: Enrico Franzone, Istituto di Neurologica, Bellaria Hospital, Azienda USL - IRCCS Instituto of Neurological Sciences, Bologna, Italy

Background: According to the 2016 WHO classification of Central Nervous System tumors, the assessment of exon 4 mutations in IDH1 or IDH2 genes is an essential step in the characterization of gliomas. The R132H mutation is the most frequent alteration in IDH1 gene, however other non-canonical IDH mutations have been identified. The aim of this study was to evaluate the prognostic role of IDH non-canonical mutations. Methods: We analyzed our institutional data warehouse for all consecutive patients (pts) with newly diagnosed, histologically proven grade II – IV IDH mutant gliomas. IDH sequencing was performed using the 454 GS-Junior next generation sequence (NGS) (Roche Diagnostic, Mannheim, Germany). All analyses were performed on DNA from formalin fixed and paraffin embedded (FFPE) specimens. Results: The analysis included 493 pts with IDH mutations. We found 279 (56.6%) grade 2, 173 grade 3 (35.1%) gliomas, and 41 (8.3%) IDH mutant glioblastoma. Canonical IDH1 R132H mutation was found in 428 pts (86.8%). The remaining pts showed IDH2 (3.9%) or IDH 1 non-canonical mutations (mainly R132C, R132G, R132S – 9.3%). Median follow-up time was 80.5 months. Pts with non-canonical mutations showed a younger median age (32 vs 39 years, p < 0.001). Other clinical characteristics and treatments were similar across IDH groups. Median survival was 145 months (95%CI: 137.7 - 152.9) and 198.6 (95%CI 155.2 - 242.1) in patients with IDH1 R132H and non-canonical mutations, respectively (p = 0.013). In multivariate analysis grading (p < 0.001), extent of surgery (p < 0.001), 1p19q codeletion (p = 0.003) and presence of non-canonical mutations (p = 0.022) showed a significant role for improved survival.

Conclusions: Detecting non-canonical IDH1 mutations is essential to diagnosis and for prognosis in patients with gliomas. Differential enzymatic activity of non-canonical IDH1 mutations, resulting in different levels 2-hydroxyglutarate could be the reason of improved survival.

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Glioblastoma gene expression subtypes and correlation with clinical, molecular and immunohistochemical characteristics in a homogenously treated cohort.

**Methods:** Clinical, molecular and immunohistochemistry (IHC) analysis from patients with newly diagnosed GBM homogenously treated with standard radiochemotherapy were studied. Samples were classified based on 3 gene expression profiles into three different subtypes (mesenchymal, proneural) using Support Vector Machine (SVM), the K-nearest neighbor (K-NN) and the single sample Gene Set Enrichment Analysis (ssGSEA) classification algorithms provided by GeneViG web application. Results: GLIOCAT Project recruited 432 patients from 6 catalan institutions, all of which received standard first-line treatment (2004-2015). Best paraffin tissue samples were selected for RNAseq and reliable data were obtained from 124.82 cases (66%) were classified into the same subtype by all 3 classification algorithms. SVM and ssGSEA algorithms obtain more similar results (87%). No differences in clinical variables were found between the 3 GBM subtypes. Proneural subtype was enriched with IDH1 mutated and G-CIMP positive tumors. Mesenchymal subtype (SVM) was enriched in unmethylated MGMT tumors (p = 0.008), and classical (SVM) in methylated MGMT tumors (p = 0.008). Long survivors (>30 months) were rarely classified as mesenchymal (0-7.5%) and were more frequently classified as Proneural (23.1-26%). Clinical (age, resection, KPS) and molecular (IDH1/2, MGMT) known prognostic factors were confirmed in this serie. Overall, no differences in prognosis were observed between 3 subtypes, but a trend to worse survival in mesenchymal was observed in K-NN (9.6 vs 15). Mesenchymal subtype presented less expression of Olig2 (p < 0.001) and SOX2 (p = 0.003) than the Proneural subtype. In contrast, KPS was significantly lower in the mesenchymal subtype. The other hand, classical subtype expressed more Nestin (p = 0.004) compared to the other subtypes (K-NN). Conclusions: In our study we have not found correlation between glioblastoma expression subtype and outcome. This large serie provides reproducible data regarding clinical-molecular-immunohistochemistry features of glioblastoma genetic subtypes.
2033 Poster Session (Board #222), Sun, 8:00 AM-11:00 AM
A TITE-CRM phase I/II study of disulfiram and copper with concurrent radiation therapy and temozolomide for newly diagnosed glioblastoma.
First Author: Jonathan Huynh, Washington University School of Medicine in St. Louis, St. Louis, MO

Background: Disulfiram (DSF) has shown promising activity against glioblastoma in preclinical studies and is more effective when combined with copper (Cu). Our previous phase I study established the maximum tolerated dose (MTD) of DSF when combined with adjuvant temozolomide (TMZ). This phase I/II study aims to establish the MTD when disulfiram and copper are combined with concurrent radiation therapy (RT) and TMZ and to explore preliminary efficacy. Methods: Eligible patients were treated with standard RT and TMZ plus escalating doses of DSF (250 mg - 375 mg PO QD) and Cu (2 mg PO TID), followed by adjuvant TMZ plus DSF (500 mg/day) and Cu. The time-to-event continual reassessment method (TITE-CRM) was used to continuously estimate the probability of dose-limiting toxicity (DLT) and to assign patients to doses with an estimated DLT probability of approximately 20% with a margin of 5%. Tumor mutations were evaluated with next-generation sequencing for all patients. Results: Eighteen glioblastoma patients were treated with the study therapy: 8 with DSF of 250 mg/day and 10 with 375 mg/day. The 1- and 2-year overall survival (OS) was 69%. There was no significant difference in PFS/OS when stratified by DSF doses, surgical extent, or MGMT methylation status. However, glioblastomas with IDH1 mutations (n = 6), BRAF (n = 2), or NF1 (n = 1) mutations had significantly better PFS and OS than those without the mutations: 1-year PFS: 100% vs 22%, respectively, p = 0.012; 1-year OS: 100% vs 42%, respectively, p = 0.006. Conclusions: The MTD of DSF with RT/TMZ/Cu for glioblastoma is 375 mg/day, and the recommended phase II dose is 250 mg/day. Although confirmation with larger sample size is needed, the combination demonstrates promising preliminary efficacy for the subset of glioblastomas with IDH1, BRAF, and NF1 mutations. Clinical trial information: NCT02715609.

2035 Poster Session (Board #224), Sun, 8:00 AM-11:00 AM
Clinical characteristics, treatment (Tx) patterns, and overall survival (OS) in advanced (Adv) NSCLC patients (Pts) with and without brain depositions (BM).
First Author: Emily Nash Smyth, Eli Lilly and Company, Indianapolis, IN

Background: BM in NSCLC pts are associated with significant morbidity and mortality. This analysis describes the frequency and timing of BM development, pt characteristics, systemic txs, and OS in NSCLC pts with and without BM. Methods: This retrospective observational study identified pts from Flatiron Foundation Medicine NSCLC Clinico-Genomic Database diagnosed from 1 Jan 2011 to 31 Oct 2017 with adv NSCLC and a tumor sample analyzed via FoundationOne. Tx pattern data were summarized by period (1 Jan 2011-1 Mar 2015; 2 Mar 2015-31 Dec 2017), therapy class (eg, anti-VEGFR and EGFR, platinum-based), and BM occurrence. Descriptive statistics were used to summarize data; Chi-square and t-tests assessed statistically significant differences. OS was measured by site of met (BM only vs no-BM only vs BM and no-BM) via K-M methods from adv diagnosis until death or last activity date (censored). Results: Of 3257 pts, 1018/3257 (31.3%) had BM during follow-up; 726/1018 (71.3%) presented with BM within 30 days of adv diagnosis. The median age at adv diagnosis was 66.2 yrs. Relative to pts without BM, BM pts were younger, more likely to be female, of Asian descent, have stage IV disease, ≥2 met sites (including BM) at initial presentation, ≥3 met sites (including BM) during follow-up, and non-squamous histology (all p < 0.01). Approximately 78% (n = 2534) were treated with ≥1 systemic tx; platinum-based chemo-combinations were the most common 1st-line tx, regardless of BM status. Increased use of PD-1/L1 tx was seen in 1st, 2nd, and 3rdline during the latter vs earlier period. No statistically significant difference in OS was observed in pts with BM only (17.1 mos; 95% CI 12.5-21.9), no-BM only (21 mos; 95% CI 19.4-22.8), or BM and no-BM (20.4 mos; 95% CI 18.9-23.3) (log rank p = 0.3027). Conclusions: In met NSCLC pts with a tumor sample that was molecularly profiled, OS was comparable, regardless of site(s) of disease; additional multivariate analyses including molecular profiles are needed. BM screening at initial diagnosis is important given the frequency in NSCLC. Future studies should address whether the shift in systemic tx patterns impact the development and clinical outcomes.

2034 Poster Session (Board #223), Sun, 8:00 AM-11:00 AM
GLIAXAV: A stratified phase II clinical trial of avelumab and axitinib in patients with recurrent glioblastoma.
First Author: Bart Neyns, Universiteit Ziekenhuis Brussels, Brussels, Belgium

Background: Patients (pts) with recurrent glioblastoma (rGB) have a poor prognosis, and no treatment option demonstrated to improve survival in a randomized trial. Axitinib (AXI), an oral VEGFR 1-3 inhibitor has demonstrated single agent activity in rGB and reduces the need for corticosteroids (CS). Avelumab (AVE) is a fully human anti-PD-L1 IgG1 antibody with clinical activity in various tumor types. Combination of AXI and AVE may improve the clinical outcome of pts with rGB. Methods: This open-label, dual-strata, single-center phase 2 clinical trial investigated the activity of AXI plus AVE in adult pts with rGB following prior surgery, RT, and temozolomide. Pts were stratified according to their baseline use of CS. Pts without baseline need for CS initiated treatment with AXI (5 mg oral BID) plus AVE (10 mg/kg IV Q2W) (cohort-1). Pts in need of CS initiated AXI as a monotherapy; AVE could be added to AXI after 6 wks if the CS dose could be tapered to a physiologic dose level or less (cohort-2). Six-month-PFS served as the primary endpoint (with a prespecified threshold of ≥ 50% for cohort-1) according to Fleming one-stage design. Results: Between Jun 2017 and Aug 2018, 54 pts (27 per cohort) were enrolled (med age 55 y [range 19-75]; 63% male; 91% WHO PS 0-1). All pts in cohort-1 and 16 pts (59%) in cohort-2 received at least 1 dose of AVE. The 6-month-PFS was 18% (95% CI 4-33) in both cohorts. At the time of analysis, 2 pts were progression-free and continuing study treatment. Median OS in cohort-1 and -2 was respectively 26 wks (95% CI 21-32) and 18 wks (95% CI 14-22). No clear relation was found between baseline cognitive functioning (Cogstate subtests) and PFS/OS. The best overall response rate (iRANO) was 41% and 26% respectively for pts in cohort-1 and -2. The most frequent all-grade treatment-related adverse events (TRAEs) were dysphonia (67%), lymphopenia (50%), diaphrea (48%), hypertension (48%), and fatigue (46%). The incidence of grade 3-4 TRAE was 30%; there were no grade 5 AE. Conclusions: The combination of AXI plus AVE is sufficiently well tolerated but did not meet the threshold for activity justifying further investigation in an unsselected population of patients with rGB. Clinical trial information: NCT03391314.

2036 Poster Session (Board #225), Sun, 8:00 AM-11:00 AM
Effect of grade on survival in IDH-mutant grade II and grade III gliomas.
First Author: Giuseppe Lambert, Department of Medical Oncology S. Onofrio Malpighi Hospital Bologna, Bologna, Italy

Background: The 2016 WHO classification dramatically changed the diagnosis of gliomas. Diffuse gliomas are classified according to the presence of IDH-mutation (IDH-mut) and the deletion of both 1p and 19q chromosome arms (1p/19q codeletion). Now debate is whether grade still has an independent prognostic value. The aim of this study was to find out if grade is a prognostic factor independently of molecular status. Methods: We analyzed our institutional data warehouse for all consecutive patients (pts) with newly diagnosed, histologically proven Grade II or Grade III IDH-mut gliomas. IDH 1/2 assessment by polymerase chain reaction (PCR) or immunohistochem- istry (IHC) was accepted. Next Generation Sequencing (NGS) for IDH1 (exon 4) and IDH2(exon 4) was performed on all specimens wild-type for the IDH1. Results: The analysis included all the 399 pts who had a grade II (n = 250, 62.7%) or grade III (n = 149, 37.3%). Median follow-up time was 105.3 months. After surgery, 72 pts (18%) received RT alone, 44 (11.0%) received CT alone, 135 (33.8%) received both RT and CT, and 142 (35.6%) follow-up without any treatment. Median survival was 148.1 months. In multivariate analysis Grade (HR = 0.342, 95%CI: 0.221 – 0.531; P < 0.001) and 1p/19q codeletion (HR = 0.440, 95%CI: 0.290 – 0.668; P < 0.001) were independently associated with a lower risk for death. The difference in survival remained when adjusted for his- tological subtype. Residual disease after surgery or biopsy negatively affected survival (HR 2.151, 95%CI 1.375 – 3.367; P = 0.001). Post-surgical treatment with RT + adjuvant CT improves survival in respect to follow-up and other treatments (HR: 0.316, 95%CI 0.156 – 0.641, P = 0.001). Conclusions: Grade still affects survival in IDH mutant Grade II and III gliomas. This effect was independent of moleculare features, surgical extension and post-surgical treatments. Clinical management of gliomas should consider stratifying patients into according grade as prognostic markers.

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Subjects with low IL4R expression (H-Score subjects with low IL4R expression (OS12 = 30%).

Treatment were associated only with moderate/high IL4R expression and survival findings that IL4R expression is associated with more aggressive disease. Re-

Our approach. MDNA55-05 is an open-label study of MDNA55 administered in GBM patients.

H-Score was developed using a validated immunohistochemistry-based ap-

important for treatment with targeted therapies such as the IL4 fusion toxin

Background: MDNA55: A locally administered IL4 guided toxin as a targeted treatment

2039 Poster Session (Board #228), Sun, 8:00 AM-11:00 AM

MDNA55: A locally administered IL4 guided toxin as a targeted treatment for recurrent glioblastoma. First Author: Dina Randazzo, Duke University Medical Center, Durham, NC

Background: IL4 receptor (IL4R) is frequently and intensely expressed on a variety of human cancers and is associated with poor survival outcomes. Determining the role of the IL4R biomarker in glioblastoma (GBM) will be important for treatment with targeted therapies such as the IL4 fusion toxin MDNA55. Methods: A classification for IL4Rx expression in GBM tissues by H-Score was developed using a validated immunohistochemistry-based approach. MDNA55-05 is an open-label study of MDNA55 administered intratumorally via convection enhanced delivery in recurrent GBM. Levels of IL4Rx expression were assessed retrospectively in 24 subjects in the clinical trial and were correlated with GBM history, imaging responses and survival outcomes following treatment with MDNA55 to explore clinical validation. Results: Range, linearity, specificity and sensitivity testing using a rabbit polyclonal antibody to IL4Rx were performed using normal control and a panel of normal human tissues and GBM cases from tissue banks. A total of 41 GBM samples were screened and grouped by reactivity thresholds: H-Scores ≥50 were observed in 95% of cases (39/41), H-Scores ≥200 were observed in 51% of cases (21/41), and H-Scores ≥250 were observed in 24% of cases (10/41). GBM tissues obtained at initial diagnosis from subjects enrolled in the trial show that moderate/high IL4R expression (H-Score > 75) was associated with shorter time to first relapse when compared to subjects with low IL4R expression (H-Score ≤ 75) (10.3 mos vs. 16.7 mos, respectively) after upfront standard-of-care treatment, consistent with published findings that IL4R expression is associated with more aggressive disease. Re-

2038 Poster Session (Board #227), Sun, 8:00 AM-11:00 AM

Phase II trial of palbociclib in recurrent RB-positive anaplastic oligoden-droglioma: A Spanish group for research in neurooncology (GEINO) trial. First Author: Juan Manuel Sepulveda-Sanchez, Hospital Universitario 12 de Octubre, Madrid, Spain

Background: The PRB-dependent cell cycle checkpoint is altered in the vast majority of anaplastic oligodendrogiomas (AO), either by homozygous de-

Mitigation and/or overexpression of CDK4. Palbociclib is an oral inhibitor of CDK4 and 6 that has already been shown to be highly active in breast cancer. Methods: We conducted a multicenter, open-label, phase II trial evaluating efficacy and safety of Palbociclib in patients with Ao that progressed to radiotherapy and more than one chemotherapy regimen containing Temo-zolomide and/or Lomustine. Inclusion criteria included: histologically and molecularly confirmed grade III oligodendrogioma (WHO 2016 classification, IDH1/2 mutation and 1p/19 codeletion were mandatory), recurrence after radiotherapy and 1 or 2 chemotherapy regimens and conserved RB protein expression by immunohistochemistry (IHC). Patients were treated with Palbociclib 125 mg/daily 3 weeks on/1off. The primary objective of the study was progression-free survival at 6 months (6M-PFS). Results: Between October 2015 and September 2018, 34 patients were enrolled across ten hospitals. The study was stopped early to second primary to lack of efficacy, with 74% of evaluable patients progressing within 6 months. Number of patients alive and free from progression at 6 months after the enrollment was 9 (26%) out of the first 34 patients, below the minimum number required (18 out of 40) to consider Palbociclib as an active drug in this population. With a median follow-up of 11.2 months, the median PFS was 3 months (95% CI: 2.5-3.5 months). Median overall survival (OS) was 23.1 months (95% CI: 17.2-25 months). There were no partial or complete responses and only 11 patients (32%) achieved stable disease as best response. Palbociclib was well tolerated with neutropenia (Grade 3 or 4: 40%) and thrombocytopenia (Grade 3 or 4: 15%) as the most common adverse effects (AEs). Both AEs had no significant impact since there were no episodes of febrile neutropenia or bleeding. Conclusions: Despite the good tolerance and drug exposure, Palbociclib monotherapy did not show favorable activity in recurrent AO. Clinical trial information: NCT02530320.

2040 Poster Session (Board #229), Sun, 8:00 AM-11:00 AM

Cancer differentiation analysis technology as a novel technology for cerebral cancer screening. First Author: Hongmei Tao, AnPac Bio-Medical Science and Technology Co., LTD, Shanghai, China

Background: While the current cancer screening methods mostly failed to detect cerebral cancer, a novel, promising technology named cancer dif-

ferentiation analysis (CDA) technology has been developed to measure novel bio-physical properties to obtain valuable multi-level and multi-parameter information including protein, cellular and molecular level information. Initial results showed that CDA technology is capable of detecting cerebral cancer with a high degree of sensitivity and specificity. Methods: In this study, samples from 78 cerebral cancer patients and 321 healthy individuals were measured. Peripheral blood of each individual was drawn in EDTA tubes. One class of bio-physical property in blood samples was utilized for CDA tests. CDA data were conducted using SPSS, and the results were shown in table. Results: The average CDA values of cerebral cancer and control groups were 52.30 and 33.38 (rel. units) respectively. The results indicated that cerebral cancer could be significantly distinguished from the control (p < 0.001). Area under ROC curve (AUC) was 0.980, and sensitivity and specificity was 92.3% and 96.6% respectively. Conclusions: Initial results showed that CDA technology could effectively distinguish cerebral cancer from healthy individuals. As a novel bio-physical based cancer detection approach with multi-level and multi-parameter expressions, CDA could be a potential candidate for cerebral cancer screening. Results from Statistical Analysis of CDA.

<table>
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<tr>
<th>Group</th>
<th>CDA Data</th>
<th>Gender</th>
<th>Age Range</th>
<th>Average Age</th>
<th>Median Age</th>
<th>Average Median SD of CDA</th>
<th>AUC</th>
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A gene signature of response to radiotherapy in patients with grade II-III oligodendrogliomas. First Author: Elizabeth Moyal, Institut Claudius Regaud, UCTT O, Toulouse, France

Background: Grade II and III Oligodendroglioma associate mutations of isocitrate dehydrogenase 1 or 2 genes and the whole-arm chromosomal loss of 1p and 19q and have a better prognosis than other gliomas. However, even if the preferred treatment consists of a combination of radiotherapy (RT) and chemotherapy, some patients will less respond to this treatment and will relapse faster, in part because of an heterogeneity in the response to RT. In the aim to identify factors of response to RT, we analyzed clinical and molecular data of patients with grade II-III oligodendroglioma exclusively treated with RT in the POLA cohort. Methods: Gene expression profiles on Affymetrix expression arrays of patients from the POLA cohort with co-deleted 1p/19q grade II/III gliomas treated by exclusive RT were used to identify a gene expression set predictive of radiation sensitivity. The primary endpoint was the progression free survival (PFS), defined as the time from treatment start until progression or death. A supervised approach with penalized regression was applied to select most informative predictors, and then a risk score was created based on the linear predictor given by the multivariable model. Results: Forty-five patients corresponded to the study criteria, with a median age at diagnosis of 45 (range 23–64). The supervised approach allowed identifying a three-gene prognostic set including Semaphorin -3C (SEMA3C), Neuronal Pentraxin 2 (NPTX2) and the Metabotropic Glutamate Receptor 5 (GRM5), involved in proliferation, migration and adhesion. The risk score associated to each patient was calculated as the negative log of the product of the expression levels of the identified genes (HRadj = 2.72, p = 0.00005) and remains significant when adjusted on clinical covariates age at diagnosis, necrosis, endothelial proliferation and type of surgery (complete, partial or subtotal surgery) (HRadj = 2.36, p = 0.001). Conclusions: We report an independent three genes SEMA3C-NPTX2-GRM5 risk score signature of response to radiotherapy in patients with oligodendroglioma, which highlights the heterogeneous response in this reputed good prognosis population. This signature could help in determining the adapted treatment as well as potential new targets to address.

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2045Poster Session (Board #234), Sun, 8:00 AM-11:00 AM

Health-related quality of life (HRQoL) evaluation in the REGOMA trial: A randomized, phase II clinical trial analyzing regorafenib activity in relapsed glioblastoma patients. First Author: Giuseppe Lombardi, Dipartimento di Scienze Oncologiche, Oncologia 1, Veneto Institute of Oncology IRCCS, Padua, Italy

Background: REGOMA trial showed that regorafenib (REG) significantly improved OS and PFS in relapsed glioblastoma (GBM) patients (pts) with respect to lomustine (LOM). REG showed a different toxicity profile compared to LOM. Here, we report final results of the HRQoL assessment, a secondary end point. Methods: REGOMA trial was a multicenter nonrandomized phase II trial comparing the combination of REG and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and brain module (QLQ-BN20) administered before any MRI assessments, every 8 weeks (+/- 2 weeks) until disease progression. To evaluate treatment impact on HRQoL, questionnaires at progression were excluded. Mixed-effect linear models were fitted for each of the HRQoL domain to examine the change over progression-free time within and between arms. The models included the time of questionnaire assessment, the treatment group and their interaction, as fixed effects, and a compound symmetry covariance structure for the random effects. Differences of at least 10 points were classified as a clinically meaningful change. To correct for multiple comparisons and to avoid type I error, the level of significance was set at 0.0146. Results: Of 119 randomized pts, 117 participated in the HRQoL evaluation, and 114 had a baseline assessment (n = 56 REG; n = 58 LOM). No statistically significant differences were observed in any generic or cancer specific domain during treatment in the REG and LOM arms, or between the two arms, except for the appetite loss scale which was significantly worse in REG treated pts compared to LOM (Global mean 14.7 (SD = 28.6) vs 7.6 (SD = 16.0); p = 0.008). The proportion of pts with a clinically meaningful worsening for appetite loss was not statistically different between the two arms (9 out of 24 and 0 out of 13 in the REG and LOM arm, respectively; p = 0.0146). Conclusions: In the REGOMA trial, HRQoL did not change during REG treatment. Pts treated with REG and LOM reported no significant difference in HRQoL. Clinical trial information: NCT02962222.

T0 T1 T2 p-value

Global Health Status 63.0 (21.3) 60.7 (20.2) 54.2 (23.3) 0.2
Role Functioning 73.2 (30.3) 71.3 (29.1) 63.1 (34.1) 0.07
Cognitive Functioning 78.8 (26.0) 81.3 (27.6) 75.1 (22.4) 0.9
Emotional Functioning 74.0 (23.3) 72.4 (24.6) 68.6 (16.4) 0.4
Social Functioning 78.9 (26.3) 81.5 (26.5) 76.2 (19.9) 0.007
Appetite Loss 8.9 (19.6) 18.7 (32.0) 31 (44.3) 0.12
Motor Dysfunction 17.1 (21.3) 17.8 (24.4) 19.8 (29.3) 0.3

Some HRQoL items during NEU treatment

2047Poster Session (Board #236), Sun, 8:00 AM-11:00 AM

EGFR amplification predicted selective sensitivity to PARP inhibitors with high-PARP DNA trapping potential in human GBM. First Author: W. K. Alfred Yung, The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX

Background: Poly-ADP-ribose polymerase (PARP) is an enzyme critical for regulating a variety of DNA damage repair mechanisms such as BER/SSBR, and PARP inhibitors have been shown to have single agent activity in breast and ovarian cancer patients with BRCA1/2 mutations. However, PARP inhibitors (PARPis) in patients with limited single agent sensitivity in GBM and identifying markers predicting sensitivity is critical to select individuals or certain groups of patients for PARP inhibitor therapy. Methods: Potency and selectivity of PARP inhibitors were analyzed in a panel of glioma stem cells (GSCs) with varying genetic background. In vivo anti-tumor activity was evaluated in xenograft models. Results: In this study, we report that PARP inhibitor, talazoparib, showed strong single-agent cytotoxicity and remarkable selective activity in glioma stem cells (GSCs). This single agent activity was strongly correlated with EGFR amplification. GSCs with EGFR amplification (which occurs in about 45% of GBMs) showed higher oxidative base damage, DNA breaks, and genomic instability than non-amplified GSCs. To sustain the elevated basal oxidative stress, EGFR-amplified GSCs had increased basal expression of DNA repair proteins. As a result of blocked DNA damage repair by talazoparib treatment, DNA damage accumulated and lead to increased PARP-DNA complexes, which was then trapped by talazoparib and resulted in high toxicity. The PARP-DNA trapping function of PARP is essential as olaparib and veliparib, two PARP inhibitors with weak DNA-PARP trapping potential did not show sensitivity in GSCs. In contrast, Pamiparib, another PARP inhibitor with similar PARP-DNA trapping ability to that of talazoparib, showed selective sensitivity in EGFR-amplified GSC. Conclusions: Our data showed that EGFR amplified GSCs with higher basal DNA damage exhibited therapeutic vulnerability to PARP inhibitors with high PARP-DNA trapping ability, and that EGFR amplification is a potential selection or predictive biomarker for PARP inhibitor therapy in GBM.

2048Poster Session (Board #237), Sun, 8:00 AM-11:00 AM

Interim results of a phase I/IIa trial of a therapeutic CMV vaccine against recurrent glioblastoma (GBM). First Author: Andrew B. Lassman, Columbia University Irving Medical Center, New York, NY

Background: Cytomegalovirus (CMV) antigens have been reported in over 90% of GBM tumors. CD4+ and CD8+T cells are most frequently directed against the gB and pp65 antigens, respectively, and are immunogenic targets in a CMV-based GBM vaccine. Methods: We have initiated a phase I/IIa clinical trial for patients with recurrent GBM using gB/pp65 enveloped virus-like particles (eVLPs) formulated with GM-CSF and administered intradermally. Subjects are vaccinated monthly until tumor progression, with immunomonitoring performed 2 weeks after each vaccination and MRI exams every 6 weeks. In phase I, eligible patients were age 18-70 with Karnofsky Performance Status at least 70, normal end-organ function, on stable or decreasing corticosteroids of at most 4mg dexamethasone (or equivalent), with recurrent GBM following any standard initial therapy and any number of recurrences. The primary endpoint was safety/tolerability and secondarily to assess immunogenicity. Three vaccine doses (0.4µg, 2µg, and 10µg pp65) were evaluated with 6 subjects in each cohort and DSMB safety review of the first 3 subjects in each cohort prior to enrolling additional subjects. Results: The DSMB identified no DLTs or safety concerns with any of the doses. Grade 3, 4 or 5 AEs occurred in 66%, 22% and 11% of participants, respectively, but were not related to vaccine administration. Twelve men and 6 women were enrolled with a median age 54 (range 39-66). Prior therapies included radiotherapy, temozolomide, and nivolumab. Immunological analyses demonstrate robust boosting of CMV-specific antibody titers and T cell responses against both gB and pp65 antigens in some but not all subjects, across all dose cohorts. Boosting of IFN-gsecreting T cells (measured by ELISPOT) exceeded the assay threshold for several subjects. Stable disease by MRI of 3 months or more has been observed in 2 subjects in the high dose cohort and 1 subject in the low dose cohort and may correlate with vaccine response. Conclusions: The phase I/IIa extension phase of the trial planned to begin in Q2 2019 is designed to explore efficacy in an additional 10 subjects that will receive the optimal vaccine dose and includes the additional requirements of unfeigned, measurable enhancing tumor 1-3 cm across at first reference and no prior immunotherapy. Clinical trial information: NCT03382977.

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Evaluating the capacity of connectome analysis to predict survival in high-grade astrocytoma. First Author: Rebecca A. Harrison, The University of Texas MD Anderson Cancer Center, Houston, TX.

Background: While factors such as age, histology and tumor molecular variants (e.g., IDH status) contribute to prognosis in patients with high grade astrocytoma (HGA), there remains a wide variability in patient survival outcomes. The connectome, or brain network organization, incorporates biologic, molecular and environmental processes providing a uniquely parsimonious summary of key prognostic factors. This study compared the capacity of machine learning (ML) models based on baseline connectomics and clinical variables to predict patient survival in HGA. Methods: Patients with a new diagnosis of HGA and a presurgical 3D, T1-weighted MRI available were retrospectively identified. Individual patient connectomes were derived from MRI with 90 cortical/subcortical features. Presurgical clinical features included age, gender, histology, tumor grade and IDH status. Three ML algorithms were implemented: extreme learning machine with Buckley–James estimator (ELMBJ), random survival forest (RSF) with logrank splitting and RSF with concordance index (CI) splitting. For each algorithm, we used a 60/40 training/testing split with 50 iterations and CI as the performance metric. We tested three models: 1) connectome only, 2) clinical only and 3) connectome plus clinical variables. Results: Of patients identified (n = 105), 66 had glioblastoma and 39 had anaplastic astrocytoma. Thirty-eight harbored IDH mutation. Median overall survival was 27.43 months (SD 39.57). Connectome-only models showed better prediction performance compared to clinical-only models across all algorithms (ELM: median CI = 0.522, clinical CI = 0.201). Connectome models also performed as well as combined models (median CI = 0.523 for ELMBJ). Conclusions: This study demonstrates the potential of a connectome model to predict survival of patients with HGA. Replication in a larger dataset is required to validate these results and refine ML models including examination of additional clinical features. If successful, use of a simple T1 MRI could provide additional variables to augment existing prognostic prediction, especially in scenarios where tumor genotyping is not available.

The timing of chemoradiotherapy after surgical resection and its impact on overall survival in glioblastoma. First Author: Robert H. Press, Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA.

Background: Prior studies examining time to initiate chemoradiotherapy (CRT) after surgical resection (S) in glioblastoma (GBM) have not provided clear consensus on its clinical impact. We sought to evaluate the effect that differential timing of adjuvant therapy may have on overall survival (OS). Methods: With the National Cancer Database (NCDB), patients (pts) with GBM who underwent S and adjuvant CRT from 2004-2013 were analyzed. Analysis was performed for the entire cohort as well as by Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classes (i.e. I, II, and III). Time from S to CRT was grouped weekly (i.e. 0-1, 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, >8, and >12 weeks). Pts were excluded if they died within the first 8 weeks to account for immortal time bias. Kaplan-Meier analysis, log-rank testing, and multivariate (MVA) Cox proportional hazards regression were performed with OS as the primary outcome. Results: A total of 30,414 pts were included for analysis. RPA class I, II, and III contained 903, 4,347, and 25,164 pts, respectively. The most common time to initiate CRT was week 4-5 (n = 7,389), and this group served as reference for survival analysis. On MVA, weeks 0-1 (hazard ratio [HR] 1.18, 95% confidence interval [CI] 1.02-1.35), 1-2 (HR 1.24, CI 1.17-1.32), and 2-3 (HR 1.11, CI 1.07-1.15) demonstrated worsened OS (all p < 0.03). For RPA class I pts, week 1-2 (HR 2.07, CI 1.08-3.95) was associated with worse OS (p = 0.028). For RPA class II pts, weeks 1-2 (HR 1.34, CI 1.14-1.57), 2-3 (HR 1.18, CI 1.07-1.31), and 3-4 (HR 1.10, CI 1.0-1.21) were associated with worse OS (all p < 0.05). For RPA class III pts, weeks 0-1 (HR 1.18, CI 1.02-1.38), 1-2 (HR 1.22, CI 1.14-1.3), and 2-3 (HR 1.09, CI 1.05-1.14) were associated with worse OS (all p < 0.03). For RPA class III pts, weeks 0-1 (HR 1.18, CI 1.02-1.38), 1-2 (HR 1.22, CI 1.14-1.3), and 2-3 (HR 1.09, CI 1.05-1.14) were associated with worse OS (all p < 0.03). No time point after week 3 was associated with change in OS for the overall cohort or any RPA class subgroup. Conclusions: These data provide insight into the optimal timing of CRT in GBM and describe RPA-class specific outcomes. In general, OS was negatively impacted if CRT started less than 3 weeks from S. Waiting up to 8 weeks, however, was not detrimental to OS and suggests delaying CRT beyond week 4-5 should be considered if clinically indicated with utmost concern.

Stratified monotherapy approach according to MGMT methylation status in elderly patients with glioblastoma. First Author: Mitsuki Shiraisha, Saitama Medical University International Medical Center, Saitama, Japan.

Background: The elderly patients with glioblastoma have an extremely poor prognosis. As they often have some degree of age-related vulnerability, it is especially important to minimize a risk of treatment-related adverse events by optimizing treatment intensity for this population. We conducted phasell clinical trial to investigate the efficacy of stratified monotherapy approach according to O6-methylguanine-DNA methyltransferase (MGMT) methylation status in elderly patients with glioblastoma. Methods: Patients aged 70 years or older with Karnofsky performance status (KPS) of at least 60 were eligible for this study. MGMT methylation status was quantitatively assessed by pyrosequencing based on the average methylation ratio of 16 CpG sites in the MGMT gene promoter. The patients with highly methylated MGMT promoter defined as an average methylation ratio with 30% or higher were treated with temozolomide (TMZ) monotherapy (standard 5/28 regimen), while the others with low or intermediate levels of MGMT promoter methylation were treated with radiation therapy (40Gy/15fr) alone. Results: Between April 2013 and December 2017, 70 patients were enrolled in this study. Median age was 78 years (70-91) and median KPS was 60 (60-100). Of 70 patients, 19 patients with highly methylated MGMT promoter received TMZ monotherapy, while the remaining 51 patients were treated with radiation therapy. Median progression-free survival (PFS) and median overall survival (OS) were 7.5 and 17.4 months in the TMZ group, respectively. Median PFS and median OS were 4.6 and 10.4 months in the radiotherapy group, respectively. Conclusions: For elderly glioblastoma patients with highly methylated MGMT promoter, TMZ monotherapy could be a treatment option. Clinical trial information: UMIN0000121727.

The correlation of systemic and local inflammation with survival prognosis in glioblastoma. First Author: Pegah Mir Seyed Nazari, Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria.

Background: Immune modulating therapies have been a long withstanding treatment approach in glioma. However, gliomas are characterized by a particular absence of tumor infiltrating lymphocytes in the local tumor microenvironment. We aimed to gain insight on the distinct patterns of inflammation associated with survival prognosis in glioma. Methods: Patients were recruited at time of glioma diagnosis or progression in the prospective observational Vienna Cancer and Thrombosis Study (CATS). A single blood draw was performed at study inclusion. PD-L1 expression in the tumor tissue was investigated via immunohistochemistry. Optimal cut-off according to ROC curve was used to assess cut off values for survival analysis. Results: 193 patients with glioma (75.6% glioblastoma (WHO grade IV), 19.7% anaplastic glioma (WHO grade III), and 4.7% diffuse glioma (WHO grade II)) were included. 40/193 (20.7%) glioma had an IDH1 mutation. Membranous PDL1 expression in the tumor tissue was observed in 20/193 (10.4%) patients. 1/20 patient presented with PD-L1 expression and IDH1 mutation (p = 0.082). PD-L1 significantly correlated with increased monocyte count (median: 0.657 vs. 0.450 [G/L], p = 0.008), higher C-reactive protein (CRP) (0.43 vs. 0.1 [mg/dL], p = 0.009) and higher fibrinogen (379 vs. 303 [mg/dL], p = 0.001). Presence of IDH1 mutation significantly correlated with increased platelet count (303 vs. 232 [G/L], p = 0.001) and lower Neutrophil/Lymphocyte (N/L) ratio (3.34 vs. 5.13, p = 0.016). Higher lymphocyte count (>1.484 [G/L], log-rank: p = 0.012), higher platelet count (>245.5 [G/L], p = 0.0001), as well as decreased N/L ratio (<5.13, p = 0.002) were significantly associated with increased survival prognosis. Conclusions: PD-L1 expression in tumor tissue was associated with markers of systemic inflammation in glioma patients. Systemic inflammation markers furthermore predicted improved survival. Immune modulating therapy approaches might be a promising approach in subgroups of glioma associated with increased baseline interaction of immune system and glioma.

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Evaluation of controlled IL-12 as monotherapy in subjects with recurrent GBM. First Author: Rimas Vincas Lukas, Northwestern University, Chicago, IL

**Background:** Interleukin-12 (IL-12), a master regulator of the immune system, results in anti-tumor responses in preclinical models, but safe use requires tightly controlled production. It was conditionally produced in Ph1 “main” study (NCT02026271) in subjects with recurrent glioblastoma (rGBM) using a replication-incompetent adenovirus to modify expression IL-12 under transcriptional control of the proprietary RheoSwitch Therapeutic System (Ad-RTS-hIL-12). Ad was delivered by dose of vemurafenib (V). IL-12 therapy resulted in sustained intra-tumor influx of activated T cells, consistent with immune-mediated anti-tumor effect, improving overall survival (OS). This correlated with increased circulating CD8+FoxP3+ T-cell ratio (“cytoidex”), an emerging biomarker of OS. While widely used with neureurosurgery, dexamethasone (dexam) blunts response to immunotherapies, nevertheless median mOS of subjects who received 20mg V of 12.7 mo (n=15) at 13.1 mo follow-up. However, subsanalysis (n=6) showed low-dose dexam (total ≤20 mg) during V dosing improved mOS (17.8 mo). We report a 36 subject substudy in rGBM with limited dexam, total rGBM treated (n=70+).

**Methods:** Ongoing Phase 1 substudy (NCT03679754) assesses safety and tolerability of local, inducible IL-12 by single intratumoral injection of Ad (2x10^11 viral particles) + V (20 mg PO QD x15 doses Days-0/14) in subjects not receiving dexam 4 wks prior to Ad. **Results:** As of 03Jan19, the majority of new subjects received low-dose dexam (total ≤20mg Days-0/14). The initial impact of dexam on mOS will be reported. As in the main study, Ad+V 20 mg specifically increased (median) serum IL-12 and downstream IFN-g from Days 0-3: 0.8 to 8.8 pg/mL and to 8.6 pg/mL. Between Days 0-14, there was net increase in cytoidex (from 20 to 46). The safety profile was similar to the main study with the main adverse reaction (AR) being mild to moderate cytokine release syndrome (CRS) characterized by flu-like symptoms. No grade 4 CRS was noted; all ARs were manageable and reversible upon holding V. **Conclusions:** Local, controlled IL-12 production using the Ad + V platform in subjects with rGBM safely activates the immune system and when dexam is limited, appears to further improve mOS, which warrants continued investigation. Clinical trial information: NCT03679754.

Analysis of the EF-14 phase III trial reveals that tumor treating fields after progression patterns in glioblastoma. First Author: Suniya A. Jeyapalan, Rhode Island Hospital, Brown University, Newton, MA

**Background:** The EF-14 (NCT00916409) trial showed that addition of alternating electric fields (Tumor Treating Fields, TTFields) to Temozolomide (TMZ) resulted in improved survival in newly diagnosed Glioblastoma (GBM) patients with supratentorial tumors treated compared to TMZ alone. TTFields delivery is planned to optimize dose at the tumor bed, leading to the hypothesis that TTFields treated patients are more likely to exhibit distal progressions, including progression to the infratentorial brain where TTFields dose is minimal when targeting the supratentorium. Here we present analysis of the EF-14 trial testing this hypothesis. **Methods:** Patients on treatment for more than two months who had an MRI that exhibited progression were included in the study (treatment: N=280/466, control: N=122/229). Regions of enhancing tumor, necrosis and resection were contoured on T1 contrast MRIs with histologically proven HGGs were analysed, a group with a single time point DSC perfusion MRI (45 patients) and a group with multiple time point DSC perfusion MRI (19 patients). Both groups included conventional MRI studies prior and after each perfusion MRI. This study design aimed to replicate decision making in clinical practice including multiple previous studies for each patient. SVM training was performed with all available MRI studies for each group and classification was based on different feature datasets from a single or multiple (subtracted features) time points. Classification accuracy comparisons were performed by calculating prediction error rates for different feature datasets and different time point analyses. **Results:** Our results indicate that the addition of multiple time point perfusion MRI combined with structural (conventional with gadolinium-enhanced sequences) MRI features results in optimal classification performance (median error rate: 0.016, lowest value dispersion). Subtracted feature datasets improved classification performance, more prominently when the final and first perfusion studies were included in the analysis. On the contrary, in the single time point group analysis, structural feature-based classification performed best (median error rate: 0.012). **Conclusions:** Validation of our results with a larger patient cohort may have significant clinical importance in optimising imaging surveillance and clinical decision making for patients with HGG.

Molecular genetic, host-derived and clinical determinants of long-term survival in glioblastoma: First results from the ETERNITY study (EORTC 1419). First Author: Michael Weller, Laboratory of Molecular Neuro-Oncology, Department of Neurology, and Neuroscience Center Zurich, University Hospital and University of Zurich, Zurich, Switzerland

**Background:** Glioblastoma represents the most aggressive primary brain tumor in adults, and less than 5% of patients survive 5 years from diagnosis. Factors influencing this long-term survival are poorly understood. **Methods:** In cooperation with the European Organisation for Research and Treatment of Cancer (EORTC) in Brussels, Belgium, more than 20 clinical sites in the US, Europe and Australia have registered patients with centrally confirmed glioblastoma who survived ≥ 5 years, collecting clinical data including therapy and quality of life-related factors, as well as biospecimens allowing to analyse molecular and immunological parameters. **Results:** At the cut-off of December 31, 2018, 392 patients were registered, of which 232 had glioblastoma confirmed by central pathology review; 59 dropped out due to histology other than glioblastoma. Glioblastomas were isocitrate dehydrogenase (IDH)-wildtype in 70.7% and had a positive O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status in 75.9%. Median age at diagnosis was 52 years (range: 21-77 years). There was enrichment for patients with gross total resection. Further analyses are ongoing. **Conclusions:** In a comprehensive effort, the consortium funded by the US Brain Tumor Funders’ Collaborative characterizes factors modulating long-term survival in glioblastoma in a unique large patient cohort. Clinical trial information: NCT 03770468.
2057 Poster Session (Board #246), Sun, 8:00 AM-11:00 AM
Efficacy of re-irradiation with carbon ions (RICi) in patients with recurrent high-grade glioma (HGG) compared to the standard re-irradiation with photons (RIrP): The reference multicenter cohort of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG).

First Author: Maximilian Knoll, Departments of Radiation Oncology, Neurology, Neurosurgery, Heidelberg University Hospital, National Center for Tumor Disease (NCT), UKHD and German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), Core-Center Heidelberg, Heidelberg, Germany.

Background: Local recurrence after surgery and radio(chemo)therapy remains a major obstacle in curative treatment of patients with HGG. Eradiation of radiosensitive glioma subpopulations (hypoxic- and stem cell like cells) together with formation of an antiangiogenic and immunopressive glioma microenvironment are among factors responsible for its recurrence.

Methods: 197 patients with HGG (grade III: 71, IV: 126) received RICi between Nov 2009 and Feb 2018 at a median dose of 42 GyRBE in 14 fractions. In DKTK-ROG multicenter cohort n=565 HGG patients (grade III: 63, IV: 479) underwent RIrP between 1997-2016 with a median dose of 36 Gy, 14 fractions. Median follow up was 34.2 months in the RICi cohort and 7.1 M for RIrP (DKTK) cohort. All three prognostic scores validated in DKTK-ROG cohort were evaluated and re-irradiation risk score (RRRS) considering initial grade, Karnofsky Performance Score and age at re-irradiation was utilized for stratification and matched comparisons. Results: Median PFS was 0.08[4.26-5.90] M (grade III: 6.7-6.9 M) and 0.08[5.97-7.5] M (grade IV: 7.93) after RICi. Among the three prognostic scores evaluated, RRRS most robustly correlated with OS. RICI was associated with HR of 0.52 (95% CI: 0.38-0.70, p = 0.002), and HR of 0.66 (95% CI: 0.50-0.90) for RRPM and RRRS matched analysis. Conclusions: Carbon ions demonstrated activity in HGG. This effect is most prominent in grade III while grade IV patients may further benefit from innovative multimodal strategies. Based on these encouraging results prospective randomized trials utilizing RRRS for stratification are recommended.

2058 Poster Session (Board #247), Sun, 8:00 AM-11:00 AM
Detection of targetable somatic alterations in glioblastoma (GBM) and clinical impact.

First Author: Michael Fusco, Moffitt Cancer Center, Tampa, FL.

Background: In GBM, molecular markers are utilized to establish an integrated diagnosis as described in the WHO 2016 guidelines and identify patients (pts) with molecular targets amenable to therapeutic intervention. Herein we review our experience at Moffitt Cancer Center. Methods: A retrospective chart review between 4/1/2013 and 11/1/2018 was performed to collect demographic, clinical, disease, treatment and outcome variables on 141 pts with GBM whose tumors underwent comprehensive genomic profiling by FoundationOne or CxDNA testing. Genomic data was analyzed for recurrent alterations and tumor mutational burden (TMB). Results: Median age was 58 years (range 19 to 85). 13% were IDH1 or IDH2 mutated. Among the 141 IDH-wild type (wt) pts, TERT promoter mutations occurred in 83% and CDKN2A/B co-deletion in 65%. 06-methylguanine-DNA methyltransferase (MGMT) promoter methylation was seen in 33%. A median of 5 clinically relevant alterations were identified per tumor sample (range, 2 to 34) and a median of 2 alterations (range, 0 to 6) were found to be actionable after review by our molecular tumor board. The most commonly actionable alterations were found in EGFR, BRAF and genes associated with homologous recombination deficiency (HRD) (see table). Four pts were treated with EGFR-targeted therapy, one pt with an HRD alteration received a PARP inhibitor (progression free survival [PFS] of 34 weeks), and two pts with BRAF V600E received dabrafenib/trametinib combination therapy (treatment ongoing at 14 weeks at 16 months, respectively). Median survival after first dose of PVSRIPO (DKTK) was 21.7 months and after second dose (Muts/Mb) was 27.1 Mts/Mb. One pt who received 44 months of temozolomide exposure had a hypermutated tumor (371 Muts/Mb) and was treated on trial with pembrolizumab, but progressed after 2 months. Conclusions: Though limited in patients with GBM, clinically actionable alterations are found in EGFR, BRAF and genes associated with homologous recombination deficiency. Further benefit from innovative multimodal strategies is anticipated. Based on these encouraging results prospective randomized trials utilizing RRRS for stratification are recommended.

2059 Poster Session (Board #248), Sun, 8:00 AM-11:00 AM
Carbon ion reirradiation for patients with malignant gliomas: Toxicity and first results of the prospective dose-escalation phase I/II CINDERELLA (M) for RICi.

First Author: Stephanie E Combs, German Cancer Consortium (DKTK) Core Center Heidelberg and DKTK Partner Site Munich (TUM), Munich, Germany.

Background: The prospective phase I/II CINDERELLA trial investigates toxicity and effectiveness of a dose escalated reirradiation with carbon ions in patients with recurrent gliomas. Methods: Following a dose escalating protocol, 52 patients with WHO II-IV gliomas were irradiated with carbon ions with doses of 3 GyRBE in 10 – 16 fractions in 7 dose levels. Median age was 42 years (range: 28 – 69) with 19 female and 33 male participants. Forty-one patients were diagnosed with WHO III/IV gliomas and 11 patients with WHO II gliomas. At the time of reirradiation, all patients showed recurrent alterations and tumor mutational burden (TMB).

Results: Median time between first irradiation and reirradiation was 9 months (range: 7 – 228). PTV size was 12 – 310 ml. During follow up <3 toxicities were not observed. Follow-up MRI suggested radiation necrosis in 4 patients. Median overall survival was 352 days and was not influenced by age, gender or radiation dose. A significant trend for improved survival rates was seen in patients with small target volumes (480 days [PTV < 75%]) vs. 322 days [PTV > 75%], p = 0.06) and initial low grade histology (497 days [WHO II] vs. 322 days [WHO III/IV], p = 0.069). During follow-up, 45 patients had local progression, while clinical deterioration was not seen. Median local progression-free survival was 138 days. Median overall survival after the second dose was 141 IDH-wild type (wt) pts, TERT promoter mutations occurred in 83% and CDKN2A/B co-deletion in 65%. 06-methylguanine-DNA methyltransferase (MGMT) promoter methylation was seen in 33%. A median of 5 clinically relevant alterations were identified per tumor sample (range, 2 to 34) and a median of 2 alterations (range, 0 to 6) were found to be actionable after review by our molecular tumor board. The most commonly actionable alterations were found in EGFR, BRAF and genes associated with homologous recombination deficiency (HRD) (see table). Four pts were treated with EGFR-targeted therapy, one pt with an HRD alteration received a PARP inhibitor (progression free survival [PFS] of 34 weeks), and two pts with BRAF V600E received dabrafenib/trametinib combination therapy (treatment ongoing at 14 weeks at 16 months, respectively). Median survival after first dose of PVSRIPO (DKTK) was 21.7 months and after second dose (Muts/Mb) was 27.1 Mts/Mb. One pt who received 44 months of temozolomide exposure had a hypermutated tumor (371 Muts/Mb) and was treated on trial with pembrolizumab, but progressed after 2 months. Conclusions: Though limited in patients with GBM, clinically actionable alterations are found in EGFR, BRAF and genes associated with homologous recombination deficiency. Further benefit from innovative multimodal strategies is anticipated. Based on these encouraging results prospective randomized trials utilizing RRRS for stratification are recommended.

2060 Poster Session (Board #249), Sun, 8:00 AM-11:00 AM
Oncolytic polio/hinovirus recombinant (PVSRP0O) against WHO grade IV malignant gliomas (MG): Experience with retreatment of survivors from the phase I trial. First Author: Annick Desjardins, Duke University Medical Center, Durham, NC.

Background: We completed a study evaluating a single intratumoral delivery of PVSRP0O in recurrent WHO grade IV MG patients (N Engl J Med. 2018 Jul 12;379(2):150-161). Some patients who originally benefitted from the first infusion of PVSRP0O demonstrated tumor recurrence, and we hypothesized that retreatment could trigger an immune recall effect, further extending their survival. We now report the impact of second and third intratumoral reinfusion of PVSRP00 in patients treated in the original dose finding study. Methods: Eligible patients were adults with recurrent supratentorial WHO grade IV MG who were experiencing disease recurrence after having benefited from the first infusion of PVSRP0O. Additional eligibility criteria included: solitary tumor 1-5.5cm in diameter; ≥4 weeks after chemotherapy, bevacizumab or study drug; adequate organ function; KPS ≥70%; and positive anti-poli-titer. One patient each was retreated at 1 x 10^11 TCID50 and 1 x 10^12 TCID50, and three patients were retreated on the identified phase 2 dose of 5 x 10^11 TCID50. Results: As of 2/20/2019, five patients have received a second intratumoral dose of PVSRP0O on study, one of which received a total of 3 doses. The patients who received two infusions of PVSRP0O were retreated 72 months, 43 months, 34 months, and 6 months after the first infusion. One additional patient received a second infusion of PVSRP0O 60 months after the first infusion and a third infusion of PVSRP0O 78 months after the first infusion. All patients demonstrated soap bubble degeneration on imaging, and two patients demonstrated tumor contraction. No grade 3 or higher adverse events related to PVSRP0O were observed after retreatment. Three of these patients remain alive more than 81, 80 and 70 months following the first PVSRP0O infusion and more than 9, 20 and 18 months after the second infusion, respectively. Two patients died 63 months and 20 months after the first infusion of PVSRP0O and 19.6 and 14 months after the second, respectively. The patient treated 3 times received the third infusion more than 2 months ago. Conclusions: Intratumoral retreatment of patients with PVSRP0O appears safe, and further efficacy and toxicity results have been observed. Clinical trial information: NCT01431893.
Are patients with oligodendroglioma at higher risk for radiation neurotoxicity?

First Author: Haroon Ahmad, University of Virginia, Charlottesville, VA

Background: Symptomatic radiation neurotoxicity (RN), manifesting on MRI as focal necrosis and/or T2 signal abnormality, is a dreaded complication of radiation therapy (RT). Whether RT is standard fractionated or accelerated, the long-term benefit vs risk profile in low-grade gliomas is not well defined. Patients with oligodendroglioma carry a better overall survival than those with astrocytoma. Anecdotally, they are more prone to experience RN than astrocytomas, as suggested by Acharya et al in 2017. We hypothesized that, independent of grade, oligodendrogliomas have a higher incidence of RN as compared to astrocytomas.

Methods: We reviewed the records of 628 patients with WHO grade II and III gliomas from our institution. Study population comprised 326 patients with: standard fractionated RT, pathology confirmation by a neuropathologist, and follow up of at least 2 years after diagnosis. RN was defined as either histologically confirmed by pathology or requiring intervention for clinically presumed RN (bevacizumab or high-dose steroids.) A separate category included patients with dramatic cognitive decline with increased T2 signal abnormality, in the absence or tumor progression. Results: There were 131 patients with oligodendroglioma, based on 1p/19q co-deletion (105 cases) or histology in the absence of molecular testing (26 cases). The remaining 195 patients had astrocytoma with intact 1p/19q. Oligodendrogliomas had an increased incidence of RN (p = 0.0063). An additional four patients with oligodendroglioma and two with astrocytoma had significant cognitive deterioration with increased T2 signal abnormality, without tumor progression. Conclusions: The greater than two-fold increase in RN incidence for oligodendrogliomas is significant and suggests patients with oligodendrogliomas may be more at risk to develop RN compared to astrocytomas. In patients with oligodendroglioma and brain metastasis, the concomitance of fractionated RT needs to be weighed against the increased potential for RN.

Analysis of baseline imaging and patient characteristics variables that correlate with development of RN are ongoing and will be presented at the meeting.

Are patients with oligodendroglioma at higher risk for radiation neurotoxicity? Yes, there is a higher risk of RN in patients with oligodendroglioma compared to patients with astrocytoma. The increased risk is significant and suggests patients with oligodendrogliomas may be more at risk to develop RN compared to astrocytomas. The concomitance of fractionated RT needs to be weighed against the increased potential for RN.

Prospective phase II trial in patients with first relapse of high-grade astrocytoma using TVB-2640 in combination with bevacizumab versus bevacizumab alone.

First Author: Brandon Konkel, Cancer Therapy and Research Center at UT Health Science Center, San Antonio, TX

Background: Recurrent glioblastoma (rGBM) following chemoradiation is associated with a poor prognosis. While bevacizumab is the most common salvage therapy, responses remain brief and without an associated survival benefit. Resistance may involve overexpression of Fatty Acid Synthase (FASN). Our institution has conducted a phase 2 study of bevacizumab with FASN inhibitor TVB-2640 in patients with GBM in first relapse. Methods: This is a prospective, phase 2 study of bevacizumab with TVB-2640 in patients with GBM in first relapse. Primary end point is progression-free survival (PFS). Inclusion criteria are: age ≥ 18, ECOG 0 to 2, GBM progression following standard combined modality treatment. Randomization into two arms for the first 28 days is included for exploratory biochemical analysis: patients in arm 1 receive bevacizumab every 2 weeks in combination with TVB-2640; those in arm 2 receive bevacizumab alone every 2 weeks. MR-Spectroscopy (MRS) and serum sampling for exosome analysis are obtained on patients at day 1 and 28 of first cycle. Starting on cycle 2 day 1, all patients concurve to a single arm and continue to receive bevacizumab in combination with TVB-2640. Results: We have enrolled 24 patients to date; 23 have started treatment. Of those 23 patients, 10 have died, 4 have progressed but are still alive, 2 withdrew, and 7 are still active on trial. The PFS6 and OS9 are both currently 50%, which compares favorably with historical controls. There have been no reports of grade 4 or 5 treatment-related AEs (of note, 2 deaths were thought definitely unrelated to treatment, including 1 case of intracerebral hemorrhage, and 1 case of sepsis). There have been two cases of grade 3 hand-foot syndrome thought definitely related to treatment. The CMV (cytomegalovirus) incidence was 4/18, and the AEs were managed as hypothesized. Median PFS and OS were 22 and 30 months respectively, and three patients in Arm III are healthy and progression free at 36-39 months. OS exceeded RPA predicted survival by 3.3-fold suggesting clinical benefit. Overall survival is and OS9 are both currently 50%, which compares favorably with historical controls.

The study has completed accrual with final data expected later in 2019. Clinical trial information: NCT03032484.
Results:

success and adverse radiation effect (ARE) were analyzed with death and (DF) if a new parenchymal tumor, or leptomeningeal (LMD) for new nodular/
targeted the surgical corridor, defined as the surgical tract uninvolved by
surgical corridor defined as
within 3 months (p =0.01), but not other factors (p
prior SRS/resection for other brain metastases (23% vs. 0%, p=0.01),
follow-up was 14 months. Not targeting surgical corridor was associated with
58 lesions (57 patients) had evaluable data and a
review, from 428 lesions treated from 2005-2018 with post-resection SRS,
combination with temozolomide in Japanese patients with/without
SRS. Functional and clinical significance of major tumor infiltrating lymphocyte
subsets in lung cancer-associated brain metastases. First Author: Benjamin Y. Liu, Yale School of Medicine, New Haven, CT

Backgroun d: Despite the biological and clinical implications, the immune composition and functional characteristics of adaptive immune cells in brain metastases (BrM) are poorly understood. Using multiplexed quantitative immunofluorescence (QIF), this study evaluates the level and functional profile of major T-cell subsets in primary lung tumors, BrM, and extracranial metastases (ECM) from lung cancers. Methods: A tissue microarray was constructed from formalin-fixed, paraffin-embedded tumor samples of 94 lung cancer patients treated at Yale Cancer Center between 2002-2013. Multiplexed QIF was used to evaluate the cases with a panel containing phenotype markers for major T-cell subsets (CD3, CD4, CD8 and FOXP3), and cell-localized activation and proliferation (granzyme-B and Ki-67). Signal for each marker was measured in marker-selected tissue compartiments using the Automated Quantitative Analysis (AQUA) platform. Associations between markers and major clinicopathologic variables were studied. Results: In total, 40 primary lung tumors, 63 BrM, and 15 ECM were analyzed, including paired samples from 22 patients. Lung cancer histology included adenocarcinoma 62.5%, squamous cell carcinoma 11.5%, small cell 9.4%, and other non-small cell 16.7%. BrM had both significantly lower levels of CD3+ T-cells (p<0.0001) and T-cell granzyme B (p=0.0188) compared with primary lung tumors. No significant differences were observed in T-cell Ki-67 levels across tissues. FOXP3 measured in CD4+ T-cells were significantly lower in BrM compared with primary malignancies (p=0.0002) and ECM (p=0.0404). Among patients with BrM, higher levels of CD3+ T-cells in BrM were associated with longer overall survival. Conclusions: Lung cancer-associated BrM have lower T-cell infiltration, cytolytic function, and regulatory T-cells than primary lesions. These results indicate lower adaptive anti-tumor responses in BrM and suggest the presence of a tolerogenic microenvironment in the brain. Overcoming this could be used to design optimal treatment strategies.

2065 Poster Session (Board #254), Sun, 8:00 AM-11:00 AM
Phase I/II study of depatuxizumab mafodotin (ABT-414) monotherapy or combination with temozolomide in Japanese patients with/without EGFR-amplified recurrent glioblastoma. First Author: Yoshihata Narita, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan

Background: The poor prognosis of glioblastoma (GBM; WHO grade IV) results from a high rate of disease recurrence and lack of effective treatment options. Depatuxizumab mafodotin (depatux-m, ABT-414) is comprised of an EGFR-directed antibody, depatuxizumab (depatux, ABT-806), conjugated to the microtubule toxin monomethyl auristatin F (MMAF, mafodotin). Once bound with tumor cells, depatux-m is internalized and releases the microtubule toxin monomethyl auristatin F (MMAF, mafodotin). gate to the microtubule toxin monomethyl auristatin F (MMAF, mafodotin).

options. Depatuxizumab mafodotin (depatux-m, ABT-414) is comprised of

Preliminary safety, PK and efficacy in an ongoing phase 1/2 study of Japanese patients with/without EGFR-amplified recurrent GBM (rGBM). Methods: M13-714 (INTELLIGENCE-J, NCT02990263) is a non-randomized, phase 1/2 study in Japanese patients. Phase 1 assessed tolerability and PK where the dose escalation of depatux-m was from 0.5 to 1.25 mg/kg/Q2W at day 1 and 15 during 28-day cycle until progression disease (PD) or intolerable toxicity. Phase 2 assessed efficacy and safety of depatux-m in EGFR-amplified, rGBM and patients received 1.0 mg/kg of depatux-m on day 1 and 15 + 150 mg/m2 temozolomide (TMZ) on days 1-5 during each 28-day cycle until PD or in tolerable toxicity. Results: As of 10 Jan 2019, 38 patients (WHO grade ≥3) were enrolled (9 in phase 1, 29 in phase 2). There was no dose limiting toxicity in phase 1. The recommended phase 2 dose was 1.25 mg/kg where the most common adverse events (AEs) were punctate keratitis in 21 patients (72%); lymphopenia in 14 patients (45%), thrombocytopenia in 13 patients (41%). Grade 3/4 AEs included thrombocytopenia and lymphopenia in 20 patients (69%), Ocular AEs were reported in 27 patients (93%) including punctate keratitis (72%). PK results (31 patients) in both phases were similar to those of non-Japanese patient. Progression Free Survival (PFS) of 27 patients in phase 2 for 12 and 16 months were 8% and 3% respectively. PFS was 4 months. The overall survival (OS) for 24, 12 and 6 months were 28%, 62.5% and 93% respectively. The median OS was 15.5 months. Conclusions: Preliminary safety, PK and efficacy in Japanese patients with/without EGFR-amplified, rGBM suggests depatux-m was tolerated and showed encouraging anti-GBM effects. Clinical trial information: NCT02950263.

2068 Poster Session (Board #257), Sun, 8:00 AM-11:00 AM
Stereotactic radiosurgery for resected brain metastases: Does the surgical corridor need to be treated? First Author: Siyu Shi, Stanford Cancer Institute, Palo Alto, CA

Background: Post-operative stereotactic radiosurgery (SRS) is the standard of care for resected brain metastases, but SRS techniques are not standar-dized. Although expert consensus guidelines recommend that the surgical corridor leading to the resection cavity be included in the SRS plan, this statement is not based on data. We analyzed the patterns of failure and toxicity with post-resection SRS, with the hypothesis that the corridor needs not be targeted with SRS. Methods: In this IRB-approved retrospective review, from 428 lesions treated from 2005-2018 with post-resection SRS, 58 lesions (57 patients) had evaluable data and a ‘deep’ tumor with a surgical corridor defined as ≥ 1.0 cm from the surface pre-operatively. SRS targeted the surgical corridor, defined as the surgical tract uninvolved by tumor on pre-operative imaging, in 33(57%). Brain failure was defined as local (LF) if within the surgical cavity involved with tumor pre-resection, corridor (CF) if within the surgical tract leading to the surgical cavity, distant (DF) if a new parenchymal tumor, or leptomeningeal (LMD) for new nodular/classical leptomeningeal enhancement. The cumulative incidences of failure and adverse radiation effect (ARE) were analyzed with death and whole brain radiation therapy as competing risks. Results: The median follow-up was 14 months. Not targeting surgical corridor was associated with prior SRS/resection for other brain metastases (23% vs. 0%, p=0.01), deeper tumors (median 2.1 cm vs. 1.4 cm, p<0.01), and systemic treatment within 3 months (p =0.01), but not other factors (p=0.10). The 12-month failure rates, if surgical corridor was not treated vs. treated, respectively, were: CF 8% (1-24%) vs. 0% (p=0.12), LF 4% (0-17%) vs. 13% (4-27%) (p=0.32), LMD 40% (19-61%) vs. 10% (2-23%) (p=0.03), DF 65% (43-81%) vs. 35% (19-52%) (p=0.02), and ARE 8% (1-22%) vs. 13% (4-28%) (p=0.35). After adjusting for systemic treatment, differences were not statistically significant (p>0.05). Conclusions: Omitting the surgical corridor in post-operative SRS for resected brain metastases was not associated with statistically significant differences in recurrences or adverse radiation effect. Surgical corridor does not need to be included in all post-resection SRS.

2069 Poster Session (Board #258), Sun, 8:00 AM-11:00 AM
Insight into the brain metastasis journey: Initial survey results from patients and caregivers. First Author: Nicole Willmarth, American Brain Tumor Association, Chicago, IL

Background: Brain metastases (BM) are the most common central nervous system tumors in the US. Though the exact incidence is unknown, BM are estimated to occur in up to 10-20% of all cancers. Despite the high frequency, there is little systematic knowledge about how BM are typically diagnosed and treated. The American Brain Tumor Association (ABTA) seeks to understand the BM journey: symptoms, diagnosis, treatment, and end of life, through a survey of BM patients and caregivers. Methods: Two surveys were developed by the ABTA with vendor, PSB Research, after careful literature review. The surveys were reviewed by a panel of clinicians who treat BM patients. Online survey research was conducted between 8/13-9/16/18, with one survey for adults with BM (N = 237) and another for caregivers (N = 211). Respondents came from PSB’s panels and ABTA collaborators: LUNGevity, Melanoma Research Foundation and the Kidney Cancer Association. Results: Ninety percent of patients, and a similar number of caregivers, were surprised by the diagnosis, with only 20% of patients knowing about BM before diagnosis. Most caregivers were the adult child of a patient. The impact of the diagnosis was primarily emotional. Top concerns after diagnosis, for both patients and caregivers, were likelihood of treatment success and impact on quality of life. Although a majority of patients were happy with the quality of information given, they stated a need to receive a greater quantity of information about treatment success and options. Only 30% of patients were referred to a patient advocacy organization. When referred, information on treatment success rates and options was most sought. Conclusions: Direct patient and caregiver feedback provides valuable insight towards understanding the BM journey and resources needed to support patients and caregivers. A subsequent survey among oncologists and other clinicians, planned for spring 2019, will add to these findings.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
A phase II trial of bevacizumab in patients with recurrent solid tumor brain metastases who have failed whole brain radiation therapy (WBRT). First Author: Patrick Roth, University Hospital Zurich, Zurich, Switzerland

Background: Brain metastases (BM) are the most common intracranial malignancy with overall a poor prognosis estimated at approximately 4 months from time of initial diagnosis for treated patients, and even lower after failing WBRT after which treatment options have been limited and outcomes poor. Methods: This is an open label phase 2 study where patients who have previously failed WBRT received bevacizumab at a dose of 10 mg/kg intravenously every two weeks until CNS disease progression in cycle being defined as 4 weeks. The primary endpoint was objective radiographic tumor response as defined by modified Response Assessment in Neuro-oncology (RANO) criteria. Secondary endpoints included progression free survival (PFS) at 6 months, time to progression, time to response, duration of response, overall survival (OS), quality of life (QOL) as measured by the FACT-G and FACT-Br and safety. Results: A total of 27 patients were consented and registered to study of which 24 were evaluable for ORR (3 came off study prior to first follow up MRI brain). Median age was 53 (range 27-73), median number of cycles was 5.5 (range 1-20) with a median follow up of 6.7 months (range 2.4-47.9mo). Of the 24 evaluable patients, there were 6 Partial response, 16 stable disease and 2 progressive disease. The 6 month PFS: 46% (95% CI: 25% - 67%) and median PFS was 5.3 months. Median OS was 9.5 months (95% confidence interval 6.3m – 15.0m). For the patients who completed sequential QOL assessments, there was no significant decline in QOL. All patients had a measurable increase in the FACT-Br scores. Overall, treatment was well tolerated with grade 3 adverse events seen: hypertension (n = 3), headache (n = 1) and thrombotic event (n = 1). Conclusions: For this WBRT failure BM population, we were able to show a 25% disease response to bevacizumab therapy along with good drug tolerability and no noted central nervous system bleeding. Improved survival as compared to historical controls was seen 9.5 m. Of the 24 evaluable patients, 81% (22/24) experienced clinical benefit defined as stable disease or better. Bevacizumab therapy could be a viable option for solid tumor BM patients who experience progression following WBRT, however a larger trial is required to confirm this data. Clinical trial information: NCT01898130.
Phase I study of PD-L1 inhibition with avelumab and laser interstitial thermal therapy in patients with recurrent glioblastoma. First Author: Adilia Hormigo, Icahn School of Medicine at Mount Sinai, New York, NY

**Background:** Glioblastoma (GBM) is the most frequent malignant brain tumor in the adult with a dismal prognosis and limited treatment options. Current advances have highlighted how tumors and specifically GBM evade the immune system by exploiting the mechanisms of tolerance and inducing local and systemic immunosuppression. Another hurdle in the treatment of GBM is the blood-brain barrier (BBB). Recent work suggests that MRI-guided laser interstitial thermal therapy (LITT) can increase the permeability of the BBB and may have an abscopal effect. Therefore, utilizing MRI-guided LITT, a potential immunogenic cell death-inducing procedure that disrupts the BBB and makes Avelumab a PD-L1 monoclonal antibody being more accessible to GBM tumors, seem a valid approach for immunomodulation and successful implementation of a combined regimen to treat brain cancer.

**Methods:** This is a prospective non-randomized open label to characterize the tolerability and safety profile of Avelumab in combination with LITT in patients with recurrent glioblastoma who were treated with radiation therapy with concurrent Temozolomide chemotherapy at diagnosis, and whose tumor at recurrence measures less then 3 cm³. Avelumab is administered within a week after real-time MRI-guided LITT therapy and every 2 weeks thereafter.

**Results:** On part A patients are treated with intravenous Avelumab alone and on part B patients receive Avelumab in combination with MRI-guided LITT. Part A completed enrollment without DLT. Enrollment on part B began in October 2018. A Simon minimax two-stage design is being used for efficacy. Toxicity will be scored using the NCI-CTCAE v4.03 criteria.

**Conclusion:** Blood samples and tumor tissue will be collected for correlative studies. Quantification of the changes in inflammatory and immunosuppressive profiles across time points for patients receiving treatment with Avelumab will be obtained. This information will instruct future immunotherapy approaches to treat GBM and the rationale for those combinations. Clinical trial information: NCT03431806.

TPS2075 Poster Session (Board #262a), Sun, 8:00 AM-11:00 AM

**A phase I/II trial of CB-839 (telaglenastat) in combination with radiation therapy and temozolomide in patients with IDH-mutated diffuse astrocytoma and anaplastic astrocytoma (NCT03528642).** First Author: Sani Harder Kizilbash, Mayo Clinic, Rochester, MN

**Background:** IDH mutant astrocytomas express high levels of 2-hydroxyglutarate (2-HG), an oncogenic metabolite which drives gliomagenesis. Excess 2-HG inhibits branched chain amino acid transaminase, which catalyzes glutamate synthesis from branched chain amino acids. This defect causes these tumors to become more reliant on glutaminase for glutamate biosynthesis from glutamine. CB-839 (telaglenastat) is a novel glutaminase inhibitor which is well tolerated in humans. McBrayer et al have recently demonstrated that CB-839 further depletes intracellular glutamate and glutathione in IDH mutant glioma cells, and enhances RT (radiation therapy) efficacy in an orthotopic glioma model. **Methods:** NCi #10218 is a CTEP supported phase I clinical trial investigating the safety and tolerability of CB-839 when combined with RT/TMZ (temozolomide) in patients with previously untreated IDH mutant grade II/III astrocytoma. Patients with grade II and III astrocytomas will be treated with 50.4 and 59.4 Gy of RT, respectively, with standard doses of concurrent TMZ. CB-839 will also be administered orally concurrently with RT, with doses escalated in cohorts based on a standard 3+3 design. After defining the maximum tolerated dose (MTD) of CB-839, an expansion cohort will evaluate the pre- and post-CB-839 therapy metabolome of patients with IDH mutant astrocytoma. Enrollment to this cohort will require measurable disease and patients will additionally be treated with a 7 day run-in of CB-839 at MTD prior to RT. The effect of CB-839 on the metabolome will be studied in both plasma (LC/MS/MS) and tumor (magnetic resonance spectroscopy), along with PK to confirm adequacy of systemic exposure. Preliminary data on neurocognitive endpoints will also be acquired. NCi #10218 is currently activated for enrollment to cohort 1. Clinical trial information: NCT03528642.

TPS2076 Poster Session (Board #262b), Sun, 8:00 AM-11:00 AM

**Oral DNA vaccination targeting VEGFR-2 combined with anti-PD-L1 avelumab in patients with progressive glioblastoma, a phase II study: NCT03750071.** First Author: Wolfgang Wick, National Center for Tumor Diseases (NCT), UKHD and German Cancer Research Center (DKFZ), Heidelberg, Germany

**Background:** The vaccine (VXM01) is a VEGFR-2 coding DNA vaccine, using a Salmonella Ty21a carrier for oral application. VEGFR-2 is over-expressed in glioblastoma and serves as a promising target for VEGFR-2 primed T cells with the potential to alter tumor angiogenesis and/or eliminate VEGFR-2 expressing tumor cells. VXM01 was well tolerated in a previous phase I/II study involving 14 patients with progressive glioblastoma multi-forme. Immunological correlates of vaccination and anti-tumor immunity in the blood and in the tumor were detected. At least one objective clinical response was attributed to vaccine monotherapy, with one more PR achieved in combination with nivolumab. Prolonged overall survival was associated with peripheral immune responses against VEGFR-2, J Clin Oncol 36, 2018 (suppl; abstr 2017). A combination study with the anti PD-L1 checkpoint inhibitor monoclonal antibody avelumab is currently underway. **Methods:** A multicentre, open-label phase I/II study (EudraCT.gov no. 2017-003076-31), will enrol 30 patients with progressive glioblastoma, previously treated with temozolomide/radiotherapy. The primary objective is to evaluate safety and tolerability of the vaccine in combination with avelumab. In a 1+2 safety run in, two cohorts of non-re OPERable patients will be vaccinated with one of 2 doses of the oral vaccine (10⁵ or 10⁷ CFU) with concurrent intravenous avelumab. Prolonged overall survival was associated with peripheral immune responses against VEGFR-2, J Clin Oncol 36, 2018 (suppl; abstr 2017). A combination study with the anti PD-L1 checkpoint inhibitor monoclonal antibody avelumab is currently underway. **Methods:** A multicentre, open-label phase I/II study (EudraCT.gov no. 2017-003076-31), will enrol 30 patients with progressive glioblastoma, previously treated with temozolomide/radiotherapy. The primary objective is to evaluate safety and tolerability of the vaccine in combination with avelumab. In a 1+2 safety run in, two cohorts of non-re OPERable patients will be vaccinated with one of 2 doses of the oral vaccine (10⁵ or 10⁷ CFU) with concurrent intravenous avelumab. Vaccinations for all patients will be on day 1, 3, 5, and 7, followed by 4-weekly boosts until progression. Avelumab 800 mg will be administered orally concurrently with RT, with doses escalated in cohorts based on a standard 3+3 design.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: People with HIV have been excluded from immuno-oncology (IO) studies. Anti-PD-1/PD-L1 therapies are approved for a growing number of cancers. We evaluated pembrolizumab (pembro) in people with HPV and cancer. Methods: CITN-12 is a multicenter phase 1 trial. Key eligibility: advanced cancer; ECOG ≤1; CD4 ≥ 100 cells/μL; ≥ 4 weeks antitumor therapy (ART); HIV viral load (VL) < 200 copies/mL. Exclusion: uncontrolled HBV/HCV, autoimmune disease. Participants (pts) accrued into CD4-based cohorts (C): C1 100-199; C2 200-350; C3 350-500; C4 500+; C5 200 mg IV administered Q3W for up to 35 doses. Adverse events (AE) evaluated by CTCAE. Immune related AE (irAE) were assessed by CTCAE. Immune related AE

Results: Twenty HIV-1 individuals with advanced solid tumors were enrolled (Table). All participants maintained their standard-of-care antiretroviral therapy. Basal plasma viremia was undetectable and CD4+ T-cell count was over 200/mm3. There were no durvalumab-related serious adverse events. Only 8 patients (40%) presented drug-related adverse events (all grade 1-2) including diarrhea (15%), rash (15%), nausea (15%) and asthenia (10%). Best response includes: partial response in 5 (25%) (4 NSCLC and 1 anal cancer), stable disease in 4 (20%) (3 NSCLC and 1 melanoma) and progression in disease in 1 (5%) patients. At data cut-off, 8 patients (40%) remained on therapy for a median of 10.5 months (range: 6-19 m). Median DOR has not been reached (range 1m to 19 m). Plasma viremia remained suppressed during the study suggesting no viral reactivation upon durvalumab treatment.

Conclusions: DURVAST study demonstrates durvalumab safety in HIV+ cancer patients and suggests an excellent tolerance profile. Understanding how chronic viral infection could contribute to a better tolerance towards immune checkpoint inhibitors will open a new way for the development of safer anti-cancer immunotherapy strategies. Clinical trial information: NCT03094286.

A phase II study of pembrolizumab for HPV-associated papilloma patients with laryngeal, tracheal, and/or pulmonary involvement

Background: Recurrent respiratory papillomatosis (RRP) is caused by human papillomavirus (HPV) types 6 & 11. RRP proliferates in the respiratory tract impacting breathing, swallowing, and voice and carries a 1-4% risk of malignant transformation. There is no curative therapy for RRP. Given the lack of anti-HPV therapies and the potential for RRP to transform to a cancer, patients with laryngeal/pulmonary papillomas may benefit from immunotherapies. Methods: 20 patients received pembrolizumab at the recommended dose of 1500 mg Q4W. Safety was evaluated by CTCAE. Immune related AE (irAE) were assessed by CTCAE. Immune related AE

Results: Pembrolizumab was administered for a median of 4.3 months (range 0.8-17 m). Thirty-three patients (17%) experienced irAEs, the most common (6%) included anal and squamous skin. Prior radiation (19), median KS cohort (C4).

Conclusions: Pembrolizumab was well tolerated in patients with laryngeal/pulmonary papillomas. A future trial of pembrolizumab versus placebo is needed to determine clinical benefit in this population. Patients with HIV meeting appropriate eligibility criteria should be included in IO studies. Clinical trial information: NCT02595866.
Results: A bivalent SMAC mimic targeting cIAP1. Synergistic effects of combining birinapant with immune checkpoint inhibitors have been demonstrated in preclinical models. Based on these observations, a clinical trial with birinapant and pembrolizumab was initiated (NCT02587962).

Methods: Patients ≥18 years with advanced solid tumors without further standard therapeutic options were eligible for inclusion. Birinapant (5.6–22 mg/m²) was administered IV on day 1 and 8 in addition to pembrolizumab 200 mg on day 1 in a 21-day cycle until disease progression using standard 3+3 dose-escalation. The primary objective was to determine the safety and tolerability of the recommended phase 2 dose (RP2D) of birinapant in combination with pembrolizumab. Secondary and exploratory objectives included antitumor activity assessed by RECIST 1.1 and iRECIST, pharmacokinetics and assessment of biomarkers including serum cytokines, cIAP1, PD-L1 expression and tumor infiltrating lymphocytes. Results: Nineteen patients were enrolled at 4 dose levels of 5.6 (n = 3), 11 (n = 3), 17 (n = 6) and 22 (n = 7) mg/m². Most common tumors were pancreatic (n = 5), colorectal (n = 4), ovarian (n = 3) and sarcoma (n = 3). Median prior therapies were 4 (0–12). The most common AE related to any of the study drugs was rash (50%), followed by infusion related reactions (41%), pyrexia (27%), fatigue (23%), chills (23%) and nausea (23%). AE grade 3 or 4: one AE, one neutropenia and one hypokalemia, all of them grade 3. Serum CRP and IL-6 were reduced after two weeks of treatment. There were linear increases of AUC and Cmax (10–20 mg/m²) and CAN04 exposure at 10 mg/kg was above the levels associated with signs of efficacy in preclinical models. In pts receiving at least one dose of CAN04, 9/20 (45%) had SD by iRECIST (7/20 had SD by RECIST 1.1) at 8 weeks follow up. Two pts, one with NSCLC and one with PDAC, had PD for 6 and 4 months (latter still on therapy). Conclusions: CAN04 demonstrated a manageable safety profile and a RP2D of 10 mg/kg has been established. The dose expansion phase of the trial will evaluate CAN04 as monotherapy as well as in combination with relevant chemotherapy regimens in NSCLC and PDAC in separate arms. Clinical trial information: NCT03267316.

Determination of the recommended phase II dose of birinapant in combination with pembrolizumab. Results from a phase 1b dose escalation trial with 1, 3, 6 or 12 mg/kg of birinapant in combination with pembrolizumab. First Author: Russell J. Schilder, Thomas Jefferson University, Philadelphia, PA

Background: Birinapant is a bivalent SMAC mimic targeting cIAP1. Synergistic effects of combining birinapant with immune checkpoint inhibitors have been demonstrated in preclinical models. Based on these observations, a clinical trial with birinapant and pembrolizumab was initiated (NCT02587962).

Methods: Patients ≥18 years with advanced solid tumors without further standard therapeutic options were eligible for inclusion. Birinapant (5.6–22 mg/m²) was administered IV on day 1 and 8 in addition to pembrolizumab 200 mg on day 1 in a 21-day cycle until disease progression using standard 3+3 dose-escalation. The primary objective was to determine the safety and tolerability of the recommended phase 2 dose (RP2D) of birinapant in combination with pembrolizumab. Secondary and exploratory objectives included antitumor activity assessed by RECIST 1.1 and iRECIST, pharmacokinetics and assessment of biomarkers including serum cytokines, cIAP1, PD-L1 expression and tumor infiltrating lymphocytes. Results: Nineteen patients were enrolled at 4 dose levels of 5.6 (n = 3), 11 (n = 3), 17 (n = 6) and 22 (n = 7) mg/m². Most common tumors were pancreatic (n = 5), colorectal (n = 4), ovarian (n = 3) and sarcoma (n = 3). Median prior therapies were 4 (0–12). The most common AE related to any of the study drugs was rash occurring in 3 patients. Ten patients had 17 SAEs of which only one (stomatitis) was judged related to birinapant. Increased ALT/AST (G3/G2) leading to missed day 8 dose constituted a DLT at 22 mg/m². Grade 2 ipase increases were seen in 2 patients. No cases of Bell’s palsy were detected. ORR by RECIST 1.1 was 5.6% (n = 1) in 18 evaluable patients. The responding patient had microsatellite stable colorectal carcinoma (MSS-CRC) and remains on therapy for 13+ months after first dose. By iRECIST, ORR was 11.1%, CBR (PR+SD) by RECIST was 22.2%. The exposure to birinapant generally increased with dose. The RP2D was determined to be 22 mg/m².

Conclusions: Birinapant and pembrolizumab is a safe and tolerable combination that has shown encouraging signals of efficacy. A phase 2 study evaluating efficacy and tolerability of birinapant in combination in MSS-CRC is ongoing. Clinical trial information: NCT02587962.
2508 Oral Abstract Session, Sun, 8:00 AM-11:00 AM
First-in-human study of REGN3767 (R3767), a human LAG-3 monoclonal antibody (mAb), cemiplimab in patients (pts) with advanced malignancies. First Author: Kyonghee Kim, South Texas Accelerated Research Therapeutics, San Antonio, TX

Background: We present initial safety, pharmacokinetics (PK), and efficacy from the dose escalation study of R3767, alone (mono) or in combination with cemiplimab (REGN2810), a PD-1 mAb (combo), in pts with advanced malignancies (NCT03005782).

Methods: Pts who had progressed on prior therapy(ies) and/or for whom no therapy with clinical benefit was available were enrolled; most pts had received no prior anti-PD-1/PD-L1 therapy. R3767 1, 3, 10, or 20 mg/kg every 3 weeks (Q3W) ≤ cemiplimab 3 mg/kg or 350 mg Q3W IV for ≤51 weeks. Crossover from mono to combo was allowed at progression. R3767 PK were evaluated. Tumor measurements were performed Q6W for the first 24 weeks and subsequently Q9W.

Results: As of November 30th, 2018, 12 pts had received R3767 20 mg/kg or 1600 mg fixed dose equivalent Q3W as mono therapy. R3767 PK were evaluated. Tumor measurements were performed Q6W for the first 24 weeks and subsequently Q9W. Data cut-off was Aug 25, 2018. Results: Mono: 27 pts (median age: 66 yr; ECOG PS: 0 [n=4], 1 [n=23]) were treated. There were no dose-limiting toxicities (DLTs). The most common treatment-emergent adverse event (TEAE) was nausea (22.2%). Grade ≥3 immune-related adverse events (irAEs) of increased alanine and aspartate aminotransferases (each 3.7%) were reported. By investigator-assessment (per RECIST 1.1; INV), best response was stable disease in 11 pts. Combo: 42 pts (median age: 60 yr; ECOG PS: 0 [n=15], 1 [n=27]) were treated. One pt treated with R3767 7 mg/kg Q3W + cemiplimab 3 mg/kg Q3W experienced DLT of grade 4 elevated blood creatinine phosphokinase, associated with grade 3 myasthenia syndrome and grade 1 elevated troponin. The most common irAEs observed for nausea (21,4%). Grade 3 irAEs of hypothyroidism (2.4%) was also reported. By INV, 2 (both small cell lung cancer) combo pts and 2 (endometrial cancer and cutaneous squamous cell carcinoma) of 12 additional pts who crossed over from mono to combo had partial responses. PK: R3767 concentration in serum increased in a dose-dependent manner and were unaffected by combo. Conclusions: The safety profile of R3767 cemiplimab was generally tolerable; PK was linear. Early efficacy signals were detected despite the difficult-to-treat pt population. Biomarker studies are ongoing. R3767 20 mg/kg or 1600 mg fixed dose equivalent Q3W as mono and combo were selected for further evaluation. Clinical trial information: NCT03005782.

2510 Clinical Science Symposium, Tue, 8:00 AM-9:30 AM
Results of a phase I study of bispecific anti-CD19, anti-CD20 chimeric antigen receptor (CAR) modified autologous T cells for relapsed/refractory diffuse large B-cell lymphoma. First Author: Nirav Niranjan Shah, Medical College of Wisconsin, Milwaukee, WI

Background: Anti-CD19 CAR T-cell therapy is a breakthrough treatment (tx) for patients (pts) with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (NHL). Despite impressive outcomes, non-response and relapse with CD19 negative disease remain challenges. Through dual B-cell antigen targeting of CD20 and CD19, with a first-in-human bispecific lentiviral CAR-CLDN18.2 T cells, patients with confirmed CLDN 18.2 positive advanced gastric cancer were treated with 1–5 cycles (total of 0.5 – 5 X 10^9) of CAR-positive T-cell infusions. There were no serious adverse events, treatment-related death or serious neurotoxicity. In this ongoing, R3767 1, 3, 10, or 20 mg/kg every 3 weeks (Q3W) was selected for expansion. In terms of safety, 6 pts developed Grade 1-2 toxicities observed were grade 1 or 2. Among the 11 evaluable subjects, 1 achieved a complete response (gastric adenocarcinoma), 3 had partial responses (2 gastric adenocarcinomas and 1 pancreatic adenocarcinoma), 5 had stable disease and 2 had progression of disease. The total objective response rate was 33.3%, with median PFS of 130 days estimated using Kaplan-Meier method (95% CI (28, 320)). Conclusions: This clinical study indicated that CAR-CLDN18.2 T-cell therapy were safe and well tolerated and may have promising therapeutic efficacy in patients with advanced gastric and pancreatic adenocarcinoma. Clinical trial information: NCT03195819.

2509 Clinical Science Symposium, Tue, 8:00 AM-9:30 AM
Phase I trial of Claudin 18.2-specific chimeric antigen receptor T cells for advanced gastric and pancreatic adenocarcinoma. First Author: Xianbao Zhao, Department of Oncology, Changi Hospital, Second Military Medical University, Shanghai, China

Background: As a promising approach for some cancers, chimeric antigen receptor T cell therapy has limited success in solid tumors. Claudin18.2 (CLDN 18.2) is a stomach-specific isoform of Claudin-18, and highly expressed in gastric and pancreatic adenocarcinoma, the advanced form of both of which have urgent unmet medical needs. We previously developed an anti-CLDN18.2 specific CAR (CAR-CLDN18.2) T cells to eradicate CLDN 18.2-positive gastric cancer xenografts without obvious on-target off-tumor toxicity (Huang J. JNCI 2018). Methods: In this single-arm, open-label, first-in-human phase I pilot study (NCT03159819) to investigate the safety and explore the efficacy of the autologous CAR-CLDN18.2 T cells, patients with confirmed CLDN 18.2 positive advanced gastric or pancreatic adenocarcinoma aged 18 to 70 years received 1 or more cycles of CAR-CLDN18.2 T cell infusion(s) after lymphodepletion pretreatment (fludarabine and cyclophosphamide, with or without nab-paclitaxel) until disease progression or presence of intolerable toxicity. Adverse Event (AE) grade categorization is according to CTCAE 4.0, and tumor response was assessed per RECIST 1.1. Results: As of November 30th, 2018, 12 subjects with metastatic adenocarcinoma (7 gastric and 5 pancreatic) were treated with 1–5 cycles (total of 0.5 – 5 X 10^9) of CAR-positive T-cell infusions. There were no serious adverse events, treatment-related death or serious neurotoxicity. In the study, the safety profile of the CAR-CLDN18.2 T cells was stable disease in 11 pts. Combo: 42 pts (median age: 60 yr; ECOG PS: 0 [n=4], 1 [n=23]) were treated. One pt treated with R3767 7 mg/kg Q3W + cemiplimab 3 mg/kg Q3W experienced DLT of grade 4 elevated blood creatinine phosphokinase, associated with grade 3 myasthenia syndrome and grade 1 elevated troponin. The most common irAEs observed for nausea (21.4%). Grade 3 irAEs of hypothyroidism (2.4%) was also reported. By INV, 2 (both small cell lung cancer) combo pts and 2 (endometrial cancer and cutaneous squamous cell carcinoma) of 12 additional pts who crossed over from mono to combo had partial responses. PK: R3767 concentration in serum increased in a dose-dependent manner and were unaffected by combo. Conclusions: The safety profile of R3767 cemiplimab was generally tolerable; PK was linear. Early efficacy signals were detected despite the difficult-to-treat pt population. Biomarker studies are ongoing. R3767 20 mg/kg or 1600 mg fixed dose equivalent Q3W as mono and combo were selected for further evaluation. Clinical trial information: NCT03005782.
**2512 Poster Discussion Session; Displayed in Poster Session (Board #156), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM**

Ipi/lumimab versus placebo after complete resection of stage III melanoma: Long-term follow-up results the EORTC 18071 double-blind phase 3 randomized trial. First Author: Alexander M. M. Eggermont, Gustave Roussy Cancer Centre and University Paris-Saclay, Paris, France

**Background:** Since 2015, (ipi/lumimab (Ipi)) is an approved treatment for stage III melanoma based on a significantly (P=0.0013) prolonged recurrence-free survival (RFS) (Eggermont et al, Lancet Oncol, 2015). At a median follow-up of 5.3 years, RFS (HR=0.76) and distant metastasis-free survival (DMFS) (HR=0.76), assessed by an IRC, and overall survival (OS) (HR=0.72) were prolonged in the Ipi group as compared to the placebo (Pbo) group (Eggermont et al, NEJM, 2016), despite a 53.3% (Ipi) vs 46.6% (Pbo) treatment discontinuation rate due to adverse events. **Methods:** In this randomized double-blind trial, eligible patients (pts) included those ≥18 yrs of age who underwent complete resection of stage III cutaneous melanoma (including lymph node metastasis ≤1 mm or in-transit metastasis). 951 pts were randomized (stratified by stage and region) 1:1 to Ipi 10 mg/kg (n=475) or placebo (Pbo, n=476) q3w for 4 doses, then every 3 mos for up to 3 yrs until completion, disease recurrence, or unacceptable toxicity. Here, we report the long-term results in patients with high-risk stage III melanoma. Clinical trial information: NCT00636168.

**Results:** Median follow-up was 6.9 yrs. The RFS, DMFS and OS benefit observed in the Ipi arm was long-lasting (almost 10% difference at 7 years) and consistent across subgroups: no significant predictive factors could be detected. **Conclusions:** In this phase III trial, Ipi, administered at 10 mg/kg, as adjuvant therapy, provided, at a 6.9 yrs median follow-up, a sustained improvement in the RFS, DMFS, and OS long-term results in patients with high-risk stage III melanoma. Clinical trial information: NCT00636168.

**2513 Poster Discussion Session; Displayed in Poster Session (Board #157), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM**

**CX-072, a PD-L1 Probody therapeutic, as monotherapy in patients with advanced solid tumors: Preliminary results of PROCLAIM-CX-072.** First Author: Aung Naing, MD Anderson Cancer Center, Houston, TX

**Background:** Anti-programmed cell death ligand 1 (PD-L1) immunotherapies have improved survival in many cancers, but immune-related adverse events (irAEs) have been observed, especially in combination therapy. CX-072 is an investigational Probody therapeutic directed against PD-L1, designed to be preferentially activated in the tumor microenvironment and to reduce irAEs. **Methods:** This is an ongoing phase 1/2a study (PROCLAIM-CX-072; NCT03013491) evaluating CX-072 in patients (pts) with metastatic or unresectable solid tumors with no further standard curative treatment options and with no prior anti-PD-1, PD-L1 or anti-CTLA4 treatment. Pts were unselected for PD-L1 expression. We report preliminary results from expansion cohorts in anal squamous cell carcinoma (SCCA), cutaneous squamous cell carcinoma (cSCC), small bowel adenocarcinoma (SBA), triple-negative breast cancer with skin lesions (TNBC), or undifferentiated pleomorphic sarcoma (UPS). Pts were treated with CX-072 monotherapy 10 mg/kg intravenously every 14 days. **Results:** As of 30 Nov 2018, 51 pts received CX-072 10 mg/kg monotherapy: SCCA (n = 9), cSCC (n = 5), SBA (n = 9), TNBC (n = 9), and UPS (n = 19). Median age was 63 yr (range, 32-80), 67% were female, and pts had a median of 3 prior regimens (range, 1-12). Median treatment duration was 1.8 mo (range, 0.3-14.7). A grade 3/4 treatment-related adverse event (AE) was observed in 1 pt (19%). No grade 4 or 5 treatment-related AEs were observed. Two pts discontinued treatment due to AEs: nausea (pt with SCCA) and sepsis (pt with SBA), neither treatment-related. Partial responses (confirmed and unconfirmed) were observed in cSCC (n=1), TNBC (n=2), and UPS (n=1) (Table). **Conclusions:** CX-072 10 mg/kg monotherapy demonstrated antitumor activity in heavily pretreated patients with advanced disease in cSCC, TNBC with skin lesions, and UPS, with a safety profile that compares favorably to historical controls. Clinical trial information: NCT03013491.

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Analysis of early mortality in randomized clinical trials evaluating anti-PD-1/ PD-L1 antibodies: A systematic analysis by the United States Food and Drug Administration (FDA). First Author: Flora Mulkey. U.S. Food and Drug Administration, Silver Spring, MD

**Background:** Many studies exhibit what seems to be dis-proportionately higher early mortality (EM) in anti-PD-1/PD-L1 containing arms (IO) when compared to control arms (AC), resulting in early crossing of the Kaplan-Meier overall survival curves. We re-analyzed the EM with the intent to be specific to certain demographic and disease characteristics.

**Methods:** Data from 16 randomized AC trials submitted to FDA containing 6055 IO and 3604 AC patients in HNSCC, Melanoma, NSCLC, RCC, and Urothelial Carcinoma were evaluated for signs of EM. Study-specific and pooled piecewise hazard ratios (HRs) were used to quantify EM from 0 to 60 and > 60 days. Additionally, HRs up to 60 days were used to assess the extent specific subgroups account for EM. **Results:** Piecewise HRs comparing OS between IO and AC changed direction, > 1 < 1 in 11 trials; melanoma (5/6), NSCLC (3/7), HNSCC (1/1), RCC (1/1), and urothelial cancer (1/1). When pooled, NSCLC studies retained this EM pattern, although attenuated, with HR (95% CI) of 1.12 (0.91, 1.38) ≤60 days and 0.66 (0.61, 0.72) after 60 days. This was not observed in the pooled melanoma studies: 0.88 (0.63, 1.24) ≤60 days and 0.59 (0.53, 0.67) after 60 days. EM in both arms was associated with poor ECOG performance status (PS), increased LDH, and high tumor burden. Comparing AC patients who had progressed were female in the melanoma trials (41% vs. 28%), a smaller proportion had squamous histology in the NSCLC trials (32% vs. 41%), and a larger proportion were PD-L1 negative (56% vs. 36% melanoma; 60% vs. 43% NSCLC). Analysis of the pooled melanoma studies suggests PD-L1 negative melanoma patients with high baseline tumor burden and PS played a role in EM with HR before 60 days of 1.49 (0.75, 2.97). However, these results were not reproducible in NSCLC. **Conclusions:** Potential risk factors for EM were assessed in individual and pooled trials. While several factors—negative PD-1/PD-L1 status and high ECOG, LDH and tumor burden—seem to play a role in EM, these high-risk subgroups do not fully explain the EM patterns observed in the IO treated patients.

2518 Poster Discussion Session; Displayed in Poster Session (Board #162), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM

Safety and efficacy of cryopreserved autologous tumor infiltrating lymphocyte therapy (LN-144, lifileucel) in advanced metastatic melanoma patients who progressed on multiple prior therapies including anti-PD-1. First Author: Amod Sananik, H. Lee Moffitt Cancer Center, Tampa, FL

**Background:** Treatment options are limited for patients with advanced melanoma who have progressed on checkpoint inhibitors and targeted therapies such as BRAF/MEK inhibitors (if BRAF-V600E mutated). Adoptive cell therapy utilizing tumor-infiltrating lymphocytes (TIL) has shown antitumor efficacy with durable long-term responses in heavily pretreated melanoma patients. Safety and efficacy of lifileucel (LN-144), a centrally manufactured autologous TIL therapy are presented. **Methods:** C-144-01 is a global Phase 2 open-label, multicenter study of the efficacy and safety of lifileucel in patients with unresectable metastatic melanoma. We report on Cohort 2 (N = 55) patients who received cryopreserved lifileucel. Tumors resected at local institutions were processed in central GMP facilities for TIL production in a 22-day process. Final TIL infusion product was cryopreserved and shipped to sites. Patients received one week of cyclophosphamide/fludarabine pre-conditioning lymphodepletion, a single lifileucel infusion, followed by up to 6 doses of IL-2. **Results:** In 55 patients with Stage III/IV unresectable melanoma, 3.1 mean prior therapies (anti-PD1 100%; anti-CTLA-4 80%; BRAF/MEK inhibitor 24%), high baseline tumor burden (110 mm mean target lesion sum of diameters), ORR was 38% (2 CR, 18 PR, 1 UOR). Of 21 responders, 4 have progressed to date with median follow up of 7.4 months. Overall disease control was 76%. Improved responses in some patients were observed with longer follow up. Most (54) patients progressed on prior anti-PD1 and those with PD-L1 negative status (TPS < 5%) were among responders. Mean cells infused was 28 x10^9. Median IL-2 doses administered was 6.0. Adverse events resolved to baseline, 2 weeks post TIL infusion, a potentially important benefit of one-time TIL therapy. **Conclusions:** Lifileucel treatment results in 38% ORR in heavily pretreated metastatic melanoma patients with high baseline disease burden who received prior anti-PD1 and BRAF/MEK inhibitor if BRAF-V600E mutation present. Lifileucel was well tolerated and supported lifileucel registration. Clinical trial information: NCT02360579.

Impact of bridging chemotherapy on clinical outcome of CD19 CAR T therapy in adult ALL. First Author: Karlo Perica, Memorial Sloan Kettering, New York, NY

**Background:** Autologous chimeric antigen receptor (CAR) T cell therapy has shown to be effective in CD19+ relapsed or refractory (R/R) B-ALL but requires a 2-4 week period of cell processing and manufacture. During this “bridging period,” patients are vulnerable to disease progression and death owing to treatment interruptions, high intensity therapy was associated with a higher rate of adverse events (AE) with no benefit of one-time TIL therapy. Of 53 patients who received CAR T cell therapy at MSKCC, Bridging therapy was defined as any therapy given from trial enrollment to cell infusion and classified as either high intensity (remission-inducing or myelosuppressive regimens, eg hyper-CVAD or high-dose cytarabine based regimens) or low intensity (maintenance and/or less myelosuppressive regimens, eg POMP, Blinatumomab, TKI). **Results:** Of 53 patients who received CAR T cell infusion, 19 were bridged with a high intensity regimen and 34 with a low intensity regimen. There was no difference in number of prior therapies, pre-bridging chemotherapy disease burden, and prior transplant status between groups. High intensity therapy was associated with a higher rate of Gr3-4 toxicities during the bridging period (78% vs 32%, p < 0.002 by Fisher’s Exact) but not with response to bridging or CAR T cell therapy, relapse free survival, post-CAR Gr3-4 cytokine release syndrome (CRS) or neurotoxicity (NT). Patients in both groups who converted from morphologic to molecular disease during bridging (n=9) had a decreased rate of eventual severe CRS (0% vs 41%, p=0.01) or NT (0% vs 55%, p < 0.01) compared to donors with persistent morphologic disease. In all patients enrolled on trial (n=83), use of high compared to low intensity bridging was not associated with higher rates of successful CAR T cell infusion (63% vs 79%, p=0.05) or a combined endpoint of CAR T cell infusion or alternative therapy including transplant (80% vs 86%, p > 0.05). High intensity bridging therapy was associated with higher rates of adverse events with no benefit of one clear benefit in outcome in R/R ALL receiving CD19 CAR T cells. Selection of bridging regimen therefore requires consideration of previous treatments and patient status to maximize the efficacy and safety. Clinical trial information: NCT01440469.
First-in-human first-in-class phase I trial of mur lentamab, an anti-Mullerian-hormone receptor II (AMHRII) monoclonal antibody acting through tumor-associated macrophage (TAM) engagement, as single agent and in combination with carboplatin (C) and paclitaxel (P) in AMHRII-expressing advanced/metastatic gynecological cancer patients (pts). First Author: Alexandra Lenard, Gustave-Roussy Cancer Campus, Villejuif, Groupe d’Investigateurs Nationaux pour l’Etude des Cancers Ovariens, France

Background: Membranous expression of AMHRII is found in ~70% of gynecological tumors. Mur lentamab (M) binds with high affinity both AMHRII (at cell membrane) and CD16 (on macrophage), via its low fucos C. M programs TAMs, restoring their antitumor functions (phagocytosis) resulting in cytotoxic T cell reactivation.

Methods: Pts with advanced/metastatic AMHRII-expressing ovarian, cervical or endometrial cancer with measurable disease and performance status ≤1 received M as single agent (SA) in 8 dose escalating and 2 expansion cohorts. Combination with CP was studied in 2 escalating cohorts. Safety, recommended dose determination, antitumor activity, pharmacodynamics (PD) effects (circulating immune cells and tumor microenvironment (TME) from paired biopsies) were assessed. Results: 68 heavily pretreated (median 4 prior lines) pts received M for 0.5 to 11 months (mo) (59 pts M SA and 9 pts M + CP). No dose limiting toxicity was reported. Most common toxicity was G1-2 asthenia (29.9%). Eight pts (12%) had G ≥ 3 reversible toxicities (asthenia, nausea/vomiting, anorexia, arthralgia). No antidrug antibody was detected. A plateau phase of response (PR) was achieved with M SA in a granulosa pt. In CP combination, 4/9 pts (44%) responded to treatment (1 Complete Response and 3 PRs). Overall, 22/67 (33%) pts were progression-free at 4 mos. Among 17 pts treated ≥ 6 mos, 6/9 (67%) granulosa pts with M SA and 4/5 (80%) endometrium and cervix with CP combination had a longer DFS than under monotherapy. M safety was assessed for 38% of pts. No DLTs were reported, and treatment-related adverse events were very well tolerated, demonstrated immune PD effects and showed hints of antitumor activity. These results together with its innovative immunologic mode of action support development of M as an AMHRII-expressing cancers, in combination with chemotherapy or other immune oncology drugs. Clinical trial information: NCT02978755.

Regorafenib plus nivolumab in patients with advanced gastric (GC) or colorectal cancer (CRC): An open-label, dose-finding, and dose-expansion phase 1b trial (REGONIVO, EPCO1603). First Author: Shotia Fukushima, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Immune suppressive cells such as regulatory T cells (Treg) or tumor-associated macrophages (TAMs) may contribute to resistance to anti-PD-1/PD-L1 inhibitors (I). Regorafenib, a potent inhibitor of angiogenic and oncogenic kinases, reduced TAMs in tumor models. The combination of regorafenib plus A-PD1 exhibited superior tumor growth suppression compared to either treatment alone in murine models. Methods: In this study, we enrolled patients (pts) with previously treated, advanced GC or CRC. The pts received regorafenib plus nivolumab in a dose-finding phase to estimate the maximum tolerated dose (MTD). Additional pts were enrolled in a dose-expansion phase to further establish the safety and determine the preclinical efficacy. Regorafenib of 80 to 160 mg was administered once daily for 21 on 7 days off with intravenous nivolumab 3 mg/kg every 2 weeks. The primary endpoint was the dose-limiting toxicity (DLT) duration of cycle one (4 weeks) to estimate the MTD and the recommended dose. Results: Pts were enrolled (25 GC; 25 CRC) until October 2018. The median primary treatment line was 3 (range 2-8). During dose-escalation, 3 DLTs were observed with regorafenib 160 mg, including grade (G) 3 maculopapular rash, mucositis and proteinuria (50%) in 1 pt with regorafenib 80 mg and 120 mg. In the dose-escalation cohort with regorafenib 120 mg, the dose was reduced to 80 mg owing to frequent G3 skin toxicities. Grade ≥ 3 treatment related adverse events occurred in 17 pts; the common events (>5%) being rash (14%), palmar-plantar erythrodysesthesia (10%), and proteinuria (8%). Objective tumor responses were observed in 12/35 (34%) treated pts, including 11 MSS GC, 7 M5 CRC and 1 MSI-H CRC for response rates of 44% in GC and 29% in MSS CRC. Three of the 7 A-PD1 pretreated GC pts achieved a partial response. The pre-post treatment tumor samples showed a reduction of FoxP3+CD45RA-Tregs fraction at the tumor response. Conclusions: The combination of regorafenib 80 mg and nivolumab was well-tolerated and showed clinical benefit in terms of antitumor activity in MSS GC and CRC pts, which warrants further investigations in a larger cohort. Updated biomarker analysis will be presented. Clinical trial information: NCT03406871.

A phase I multicenter study to assess the safety, tolerability, and immunogenicity of mRNA-4157 alone in patients with resected solid tumors and in combination with pembrolizumab in patients with unresectable solid tumors. First Author: Howard A. Burns, Sarah Cannon Research Institute, Nashville, TN

Background: T-cell targeting of mutation-derived peptides (neoantigens) has been demonstrated to drive antitumor responses. Increased tumor suppressor protein p53 expression is observed in a wide range of human cancers. As a result there is intense interest in targeting p53 for cancer therapy. Intracellular p53 is inaccessible to therapeutic antibodies that bind cell surface proteins. However, intracellular p53 is able to bind into peptidic epitopes that project from the cell surface in association with HLA class I molecules. Thus p53 peptide-HLA (p53-HLA) complexes can be antibody targets. Methods: Using phage display we identified a novel anti-p53-HLA single chain variable fragment (scFv) clone-43 that recognizes a wild-type p53 10-mer epitope bound to HLA-A*24:02. By coupling our clone-43 scFv with an anti-CD3 scFv, we generated a single chain diabody (scDb) designed to activate T-cells against p53-expressing target cells. Results: In-vitro co-culture of clone-43 scDb with donor human T-cells and p53 expressing human M5 cancer cells results in significant off-tumor hematopoietic cell death is contrary to tope results in significant off-tumor hematopoietic cell death is contrary to
2525 Poster Session (Board #169), Sat, 8:00 AM-11:00 AM
First-in-human, dose-escalation, phase (ph) I trial to evaluate safety of anti-Axl antibody-drug conjugate (ADC) enatumab vedotin (Enav) in solid tumors. First Author: Mahtab Amini-Moghaddam, The Alfred Hospital, Melbourne, Australia. Background: Axl, a transmembrane receptor tyrosine kinase, is aberrantly overexpressed in various human cancers and associated with poor prognosis and treatment resistance. Enav, a novel ADC of anti-Axl human IgG1 and monomethyl auristatin E, demonstrated potent anti-tumor activity in xenograft models. Methods: In a ph1 trial (NCT02988817), patients (pts) with relapsed/refractory cancer received single agent Enav, 0.3–2.8 mg/kg once ever 4 wks (1Q3W) or 0.45–1.4 mg/kg 3 times over 4 wks (3Q4W). A total of 1200 mg was targeted in all dose levels. Dose escalation was based on DLT, safety, PK, and antitumor activity of Enav in first treatment cycle. Upon determining maximum tolerated dose (MTD) per arm and recommended ph2 dose (RPD), ph2a (dose expansion) will enroll ≥297 pre-treated pts with advanced/metastatic cancer in 7 cohorts. Results: 47 pts with NSCLC (n=8), melanoma (n=9), ovarian (n=22), cervical (n=3) and endometrial (n=5) cancer enrolled in ph1 (1Q3W n=35; 3Q4W n=19). Most pts were ≥60 y (94%) and aged <65 y (66%). MTD was 2.2 mg/kg in 1Q3W arm and 1.0 mg/kg in 3Q4W arm; RP2D was 2.2 mg/kg 1Q3W. Enav median elimination half-life: 0.9–2.2 d across doses/schedules. In 47 enrolled pts, there were 6 DLTs (Table). Most common AEs (any G; ≥40% pts) were fatigue (64%), nausea (53%), constipation (27%), anemia (14%) and proteinuria (13%). Of 31 pts (1Q3W arm) who had partial response (1 NSCLC [2.2 mg/kg dose]; 2 ovarian [1.5 and 2.4 mg/kg dose levels]). Conclusions: The RP2D of single agent Enav in pre-treated pts with solid tumors was 2.2 mg/kg 1Q3W. Enav had encouraging preliminary anti-tumor activity and will be evaluated in the dose expansion phase IIa to further assess safety, tolerability, PK, antitumor activity and Axl expression. Funding: Gennab A/S. Clinical trial information: NCT02988817.

2526 Poster Session (Board #170), Sat, 8:00 AM-11:00 AM
A phase la/ib trial of the anti-PD-L1 human monoclonal antibody (mAb), CS1001, in patients (pts) with advanced solid tumors or lymphomas. First Author: Shu-Hong Templeton, Beijing Cancer Hospital, Beijing, China. Background: CS1001 is the first full-length, fully human anti-PD-L1 mAb developed by the OMT transgenic rat platform, which mirrors natural IgG4 human antibody with expected PK profiles, and may potentially reduce the risk of immunogenicity and toxicity in pts. This first-in-human Phase la/ib study of CS1001 was conducted to evaluate the safety, tolerability, PK profile, and antitumor activity of CS1001 in pts with advanced solid tumors or lymphomas. Methods: Pts with advanced solid tumors or lymphomas were enrolled in the dose escalation Phase la, receiving CS1001, 3QW, IV, at escalating doses from 3, to 10, 20, 40 mg/kg and 1200 mg. Dose escalation was aided by a 3+3 dose escalation scheme. DLT was evaluated within 3 weeks after the initial dose. Pts with various tumor types were enrolled in the dose expansion Phase Ib to assess anti-tumor activity and safety, including NSCLC, esophageal carcinoma, GC, HCC, cholangiocarcinoma, etc. Safety was assessed by monitoring AEs and the associated grades per NCI CTCAE v4.03, tumor assessed per RECIST v1.1 (solid tumors) or Lugano (2014) (lymphomas). Results: As of 30 Nov 2018, 29 pts, median age of 53 (23-79) yrs, were enrolled in Phase la, 3 mg/kg (N=3); 10 mg/kg (A); 20 mg/kg (2); 40 mg/kg (3) and 1200 mg flat dose (16). A total of 20 pts discontinued treatment due to disease progression (14), death (2), withdrawal by pts (2) and AEs (2); (Grade [G] 4 hepatic function abnormal and G3 pulmonary tuberculosis, both were not related to treatment). 9 pts remain on treatment. Median treatment duration was 126 (21-408+) days. No DLTs were observed. 27 of 29 evaluable pts were TRAEs (54%) including anaemia (14), proteinuria (13) and blood bilirubin increased (8). G3 TRAEs include anaemia (2) and platelet count decreased (1). 3AEs were reported in 6 pts and they were TRAEs. Three G4 AEs were reported: anaemia (1), hypokalaemia (1) and hepatic function abnormal (1), they were not TRAEs as determined by the investigators. In AEs occurring in ≥20% of 29 evaluable pts, 7 pts had PR and 8 had SD, mDoR was not reached. In Phase Ib, 97 pts were enrolled, with 65 pts on treatment and 32 pts discontinued from treatment. The most frequent reason for the discontinuation was disease progression (21%). Phase Ib enrolment is still ongoing. Conclusions: CS1001 is well tolerated without DLT across tested dose levels. Evidence of anti-tumor activities was observed. Currently, 1200 mg flat dose Q3W is being explored in various tumor types in Phase Ib, and safety and efficacy results will be displayed in the presentation. Clinical trial information: NCT03312842.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Results: were treated at doses of 3 or 10 mg/kg Q3W with mandatory pre- and on-separate dose exploration cohort in which B7-H4+ (H-score \( g \) weeks (Q3W) in an accelerated titration followed by 3+3 design and a calculation in which B7-H4-unselected patients with advanced solid tumors FPA150 in advanced solid tumors. We report preliminary results from an ongoing phase 1a/1b study of toxicity. It is the first therapeutic molecule targeting B7-H4 to enter the clinic. We report preliminary results from an ongoing phase 1a/1b study of FPA150 is a fully human antibody against B7-H4 that blocks inhibition of regulator of T cell function, expressed at high levels on several cancers, including historically refractory melanoma, renal cell carcinoma, and lung cancer. B7-H4 is a member of the B7 family of immune checkpoint receptors that plays a role in the induction of T cell anergy and is expressed at high levels on several cancers, including historically refractory melanoma, renal cell carcinoma, and lung cancer.

Background: B7-H4, a transmembrane protein of the B7 family, is a negative regulator of T cell function, expressed at high levels on several cancers, including historically refractory melanoma, renal cell carcinoma, and lung cancer. B7-H4 is a member of the B7 family of immune checkpoint receptors that plays a role in the induction of T cell anergy and is expressed at high levels on several cancers, including historically refractory melanoma, renal cell carcinoma, and lung cancer.

Methods: Phase 1a included dose escalation in which B7-H4-unselected patients with advanced solid tumors were treated with FPA150 at doses between 0.01 to 20 mg/kg every three weeks (Q3W) in an accelerated titration followed by 3+3 design and a separate dose exploration cohort in which B7-H4+ (H-score \( g \)) patients were treated at doses of 3 or 10 mg/kg Q3W with mandatory pre- and on-treatment biopsies. Results: As of 12/31/2018, 24 patients with a median of 3 prior therapies were treated with FPA150, 6 of whom were in the B7-H4+ dose exploration cohort. Seven patients from dose escalation were also retrospectively identified as B7-H4+. Most patients received FPA150 at 3 mg/kg (n=8) or 10 mg/kg (n=6). Median number of doses was 3 (range 1-11). No dose-limiting toxicities or treatment-related serious adverse events were reported, and there were no treatment-related AEs (TRAEs) leading to discontinuation of FPA150. Most TRAEs were Grade 1-2, with diaphoresis being the most common (n=5, 37%). Grade 3-4 TRAEs were reported in 1 patient. FPA150 displayed approximately dose-proportional exposure at doses \( g \) 0.3 mg/kg with half-life of 1-2 weeks. Conclusions: FPA150 monotherapy demonstrated a favorable safety profile and evaluation of anti-tumor activity is ongoing. 20 mg/kg Q3W was selected as the recommended dose. Phase 1b included dose escalation with B7-H4+ patients. FPA150 mediated enhanced tumor control in 1 patient. We will present updated safety, PK, and preliminary biomarker and efficacy data. Clinical trial information: NCT03514121.

Correlation of circulating EBV-targeted T lymphocyte precursors (EBV-CTLp) and clinical response following tab-cel infusion (tab-cel) in EBV-driven disease. First Author: Blake T. Aftab, Atara Biotherapeutics, Thousand Oaks, CA

Background: EBV is implicated in a variety of diseases. Themedicinal scaffold, allogeneic T-cell immunotherapy utilizing endogenous T cell receptors targeting EBV antigens. We hypothesized that the clinical activity of EBV-CTLp is mediated by expansion and persistence of EBV-specific T cells. Therefore, we quantified circulating EBV-CTLp after tab-cel administration and examined the correlation between expansion and clinical response. Methods: Samples from 10 patients with EBV* post-transplant lymphoproliferative disease (PTLD) and other EBV-associated diseases enrolled in a multicenter expanded access protocol (EAP) study (NCT02822495) were analyzed. To evaluate CTLp frequencies, limited dilution analysis was performed on samples taken at baseline and day 34 post first tab-cel dose (end cycle 1). The day 34 persistence of circulating EBV-CTLp from best overall response to initial tab-cel product was tested using the two-tailed Mann-Whitney test. Changes in inflammatory cytokines were also measured. Results: Responders represented in this sampling (n=5; 2 PR and 4 CR) showed a median 5.8-fold increase in circulating CTLp from baseline and day 34 (range: 0.8 to 133-fold). Five of 6 responders showed an increase in EBV-CTLp at day 34 of \( g \) 3.8 fold while 1 pt showed no change in CTLp (0.8-fold change). In contrast, the 4 non-responders (3 SD; 1 PD) showed a median 0.3-fold decrease in EBV-CTLp from baseline (range: 1.2 to 0.02-fold; ns). Cumulative analyses revealed a statistically significant correlation between the fold-change of circulating CTLp at day 34 and clinical response (p=0.038) which did not appear to correlate with the type of the EBV-associated disease. Inflammatory cytokines showed no meaningful change from baseline. The safety profile remains consistent with previously reported data. Conclusions: These data support the correlation of clinical activity of tab-cel with the expansion and persistence of EBV-specific T-cells at day 34 post-treatment, as well as the use of circulating CTLp as a biomarker for response in clinical studies. Clinical trial information: NCT02822495.
2534** Poster Session (Board #178), Sat, 8:00 AM-11:00 AM Efficacy and safety of CART19/22 T-cell “cocktail” therapy in patients with refractory/replaced B-cell non-Hodgkin lymphoma. First Author: Liang Huang, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China Background: Antigen escape relapse has emerged as a major challenge for long-term disease control post CD19-directed therapies, to which dual-targeting of CD19 and CD22 has been proposed as a potential solution. Methods: Between Mar 2016 and Jan 2018, we conducted a pilot study (ChiCTR-OPN-16008526) in 13 evaluable pts (pts), 11 CD19/CD22 refractory/replaced B-cell non-Hodgkin lymphomas (B-NHL), to evaluate the efficacy and safety of sequential infusion of anti-CD19 and anti-CD22, two single-specific, third-generation CAR 19/22 T-cell “cocktail”. The cutoff date for data collection was Apr 30, 2018. Results: At a minimum follow-up of 3 months (mos), 26 of 36 evaluable pts achieved an overall response (ORR), 18 pts with a complete response (CR) and 8 with a partial response (PR). The ORR at mo 3 was consistent in different subgroups, irrespective of pathologic subtypes, cell of origin, cytogenetic or genomic aberrations. At the data cutoff, 15 of the 18 pts who had a CR at mo 3 maintained their responses, 2 of 8 pts who had a PR within 3 mos continued to have a CR without additional therapies. Collectively, the best ORR was 83.3%, with a best CR rate of 55.5% and a best PR rate of 27.8%. With a median follow-up of 5.3 mos (range, 0.4 to 16.2), the median PFS was 5.8 mos, and the median OS was not reached (NR). Pts received therapy at first relapse had better PFS than those who received therapy at the time with primary refractory diseases or at multiple relapses. Notably, pts who achieved an overall response at mo 3 (R3m) had significantly extended PFS and OS when compared with pts who did not. Repeated biopsy and IHC was conducted in 3 of the 13 pts. However, loss of CD22 was not noted no IHC translational. Of the 9 pts who achieved a median follow-up of 10.1 mos, the median PFS and median OS were NR. At data cutoff, 7 pts who had achieved R3m maintained their responses, including all the 4 pts with double-hit lymphoma. However, of the 10 pts with del(17p) or TP53 mutation, with a median follow-up of 5.3 mos (range, 2.7 to 14.5), the median PFS was 3.6 mos and the median OS was 9.9 mos. All pts experienced reversible CRS, with 21.1% were high-grade. Neurotoxicity developed in 13.2% pts and were all low-grade. Conclusions: Our results indicated that sequential infusion of CART19/22 T-cell is efficient and safe for pts with a CD19/CD22 antigen targeted therapy. A promising approach to circumvent antigen loss relapse after CAR T-cell therapy. The impact of genetic subtypes and clinical parameters further underscores the critical importance of personalized immunotherapies. Clinical trial information: ChiCTR-OPN-16008526.

2536** Poster Session (Board #180), Sat, 8:00 AM-11:00 AM Ligand-inducible, prostate stem cell antigen (PSA)-directed GoCAR-T cells in advanced solid tumors: Preliminary results with cyclophosphamide (Cy) + fludarabine (Flu) lymphodepletion (LD). First Author: Carlos Roberto Becerra, Baylor University Medical Center, Dallas, TX Background: Cell-surface protein PSA is upregulated in many solid tumors and correlates with disease stage. BPX-601, an autologous T-cell product expressing a PSA-CD3ζ CAR and a rimucilim (Rim)-inducible MyD88/CD40 co-activation switch to augment T-cell proliferation and persistence, is designed to have in vivo persistence and cytolytic activity in solid tumors. In ongoing first-in-human study assesses safety, biology, and clinical activity of BPX-601+Rim in PSA+ cancers. Updated results, including those from patients (pts) who underwent LD with Flu/Cy, are presented; Methods: BP-012 is a 2-part, open-label trial. Part 1 is a 3+3 dose escalation of BPX-601 (1.25-5.0x109 cells/kg; Day [D] 0) given prior to a single, fixed Rim dose (0.4 mg/kg; D7) in pts with previously treated PSA+ metastatic pancreatic, gastric, or prostate cancers with measurable disease. Results: As of Jan-22-2019, 15 pts have been treated. Two pts at the highest cell dose received Flu/Cy for LD on D-5 to D-3 before BPX-601; LD after Flu/Cy was 96.6% and 84.3%. Thirteen pts received Cy alone on D-3–D-1; in these pts, LD ranged from 0-68.6%. Rapid cell expansion by D4 was observed in all pts with peak vector copy number 8.3-fold higher with Flu/Cy (n = 2) vs Cy LD (n = 13). Serum IP-10, IL-6 and TNFα increased >2-fold from baseline in ≥1 pt in all Rim cohorts, with 3- to 20-fold Rim-dependent cell expansion in 6 pts. No CRS or DLTs were reported. After Rim, one Flu/Cy pt experienced a serious Grade 2 AE (encephalopathy) related to BPX-601+Rim that resolved with IV steroids; despite time-matched nonserious Grade 1 pyrexia, the pt had no other CRS symptoms. After BPX-601+Rim and ≥1 scan, best responses were 8 SD and 3 PD (1 non-evaluable); with a median follow-up of 9.8 wks, time to next treatment (tx) after BPX-601 ranged from 2.7-22.1 wks (n = 8) and ongoing b-2 free intervals range from 9.1-30.1 wks (n = 4). Conclusions: BPX-601+Rim was well-tolerated with manageable safety and early evidence of enhanced CAR T-cell expansion and prolonged persistence after Flu/Cy vs Cy. Additional pts will undergo Flu/Cy LD prior to BPX-601 with single- and repeat-dose Rim. Clinical trial information: NCT02744287.

2535** Poster Session (Board #179), Sat, 8:00 AM-11:00 AM The phase I clinical study of CART targeting BCMA with humanized alpaca-derived single-domain antibody as antigen recognition domain. First Author: Lu Ji, Department of Hematology, Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China Background: Several phase I clinical trials already shown Chimeric antigen receptor T cells (CART) targeting BCMA has the promised effects to treat the relapsed/refractory (RR) multiple myeloma (MM), RRMM. We developed CART cells (CART-BCMA) using one single-domain antibody as recognition domain. The anti-BCMA single-domain antibody was derived from the alpaca, and humanized with the affinity of 1.1nM. The CART-BCMA use the 4-1BB and CD3ζ intracellular regions as T cell activation domains. Methods: A phase I, single arm clinical study was conducted to assess safety and efficacy of CART-BCMA. The enrolled RRMM pts had received average 10 lines of prior treatment, no matter BCMA expression level on plasma cells. Patients were subjected to a lymphodepleting regimen with Cy (300-600 mg/m², d-5, -4) and Flu (30 mg/m², d-5 to d-3) before CART infusion at the dose of 2-10x10⁶ CAR+ cells/kg. The efficacy was assessed based on the IMWG Criteria, and the toxicity was graded by CTCAE 4.02. Results: As of December 31, 2018, 16 pts were infused with autologous CART-BCMA cells in at least 1 month of follow-up. Many patients had M protein in serum, but haven’t the high percent of plasma cells in bone marrow, which are difficult to be treated by CART cells because the tumor cells are aggregated, not diffused in bone marrow. 3 patients were diagnosed with extramedullary diseases, were evaluated as PR at D28 (tumor size decreasing >50%). Most patients with extramedullary disease had ≥1 prior line treatment. ORR is 84.6% (11/13); At 10 weeks, 7 pts were evaluated, ORR is 100% (sCR/CR 42.8%, VGPR 14.3%, PR 42.8%); 5 patients reached 16 weeks, 1 relapsed, 4 kept remission. The PT3 and PT6 shows the CRS grade 3 or 4, other patients shows the grade 0-2 CRS, the CRS is manageable. Conclusions: Our results demonstrate the safety and efficacy compared with other reported results of CART targeting BCMA, and supports further development of this anti-RRMM cellular immunotherapy. Clinical trial information: NCT03661554.

2537** Poster Session (Board #181), Sat, 8:00 AM-11:00 AM Effect of minimal lymphodepletion prior to ACT with TBI-1301, NY-ESO-1 specific TCR-engineered TCR-T cells, on clinical responses and CRS. First Author: Marcus O. Butler, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada Background: Adoptive transfer of T cell receptor (TCR) gene-engineered T cells can induce durable anti-cancer responses. Post-infusion cytokine release syndrome (CRS) has been associated with clinical utility. Pre-infusion lymphodepletion (LD) may influence CRS, graft persistence, and clinical response in solid tumors. As an initial proof of concept, we treated patients with TBI-1301 following LD with CY alone. Methods: Eligibility includes informed consent, HLA-A*02:01 or A*02:06 haplotype, and NY-ESO-1 expression by immunohistochemistry. Eligible patients underwent harvest of PBMC which are then processed locally to generate engineered TBI-1301 cells. The study design is to infuse 5x10⁸ cells (day 0) to patients following LD with CY (750 mg/m² on day -3 and -2). Endpoints include safety, efficacy, and biological correlates for persistence of NY-ESO-1-specific T cells post infusion. Results: Thus far, 9 patients have been treated, and 8 have received the target dose. To date, 8 patients are evaluable for response and toxicity, and no DLts have been observed. Despite LD with CY alone, all 4 patients with synovial sarcoma and 1 with melanoma experienced clinical and laboratory evidence of grade 1-2 CRS with increased CRP, ferritin, and IL-6 levels. CRS resolved spontaneously in all but one patient who required tocilizumab due to grade 2 nausea/vomiting. Two subjects experienced grade 3 tumor-associated pain. Other treatment-associated grade 3 or 4 toxicities included neutropenia and hypophosphatemia. Best overall response by RECIST is as follows: 2 partial responses, 5 stable disease, and 1 progressive disease. Biomarker analysis demonstrates persistence of transferred TBI-1301 cells, > 100 days in some patients. Conclusions: Our results demonstrate the safety and efficacy of TBI-1301 as a CD19-directed therapy. Despite LD with CY alone, grade 1-2 CRS is induced. Additional cohorts to this study will examine the role of repeat infusions to enhance anti-tumor activity. Clinical trial information: NCT02869217.
2538 Poster Session (Board #182), Sat, 8:00 AM-11:00 AM

Safety and efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical cancer. First Author: Amir A. Jazayeri, The University of Texas - MD Anderson Cancer Center, Houston, TX

Background: There is a high unmet medical need for effective treatments for patients with recurrent, metastatic, or persistent cervical cancer. Most patients are young and survival rates are poor. ORR for second line therapies is between 4 and 14% for chemotherapy and recently approved immunotherapy. Adoptive cell transfer using tumor infiltrating lymphocytes (TIL) have demonstrated durable responses in some patients with recurrent cervical cancer thus offering the potential for long-term disease control.

Methods: Study C-145-04 is an ongoing, open-label, multicenter Phase 2 clinical trial evaluating the safety and efficacy of LN-145 TIL therapy in patients with advanced cervical cancer who have undergone at least one prior line of chemotherapy. Prior checkpoint inhibitor therapy is an exclusion criterion. The primary endpoint is ORR per RECIST 1.1; secondary endpoints include duration of response (DOR), disease control rate (DCR), and LN-145 safety. Tumors surgically harvested at local institutions are shipped to central GMP facilities for TIL generation in a 22-day manufacturing process. Fresh or LN-145 TIL product infusion are administered to eligible patients. Patients receive one week of preconditioning lymphodepletion (cyclophosphamide, fludarabine), a single LN-145 infusion, followed by up to 6 doses of IL-2 (600,000 IU/kg). Results: As of 4 Feb 2019, 27 efficacy-c patients have received Gen 2 of LN-145, with a mean age of 47 years and 2.6 mean prior lines of therapy. Preliminary efficacy results: ORR was 44% (19/43, 95% CI: 31-58%). DCR was 89% at 3.5-month median study follow-up with 11/12 patients maintaining their response. Improved responses were observed in 4 patients with longer follow-up. Mean TIL cells infused was 28x10^9. Median IL-2 doses administered was 6.0. The adverse event profile was generally consistent with the underlying advanced disease and the protocol of the lymphodepletion and IL-2 regimens. Conclusions: LN-145 results in 44% ORR in previously treated cervical cancer patients with acceptable safety and efficacy profile. LN-145 offers patients a viable therapeutic option warranting further investigation. Clinical trial information: NCT03108495.

2539 Poster Session (Board #183), Sat, 8:00 AM-11:00 AM

Phase I trial of anti-CD19 chimeric antigen receptor T cells (CAR-T) with tumor necrosis alfa receptor superfamily 19 (TNFRSF19) transmembrane domain as co-engagement receptor. First Author: Paolo Fabrizio Caimi, Adult Hematologic Malignancies and Stem Cell Transplant Program, University Hospitals Seidman Cancer Center, Cleveland, OH

Background: AntiCD19 CAR-T cells have shown encouraging anti-lymphoma activity. Decreasing the time from apheresis to CAR-T infusion can make this therapy available to pts with rapid progression. We present the interim results of a phase I clinical trial using on-site CAR-T manufacture. Methods: Adult pts with B-cell malignancies who failed ≥ 2 lines of therapies were enrolled. Autologous T cells were transduced with a lentiviral vector (Len-tigen Technology, Inc.LTG1563) encoding an antiCD19 binding motif, CD8 linker and TNFRSF19 transmembrane region, and 4-IBB/CD3z domains. GMP-compliant manufacture was done using CliniMACS Prodigy, in a 12-day culture. Dose levels were 0.5, 1 and 2 x 10^9 CAR-T cells/kg. Lymphodepletion was done with cyclophosphamide (60mg/kg x 1) and fludarabine (25mg/m² x 3). Results: 7 pts (4 women, 3 men) were enroled. Median age was 60y (range 43-69). Diagnoses were DLBCL (n = 3) PMBC, follicular lymphoma (FL), transformed FL, and transformed lymphomas in situ, of whom 4/5 had symptomatic refractory disease. CAR-T cell product manufacture was successful in all pts. Median transduction rate was 44% (range 29-57%). CAR-T cell doses were 0.5 x 10^7/kg (n = 3) and 1 x 10^8/kg (n = 4). Median apheresis to infusion time was 13 days (range 13-20), 5 products were infused fresh. CAR-T persistence based on sequence data from 14 patients (6 transplanted) failed to reach McNCs between days 14-21. Five pts are evaluable for safety. CRS grade 1-2 (Lee) occurred in 4 pts; with 3 requiring treatment. Grade 4 CRES (CARTOX-10) occurred in 1 pt, with resolution after corticosteroids; considered a DLT as it lasted more than 72 hours. No treatment-related mortality has occurred. 4/5 evaluable pts have achieved response. One pt did not respond and died. After a median follow up of 3 months, all responding pts are alive and 1 relapsed 6 mo after treatment. Conclusions: Second generation antiCD19 CAR-T cells with TNFRSF19 transmembrane domain have clinical activity against refractory NHL. Short manufacture time achieved by local CAR-T cell manufacture with the CliniMACS Prodigy enables treatment of a very high risk NHL population. Clinical trial information: NCT03434769.

2540 Poster Session (Board #184), Sat, 8:00 AM-11:00 AM

Comprehensive report of anti-CD19 chimeric antigen receptor T cells (CAR-T) associated non-relapse mortality (CART-NRM) from FAERS. First Author: Kartik Anand, Houston Methodist Cancer Center, Houston, TX

Background: CAR-T cells targeting CD19 positive B-cells have improved outcomes for lymphoma with some notable toxicities. Of note, CAR-T cell associated non-relapse mortality (CART-NRM) has been observed in clinical trials. Methods: We retrospectively searched FDA adverse events reporting system (FAERS) for all adverse events (AE) related to anti-CD19 CAR-T (Tisagenlecleucel(T), Axicabtagene ciloleucel(AC), and 10% for Tisagenlecleucel(T)). The adverse event profile was generally consistent with the underlying advanced disease and the protocol of the lymphodepletion and IL-2 regimens. Conclusions: CART-NRM remains considerably high warranting further investigation. Clinical trial information: NCT01180633.

2541 Poster Session (Board #185), Sat, 8:00 AM-11:00 AM

Clonal expansion of tumor infiltrating lymphocytes (TILs) in the peripheral blood of metastatic melanoma patients of significant association with response to CTLA4 blockade-based immunotherapy. First Author: Arjun Khunger, Cleveland Clinic, Cleveland, OH

Background: Patients with metastatic melanoma were treated on a clinical trial with tremelimumab and High Dose Interferon-Alfa (HDI) (Tahlini, J Clin Oncol. 2012). We previously reported that patients who achieved disease control and clinical response had significantly greater T-cell clonality (p = 0.025) and (T-cell frequency of 0.04% or greater) than their pretreatment tumor biopsy samples (Tahlini, J Clin Oncol. 2017). In this study, we further characterize T-cell repertoire clonality and clonal expansion in the peripheral blood at different time points to evaluate the association between repertoire features and clinical response. Methods: Patients received tremelimumab 15 mg/kg i.v. every 12 weeks and HDI was given concurrently. Responses were assessed by RECIST as complete (CR) or partial (PR), stable disease (SD) or progression (PD). Peripheral blood mononuclear cells (PBMCs) from treated patients (N = 33) were obtained at baseline, day 29, and day 85 (following tremelimumab-HDI treatment); tumor samples at baseline were also obtained (N = 18). The T-cell receptor beta chain (TCRB) repertoire of PBMCs and tumor samples was immunosequenced using the immunoSEQ assay (Adaptive Biotechnologies), and repertoire clonality was assessed at baseline, day 29, and day 85. Differential abundance analysis was used to detect and quantify peripheral clonal expansion pre-versus post-treatment and identify the subset of peripheral clones also detected in the tumor repertoire. The Morisita Index of repertoire similarity was also calculated to compare global repertoire changes between pre- and post-treatment PBMC samples. Results: T-cell repertoire turnover, as measured by the Morisita Index, showed a trend towards responders (CR/PR) having greater turnover (lower Morisita Index) than non-responders. (SD/PD) post-treatment repertoire turnover for responders (CR/PR) was significantly greater than that for non-responders (SD/PD). Simi- larly, the total number of clones expanding in the peripheral repertoire varied over time within an individual (p = 0.034) but was not significantly affected by response to therapy (p = 0.275) or by on-treatment time point (p = 0.768). When the analysis was restricted to peripherally expanded clones that were also detectable in the tumor repertoire, the number of significant TCRB expansions detected in the periphery at day 29 than non-responders (p = 0.036). Conclusions: Our analysis of the peripheral T-cell repertoire following treatment showed that detection of TILs in early peripheral clonal expansion correlates with response to therapy.
Bespoke circulating tumor DNA (ctDNA) analysis as a predictive biomarker in solid tumor patients (pts) treated with single-agent pembrolizumab (P).

**Background:** Limited data exist in the clonal dynamics of serial ctDNA as a predictive biomarker in advanced solid tumor pts receiving immune checkpoint blockade. **Methods:** Pts with mixed solid tumors received single agent P (anti-PD-1) 200 mg IV Q2wk in the investigator-initiated phase II INSPIRE trial (NCT02644369). ctDNA was assessed at baseline (B) and start of cycle 3 (C3) using a pt-specific amplicon-based NGS assay (Signatera™). Sampled ctDNA was assessed by P-values at 72% (45 out of 63) of C3-specific targeted ctDNA met significance (PI-0502-2014). **Results:** Results of 70 pts are presented. Demographics: male 46%; median age=60 yrs (range 21–82); head and neck (20%), triple negative breast (14%) and ovarian (14%) cancers comprised the major malignancies. Median no. of P cycles=4 (range 2–35); follow up was 14w (range 2–29); RECIST responses: CR 2.9% (n=2), PR 17% (n=12), CBR (CR+PR+SD≥6 cycles) 31% (n=22), RECIST clinical PD (n=43/10; 65%/15%). Median PFS=3.3m and median OS=17.8m. 68/70 pts had ctDNA detected at baseline (median=16/16 variants) demonstrating 97% sensitivity. Table 1 shows ctDNA levels compared to ctDNA levels with clinical efficacy parameters, whereas ctDNA values did not reach statistical significance. **Conclusions:** A strong correlation exists between ctDNA levels with OS, PFS, CBR and ORR with P, suggesting it is a potential predictive biomarker in pts with mixed solid tumors.

**Clinical trial information:** NCT0344369.

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**Background:** CL of checkpoint inhibitors has been identified as a predictive covariate of overall survival (OS) in several tumors. Determination of CL requires post-treatment samples, which negates its utility as a baseline pharmacodynamic biomarker. This study aims to identify a baseline composite CL from ctDNA (ctDNA levels) with OS, PFS, CBR and ORR. **Methods:** ctDNA was assessed at baseline (B) and start of cycle 3 (C3) using a pt-specific amplicon-based NGS assay (Signatera™). Sampled ctDNA was assessed by P-values at 72% (45 out of 63) of C3-specific targeted ctDNA met significance (PI-0502-2014). **Results:** Results of 70 pts are presented. Demographics: male 46%; median age=60 yrs (range 21–82); head and neck (20%), triple negative breast (14%) and ovarian (14%) cancers comprised the major malignancies. Median no. of P cycles=4 (range 2–35); follow up was 14w (range 2–29); RECIST responses: CR 2.9% (n=2), PR 17% (n=12), CBR (CR+PR+SD≥6 cycles) 31% (n=22), RECIST clinical PD (n=43/10; 65%/15%). Median PFS=3.3m and median OS=17.8m. 68/70 pts had ctDNA detected at baseline (median=16/16 variants) demonstrating 97% sensitivity. Table 1 shows ctDNA levels compared to ctDNA levels with clinical efficacy parameters, whereas ctDNA values did not reach statistical significance. **Conclusions:** A strong correlation exists between ctDNA and OS, PFS, CBR and ORR with P, suggesting it is a potential predictive biomarker in pts with mixed solid tumors.

**Clinical trial information:** NCT0344369.

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**Background:** First Author: Marco Adelmo James Iafolla, Princess Margaret Cancer Centre, Toronto, ON, Canada

**Methods:** Endpoint

Clinical trial information: NCT02644369.

**Results:** Values did not reach statistical significance.

**Conclusions:**

**Clinical trial information:** NCT0344369.

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**Background:** First Author: Natalia Palazón-Carrion, Virgen Macarena University Hospital, Seville, Spain

**Methods:** **Efficacy and safety of pembrolizumab and gemcitabine in HER2-negative ABC:**

- **B**: PI-002-2014 “Peripheral blood analyses of immune response induced by 1st line tx of ABC according to clinical guidelines”
- **Methods:** MDScs (CD33+ CD11b+) levels were determined by flow-cytometry in peripheral blood samples at three time points (baseline, at cycles 3 and 6) from: 39 HER2-negative heavily pretreated pts from study “A”, 43 non-pretreated pts (all subtypes) from study “B” and 20 women from a healthy cohort (HC), with no cancer diagnosis.

**Conclusions:**

- **M:** MDScs levels from the different cohorts were compared and correlated with pts with Clinical Benefit (CB; partial/complete response + disease stabilization) vs pts with Progressive Disease (PD).
- **Results:** Tx response was assessed in 33 pts (85%) from study “A” and 39 pts (91%) from study “B”.
- **Conclusion:** In study “A”, 28% of pts showed CB vs PD vs 37% in study “B”.

**Results:**

- **PFS:** CB was observed in 11 pts (28%) from study “A” and in 34 (79%) from study “B” while PD was observed in 22 pts (56%) from study “A” and in 5 (12%) of study “B”.

**Conclusions:** Our results suggest that ABC pts show alterations in MDScs and that their decrease along tx may have a positive predictive value, highlighting the importance that immune-competent status may play in the evolution of ABC. MDScs may represent a target for therapeutic purposes in ABC.

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**Background:** First Author: Rui Wang, Bristol-Myers Squibb, Princeton, NJ

**Methods:** Pharmacodynamic (PK/PD) analysis in patients with renal cell carcinoma (RCC).

**Results:** Peripheral serum PK (NIVO CL) and ctDNA (ctDNA B levels) were assessed at baseline (B), start of cycle 3 (C3) using a pt-specific amplicon-based NGS assay (Signatera™). Sampled ctDNA was assessed by P-values at 72% (45 out of 63) of C3-specific targeted ctDNA met significance (PI-0502-2014). **Results:** Results of 70 pts are presented. Demographics: male 46%; median age=60 yrs (range 21–82); head and neck (20%), triple negative breast (14%) and ovarian (14%) cancers comprised the major malignancies. Median no. of P cycles=4 (range 2–35); follow up was 14w (range 2–29); RECIST responses: CR 2.9% (n=2), PR 17% (n=12), CBR (CR+PR+SD≥6 cycles) 31% (n=22), RECIST clinical PD (n=43/10; 65%/15%). Median PFS=3.3m and median OS=17.8m. 68/70 pts had ctDNA detected at baseline (median=16/16 variants) demonstrating 97% sensitivity. Table 1 shows ctDNA levels compared to ctDNA levels with clinical efficacy parameters, whereas ctDNA levels did not reach statistical significance. **Conclusions:** A strong correlation exists between ctDNA levels with OS, PFS, CBR and ORR with P, suggesting it is a potential predictive biomarker in pts with mixed solid tumors.

**Clinical trial information:** NCT0344369.

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**Background:** First Author: Kyoichi Kaira, Division of Respiratory Medicine, Saitama Medical University International Medical Center, Hidaka, Japan

**Methods:** Peripheral blood analyses of immune response induced by 1st line tx from study “A” and in 34 (79%) from study “B” while PD was observed in 22 pts (56%) from study “A” and in 5 (12%) of study “B”.

**Conclusions:** Our results suggest that ABC pts show alterations in MDScs and that their decrease along tx may have a positive predictive value, highlighting the importance that immune-competent status may play in the evolution of ABC. MDScs may represent a target for therapeutic purposes in ABC.
2546 Poster Session (Board #190), Sat, 8:00 AM-11:00 AM
Molecular circulating tumor DNA response to identify long-term survival in patients receiving immunotherapy with initial radiologic stable disease. First Author: Matthew David Hellmann, Thoracic Oncology Service, Developmental Immunotherapy and Tumor Immunobiology 117s, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: Early on-treatment changes in ctDNA may identify responders to immunotherapy and complement radiologic assessment of benefit. Here we investigate how early changes in ctDNA associate with long-term survival following treatment with immunotherapy, and if differential molecules in molecular ctDNA response (MCR) among patients with radiologic stable disease (SD) at first on-treatment scan could identify patients deriving benefit from treatment. Methods: Paired pre- and on-treatment (week 6-8) plasma samples from 3 cohorts of patients treated with durvalumab (D) +/- tremelimumab (D+T) were evaluated (NCT01693562, NCT02087423, NCT02261220). ctDNA was profiled with the 73-gene Guardant 360 assay. Nonsynonymous variants were summarized per patient to calculate variant allele frequency changes (dVAF) and on-treatment variant allele frequency (pVAF). A combination of dVAF and pVAF was used to define MCR. Results: The reduction of ctDNA (dVAF=0) and undetectable on-treatment ctDNA (pVAF=0) were each associated with improved OS and PFS. An optimal threshold for MCR was determined from one cohort, then applied to the other cohorts. MCR associated with significantly improved PFS and OS across all thresholds for MCR was determined from one cohort, then applied to the other cohorts. MCR associated with significantly improved PFS and OS across all cohorts (Table). MCR was then applied to a pooled subgroup of patients with initial radiologic SD from all three cohorts (n=78). Patients with radiologic SD and MCR were significantly more likely than those without MCR to derive clinical benefit from immunotherapy. MCR may be a supportive effect in patients with metastatic breast cancer and PFS. An optimal threshold for MCR was determined from one cohort, then applied to the other cohorts. MCR associated with significantly improved PFS and OS across all cohorts (Table). MCR was then applied to a pooled subgroup of patients with initial radiologic SD from all three cohorts (n=78). Patients with radiologic SD and MCR were significantly more likely than those without MCR to derive clinical benefit from immunotherapy. MCR may be a supportive effect in patients with metastatic breast cancer and PFS. An optimal threshold for MCR was determined from one cohort, then applied to the other cohorts. MCR associated with significantly improved PFS and OS across all cohorts (Table). MCR was then applied to a pooled subgroup of patients with initial radiologic SD from all three cohorts (n=78). Patients with radiologic SD and MCR were significantly more likely than those without MCR to derive clinical benefit from immunotherapy. MCR may be a supportive effect in patients with metastatic breast cancer and PFS.

2547 Poster Session (Board #191), Sat, 8:00 AM-11:00 AM
cDNA analysis for personalization of consolidation immunotherapy in localized non-small cell lung cancer. First Author: Everett J Moding, Stanford University School of Medicine, Stanford, CA

Background: Detection of molecular residual disease via circulating tumor DNA (ctDNA) analysis after chemoradiation (CRT) in localized non-small cell lung cancer (NSCLC) predicts risk of relapse. We explored the hypotheses that (1) patients with undetectable ctDNA after CRT may not require consolidation immunotherapy (CI) and (2) ctDNA analysis could monitor the effectiveness of CI in patients with residual ctDNA after CRT. Methods: We applied a custom FF-Seq ctDNA analysis to 88 plasma and matched leukocyte samples collected pre-CRT, post-CRT but pre-CI, and mid-CI in 22 patients with Stage IIB-IIIB NSCLC treated with CRT followed by CI. Identification of patient-specific tumor variants was performed using tumor mutation-informed bioinformatic strategy. Freedom from progression (FFP) defined radiographically by RECIST 1.1 criteria was compared in patients with ctDNA detected or not detected at pre-CI and mid-CI landmarks. Results: Median follow up from the start of CRT was 11 months. ctDNA detection was associated with inferior rates of FFP when compared to patients with ctDNA not detected pre-CI (12-month 33% vs. 76%, P = 0.015, HR 7.51, 95% CI 1.47-38.24) and mid-CI (12-month 0% vs. 86%, P < 0.0001, HR 123.3, 95% CI 16.21-937.8). In patients with undetectable ctDNA after CRT, FFP was similar to a historical cohort of patients with undetectable ctDNA after CRT alone (12-month 88% vs. 7%, P = 0.05, HR 0.05, 95% CI 0.001-1.91), suggesting no additional benefit from CI. All patients with detectable ctDNA pre-CI in whom ctDNA increased mid-CI developed progressive disease. Finally, in 2 patients with ctDNA detected after CRT, CI led to elimination of ctDNA at the mid-CI timepoint. One of these patients developed an isolated local recurrence 24 months after CRT, whereas the other patient remained disease free at 11 months, suggesting clinical benefit from CI. Conclusions: Our results suggest that ctDNA analysis may allow personalization and response monitoring of CI following CRT for NSCLC. Validation in more patients followed by prospective testing in clinical trials will be required to establish clinical utility of such an approach.

2548 Poster Session (Board #192), Sat, 8:00 AM-11:00 AM
Phase 1 study of LY3022855, a colony-stimulating factor-1 receptor (CSF-1R) inhibitor, in patients with metastatic breast cancer (MBC) or metastatic castration-resistant prostate cancer (mCRPC). First Author: Karen A. Autio, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Tumor-associated macrophages (TAM) correlate with increased invasiveness, growth, and immunosuppression. Activation of CSF-1R results in proliferation, differentiation, and migration of monocytes/macrophages. CSF-1R inhibition with LY3022855 (LY), a human immunoglobulin G subclass 1 (IgG1) monoclonal antibody (mAb), has shown preclinical and clinical effects. We evaluated the safety and clinical response of LY monotherapy. Methods: Patients (pts) with advanced refractory MBC and mCRPC received LY intravenously in 6-week cycles in cohorts: A) 1.25 mg/kg every 2 weeks (D); B) 1.25 mg/kg every 2 weeks concurrent with ipilimumab 10 mg/kg intravenously in 6-week cycles (D+I); C) 3 mg/kg intravenously on Day 1 every three weeks, starting one week after CRT for patients with stable disease (SD) who derive clinical benefit from immunotherapy (D); D) 1.25 mg/kg every 2 weeks in patients with metastatic breast cancer (MBC) or metastatic CRPC with high circulating tumor DNA (ctDNA) detected after CRT (B). 14 patients were treated and evaluable for safety and efficacy. The most common treatment-related adverse events of any grade were myelotoxicity (n = 17; 89%) and immune-related adverse events (n = 12; 63%). Grade 3 or 4 toxicities. Rates of immune-related disease control and objective response were 71% (2/29) and 14% (1/7), respectively. Exploratory analyses of tumour biopsies showed that median CpG site methylation at Week 4 (74.5±14.4%) was significantly higher than at Baseline (64.9±14.9%) and increased mid-CI developed progressive disease. Finally, in 2 patients with ctDNA detected after CRT, CI led to elimination of ctDNA at the mid-CI timepoint. One of these patients developed an isolated local recurrence 24 months after CRT, whereas the other patient remained disease free at 11 months, suggesting clinical benefit from CI. Conclusions: Our results suggest that ctDNA analysis may allow personalization and response monitoring of CI following CRT for NSCLC. Validation in more patients followed by prospective testing in clinical trials will be required to establish clinical utility of such an approach.

2549 Poster Session (Board #193), Sat, 8:00 AM-11:00 AM
Safety and immunobiological activity of guadecitabine sequenced with ipilimumab in metastatic melanoma patients: The phase Ib NIBIT-M4 study. First Author: Anna Maria Di Giacomo, Medical Oncology and Immunotherapy, University Hospital of Siena, Siena, Italy

Background: DNA hypomethylating agents show broad immunomodulatory activity in neoplastic cells, and may improve the effectiveness of cancer immunotherapies. The phase 1b NIBIT-M4 trial investigated a previously unexplored therapeutic strategy using the next-generation DNA hypo- methylating agent guadecitabine sequenced with ipilimumab for the treatment of advanced melanoma. Methods: Patients with unresectable Stage III/IV melanoma received escalating doses of guadecitabine 30, 45 or 60 mg/m² subcutaneously on Days 1–5 every three weeks, and ipilimumab 3 mg/kg intravenously on Day 1 every three weeks, starting one week after guadecitabine, for four cycles. Primary endpoints were the safety, tolerability and maximum tolerated dose of treatment; secondary endpoints included immune-related disease control and objective response. Genome-wide methylation, RNA sequencing, and immunohistochemistry analyses were performed on tumor samples collected at baseline, W4 and W12. (NCT02608437).

Results: 19 patients were treated and evaluable for safety and efficacy. The most common treatment-related adverse events of any grade were myelotoxicity (n = 17; 89%) and immune-related adverse events (n = 12; 63%). Grade 3 or 4 myelotoxicity occurred in 15 (79%) patients. There were no dose limiting toxicities. Rates of immune-related disease control and objective response were 8/19 (42%) and 5/19 (26%), respectively. Exploratory analyses of tumour samples (n = 8) showed that median Cpg site methylation at Week 4 (74.5%) and Week 12 (75.5%) was significantly lower (p < 0.05) than at baseline (80.3%), with a median of 2454 (Week 4) and 4131 (Week 12) differentially expressed genes identified compared to baseline, among the 136 pathways significantly modulated by treatment, the most frequently activated were immune-related. Tumour immunity contexture analysis (n = 11) demonstrated up-regulation of Human Leukocyte Antigen (HLA) class I molecules on melanoma cells, and an increase in CD8+, PD-1+ T cells and in CD20+ B cells in post-treatment tumour core specimens. Conclusions: Sequential guadecitabine and ipilimumab is safe and tolerable in patients with metastatic melanoma, and has promising immunological and anti-tumor activity. Clinical trial information: NCT02608437.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Checkpoint inhibitor (CPI) monotherapy shows limited clinical response in previously treated mTNBC patients (pts). Agents are needed that extend this benefit to more mTNBC pts. PGG is a novel, IV administered PAMP that, in pts with 20ug/ml anti-beta glucan antibody (ABaA+), activates innate immune cells. Preclinically, PGG reprograms myeloid cells to repolarize the immunosuppressive tumor microenvironment & enhance antigen presentation, driving T cell activation- the mechanistic basis to explore PGG + P in mTNBC patients. Methods: 44 mTNBC pts (1 line of chemotherapy [Tx] for metastatic disease, ABA+) received PGG (4 mpk IV weekly) + P(200 mg IV qw4) until PD or intolerable toxicity. 1st endpoints were ORR by RECIST v1.1 & safety. 2nd endpoints included OS & DCR. CT scans (q6 wks) were reviewed locally. Tumor biopsies (pre & 6 wks on Tx) & blood samples were assessed for PGG-mediated immune activation. Results: Table shows IMPRIME 1 clinical response data (Keynote086, PCD4989g shown for context). Confirmed response was also evident in pts with liver or visceral metastases, high LDH. 10 IMPRIME 1 pts met the criteria for hormonal Tx and progressed to TNBC. Of these, 5 were confirmed PR, 4 SD (3 still on Tx), 1 PD. No unexpected safety signals were observed. Conclusions: These are the first clinical data to suggest that PGG provides additional clinical benefit for pts with previously treated mTNBC and support further development of PGG for mTNBC. Clinical trial information: NCT02981303.

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<th>Keynote086 (% (N=170)</th>
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*Adams 2018, *Emens 2019 In peripheral blood, Tx increased activated (HLA-DR+/CD1c+), CD86+ monocyte & dendritic cell subsets as well as CD8 T cells (Ki67/HLA-DR/PD1+), particularly in pts. All tumor biopsy pairs showed heavy infiltration by activated myeloid (PDL1+) and CD8 T cells (Ki6/CD8/granzyme B+) after Tx. These data support the mechanistic basis for PGG-based combination with P. NCT02981303 sponsored by Biothera in collaboration with Merck & Co., Inc.

Background: Eligibility criteria protect the safety of trial pt and delineate the study population. Excessively restrictive criteria, however, can negatively impact accrual and prevent access to beneficial investigational treatments. Recently, ASCO issued a statement on the need to broaden eligibility criteria but ultimately did not receive any therapy on that trial.

**Results:** We enrolled 197 pts to the IMPRIME 1 trial from 10/2015-12/2017, and collected pt characteristics as well as clinical outcomes, and compared participants (P) to non-participants (NP).

**Conclusions:** One quarter of patients who signed consent for early-phase immunotherapy trials were unable to start on study. NP had significantly decreased OS. Detailed examination of these reasons can lead to recognition of modifiable factors and streamline the pretrial period, to guarantee this vulnerable population has maximal access to start therapy on study.
2554  Poster Session (Board #198), Sat, 8:00 AM-11:00 AM
Preliminary safety, efficacy, and pharmacokinetics (PK) results of KN046 (biscpecific anti-PD-L1/CTLA4) from a first-in-human study in subjects with advanced solid tumors. First Author: Jermaine Coward, Icon Cancer Care, Brisbane, Australia

Background: KN046 is a novel bispecific antibody that blocks both PD-L1 interaction with PD1 and CTLA-4 interaction with CD80/CD86. KN046 has a wild type IgG1 Fc portion that preserves intact effector functions, such as depletion of TumorImmunosurveillance. This first-in-human study evaluated the safety, tolerability, PK and preliminary efficacy of KN046 in subjects with advanced solid tumors. Methods: This randomized, dose-escalation design study enrolled patients (pts) with advanced unresectable or metastatic solid tumors refractory or intolerant to standard therapies. Previous treatment from PD1 or PD-L1 immune checkpoint inhibitors was allowed. KN046 was administered intravenously Q2W. Dose limit toxicity (DLT) evaluation period is 28 days. The planned dose levels (DL) were 0.3, 1, 3, 5 and 10 mg/kg. Efficacy evaluation was performed by RECIST 1.1 every 8 weeks.

Results: As of Dec 13, 2018, 10 pts had been enrolled (0.3 mg/kg, n = 1; 1 mg/kg, n = 3; 3 mg/kg, n = 3; and 5 mg/kg, n = 3). Median duration of treatment was 8 weeks (range 2-24 weeks). DLT was observed at 5 mg/kg dose (a grade 3 immune-related hepatitis without elevation in total bilirubin; retreatment was 8 weeks). 1 DLT was observed at 5 mg/kg dose (a grade 3 immune-related hepatitis without elevation in total bilirubin; retreatment was 8 weeks). 1 DLT was observed at 5 mg/kg dose (a grade 3 immune-related hepatitis without elevation in total bilirubin; retreatment was 8 weeks).

Conclusion: Seven patients experienced 1 treatment-related AE (TRAE); hypothyroidism (n = 3) was the only TRAE that occurred in >2 pts. No grade ≥3 TRAEs or serious AEs were reported. Furthermore, no AEs led to either treatment interruption or discontinuation. Tislelizumab was generally well tolerated and demonstrated antitumor activity in previously treated pts with advanced solid tumors. First Author: Miguel Angel Villalona-Calero, Magic Cancer Institute, Hong Kong, China

Background: Immune checkpoint inhibitors have demonstrated a clear survival benefit in various tumor types. However, accelerated disease progression, documented as hyperprogressive disease (HPD), was reported in a subset of patients treated with PD-1/PD-L1 inhibitors. Until now, the mechanisms underlying HPD have not been elucidated. Previous studies have demonstrated that MDM2/MDM4 amplification was associated with HPD. In the present study, we evaluated the relationship between MDM2/MDM4 amplification and HPD. Methods: We reviewed extensive clinical trials of PD-1/PD-L1 inhibitors in advanced solid tumor patients updated to January 2019, and estimated the incidence of HPD, which was defined as time-to-treatment failure (TTF) ≤2 months, and >50% increase in tumor burden compared with pre-immunotherapy imaging in this study. The proportions of MDM2/MDM4 amplification across different cancer types were obtained from The Cancer Genome Atlas (TCGA) and our own database respectively. Then we plotted the incidence of HPD and the corresponding proportion of MDM2/MDM4 amplification across various cancer types in TCGA. Results: Over 100 published clinical trials of 1318 patients treated with PD-1/PD-L1 inhibitors were included for analysis, covering 12 types of solid cancers. The incidences of HPD among these studies were ranging from 1.58% in renal clear cell carcinoma to 24.3% in sarcoma. Correspondingly, the proportions of MDM2/MDM4 amplification for these cancer types in TCGA were 0.74% in renal clear cell carcinoma to 20.38% in sarcoma. In our database, total, 60 patients with MDM2/MDM4 amplification were identified in 2931 patients with the highest proportion of MDM2/MDM4 amplification in sarcoma (22 of 152, 14.5%). A significant correlation was detected between the incidence of HPD and the corresponding proportion of MDM2/MDM4 amplification in TCGA across various cancer types (P < 0.001, R² = 0.67). Conclusions: Our results suggest that MDM2/MDM4 amplification may be associated with rapid disease progression in patients receiving PD-1/PD-L1 inhibitors among various tumor types. The exact mechanisms underlying HPD need to be further evaluated.
Antitumor activity and safety of MK-1308 (anti-CTLA-4) plus pembrolizumab (pembro) in patients (pts) with non-small cell lung cancer (NSCLC): Updated interim results from a phase 1 study. First Author: Ruth Borse, Rambam Medical Center, Technion - Israel Institute of Technology, Haifa, Israel

Background: An ongoing multicenter, open-label, phase 1 study of the anti-CTLA-4 antibody MK-1308 in combination with pembro in advanced solid tumors (NCT03179436) revealed a manageable safety profile and promising efficacy in pts with first-line (1L) advanced NSCLC. Data from a larger sample size and longer follow-up are presented. Doses were categorized as follow: FHC-high (in case of at least one cancer diagnoses in both straight and collateral family line), FHC-low while 74 (9.6%) were FHC-high. FHC-high patients had a significantly higher OS as compared to FHC-negative (55.4% vs 35.6%; p = 0.0012) and to FHC-low (41.4%; p = 0.0323). No significant differences were found in terms of ORR among subgroups (data not shown). At median follow-up of 15.8 months, median PFS was 9.1 months (95%CI: 8.0-10.4; 452 events) and median OS was 19.7 months (95%CI: 15.7-24.4; 436 censored). No significant differences were found in terms of OS or PFS between follow up patients with data available and those not available. Conclusions: FHC seems to be an independent predictor for longer OS in cancer patients treated with anti-PD-1/PD-L1. DNA damage and response (DDR) genes alterations may underlie that results.
2562 Poster Session (Board #206), Sat, 8:00 AM-11:00 AM
Open-label, multicenter, phase I study to assess safety and tolerability of adavosertib plus durvalumab in patients with advanced solid tumors. First Author: Manish R. Patel, Florida Cancer Specialists and Sarasota Cancer Research Institute, Sarasota, FL

**Background:** Adavosertib (AZD1775; A) is a highly selective inhibitor of WEE1. This Phase I study (NCT02617277) investigated a range of doses and schedules for oral A plus IV durvalumab (DV), a human monoclonal antibody targeting PD-L1, to determine the maximum tolerable dose (MTD) and recommended Phase II dose (RP2D) in patients (pts) with advanced solid tumor.

**Methods:** Four 28-day schedules (Sch) were evaluated with pts receiving DV 1500 mg on day (d) 1 of each schedule (Table). Patients continued treatment if they showed clinical benefit in the absence of any discontinuation criteria. Pts received A monotherapy for PK analysis prior to the start of combination therapy in Sch B, C (d–7 to –5) and D (d–9 to –5). MTD was determined using a 3+3 dose-escalation cohort design. Predefined dose-limiting toxicities (DLTs) were evaluated during the first cycle of study treatment. **Results:** 54 pts received A (most common primary tumor sites: colon, 19%; lung, 13%; breast, 11%). The most common grade ≥3 AES were fatigue (15%), diarrhea (11%) and nausea (9%). DLTs were nausea (n=2) and diarrhea (n=1), 7 pts (13%) had A-related SAEs, including reversible and confounded drug-induced liver injury (Sch B and C, 1 each). Disease control rate (DCR) for the total cohort was 36%. Preliminary PK at 150 mg BID suggests adequate coverage for cell kill activity and no drug–drug interaction. **Conclusions:** The MTD/RP2D was A 150 mg BID (3 d on, 4 d off; treatment d 15–19, 22–24) with DV 1500 mg (d 1 Q4W); safety profile was considered acceptable. Preliminary evidence of antitumor activity was observed. Clinical trial information. NCT02617277.

2564 Poster Session (Board #208), Sat, 8:00 AM-11:00 AM
Severe immune-related adverse events in anti-PD-1-treated patients are clustered into distinct subtypes by peripheral blood T cell profiles. First Author: Kyung Hwan Kim, Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology, Daejeon, South Korea

**Background:** Although anti-programmed death-1 (PD-1) treatment has shown remarkable anti-tumor efficacy, immune-related adverse events (irAEs) develop with heterogeneous clinical manifestations. Immunological understanding of irAEs is currently limited. In the present study, we identified peripheral blood T cells obtained from cancer patients who received anti-PD-1 treatment to determine the immunological characteristics of severe irAEs.

**Methods:** This study included 31 patients with refractorythymic epithelial tumor (TET) who were enrolled in a phase II trial of pembrolizumab (NCT02607631) and 60 patients with metastatic non-small cell lung cancer (NSCLC) who received pembrolizumab or nivolumab. T-cell profiling was performed by multicolor flow cytometry using peripheral blood obtained immediately before treatment and 7 days after the first dose of anti-PD-1 antibodies. **Results:** Severe irAEs (≥ grade 3) occurred in 7 TET patients (22.6%) and 6 NSCLC patients (10%). Patients with severe irAEs exhibited a significantly lower fold increase in the frequency of effector regulatory T (eTreg) cells after anti-PD-1 treatment, higher ratio of T helper-1 (Th1) and T helper-1 cells at baseline, and higher percentage of KI-67+ cells among PD-1+CD8+T cells post-treatment. In clustering analysis, patients with severe irAEs were grouped into four immunological subtypes, indicating that development of severe irAEs is not attributed to a single mechanism. Further investigations in larger cohorts are needed to validate our current findings.

2565 Poster Session (Board #209), Sat, 8:00 AM-11:00 AM
Association between past medical history (PMH) of autoimmune events and adverse events of special interest (AESI). First Author: Jamie Reneer Brewer, U.S. Food and Drug Administration, Silver Spring, MD

**Background:** PD-1/L1 inhibitor therapy has become the standard of care for many advanced solid tumors. A notable limitation of PD-1/L1 inhibitor therapy is the concern for AESI that are likely to be immune related. It is unclear whether a history of autoimmune events is a predisposing risk making these adverse events more likely. We aimed to evaluate the association between autoimmune-associated PMH and AESI in patients (pts) with solid tumors treated with immune-checkpoint inhibitors.

**Methods:** We pooled data across seven pivotal trials for PD-1/L1 inhibitors (5). We assessed PMH, AESI events, and type of AESI event. Grades of AESI events in the population with AESI were identified, with 1068 (61%) having an AESI and 277 (26%) having an autoimmune-related AESI. **Results:** In both studies, pts who experienced at least one AESI by study cut-offs had improved median OS (mOS; 1108: 23.1 mos [18.2, 26.9]; C10: 16.3 mos [12.5, 31.4]) relative to those who experienced none (1108: 6.3 mos [5.4, 7.3]; C10: 4.6 mos [3.3, 6.1]). Median time (weeks) to first and second irAE occurred earlier in C10 compared to 1108, 3.9 vs. 5.6 and 6.9 vs. 10.1, respectively. When analyzing time of irAE occurrence, there was a significant difference in mOS at each time interval evaluated between pts with at least one irAE and those with none, with differentiation at 6 weeks and maximal survival benefit at 24 weeks following treatment with D or D+T (Table). **Conclusions:** Early occurrence of irAEs may be predictive of survival benefit in pts treated with D or D+T. OS by 1+ or no irAEs occurring up to 6 or 24 weeks post treatment.

2566 Poster Session (Board #207), Sat, 8:00 AM-11:00 AM
Early incidence of immune-related adverse events (irAEs) predicts efficacy in patients (pts) with solid tumors treated with immune-checkpoint inhibitors (ICIs). First Author: Chris Mody, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** Treatment with ICIs can manifest immune-related adverse events (irAEs), which have correlated with clinical outcomes in certain tumors. However, timing of these events and how early irAEs correlate with outcomes is unclear. We assessed whether early occurring irAEs could predict survival in pts treated with durvalumab (D), an anti-PD-L1 and combined with tremelimumab (D+T), an anti-CTLA4 in two clinical studies.

**Methods:** Two phase Ia non-randomized clinical trials evaluated D and D+T (N=1108, N=756). Available data per internal data re-use policy) or D+T (N=1490) (C10, N=327; expansion and ICI naïve cohorts) in multiple solid tumor types were analyzed. Prevalence of pts experiencing irAEs, regardless of grade was 30% and 59% in studies 1108 and C10, respectively, with most frequent including dermatitis/rash (25%), thyroid (15%), diabetes/collitis (14%), and pancreatic enzyme elevation (5%). Overall survival (OS) was correlated with irAE timing prior to 6, 8, 12, 16 and 24 weeks following D or D+T treatment. Kaplan Meier and log-rank analyses were used. **Results:** In both studies, pts who experienced at least one irAE by study cut-offs had improved median OS (mOS; 1108: 6.3 mos [5.4, 7.3]; C10: 4.6 mos [3.3, 6.1]). Median time (weeks) to first and second irAE occurred earlier in C10 compared to 1108, 3.9 vs. 5.6 and 6.9 vs. 10.1, respectively. When associating timing of irAE occurrence, there was a significant difference in mOS at each time interval evaluated between pts with at least one irAE and those with none, with differentiation at 6 weeks and maximal survival benefit at 24 weeks following treatment with D or D+T (Table). **Conclusions:** Early occurrence of irAEs may be predictive of survival benefit in pts treated with D or D+T. OS by 1+ or no irAEs occurring up to 6 or 24 weeks post treatment.
Characteristics of patients receiving immune checkpoint inhibitors (ICI) in ASCO’s CancerLinQ. First Author: Wendy S. Rubinstein, American Society of Clinical Oncology’s (ASCO) CancerLinQ, Alexandria, VA

Background: ICI’s have demonstrated significant clinical benefit since the first FDA approval in 2011 of ipilimumab for metastatic melanoma. Five additional ICI therapies have since been approved across several indications. The objectives of this study were to describe the clinical and demographic features of patients receiving ICI treatment along with utilization patterns in real-world settings. Methods: We conducted a retrospective, observational cohort study using statistically de-identified data from January 2011 to November 2018 in CancerLinQ, ASCO’s real-world oncology database, which now contains EHR data from 49 diverse oncology practices in the U.S. Adult patients diagnosed with any cancer type who received ≥1 dose of an ICI (see Table) and had ≥2 clinical visits were eligible for inclusion. Patients were excluded if they received an ICI prior to its first FDA approval date to avoid inclusion of clinical trial patients. Descriptive statistics were used to examine treatment patterns and clinical characteristics of patients receiving ICIs. Results: This analysis included 12,712 patients who received an ICI. Median patient age was 67.4 years (IQR 59.3, 75.3); 58% were male. White race made up the highest percent (83%) of ICI patients, followed by Black race (9%) and Other (8%). The most common primary cancers at the start of treatment were lung cancer (36%), melanoma (8%), urothelial cancer (2%) and renal cell carcinoma (2%). Of the 8,444 patients with known disease stage, 5,446 (64%) had Stage IV cancer. Breakdown of ICI treatment patterns can be found in the accompanying table. Uptake of ICI’s was the most rapid for nivolumab, which had the highest use (49%), followed by pembrolizumab for rapid adoption and use (30%). Conclusions: This analysis gives insights into patient characteristics and real-world treatment patterns for ICIs. ICIs were used most widely in males, lung cancer patients and patients with advanced disease. These baseline characteristics inform our analyses of ICI use in patients with autoimmune disease, also reported herein.

ICI Medication | N (%) | N (%)
--- | --- | ---
Atezolizumab | 644 (5) | 22 (0)
Avelumab | 619 (5) | 116 (1)
Durvalumab | 1303 (10) | 6219 (49)
Pembrolizumab | 3789 (30) |

Cardiovascular complications of immune checkpoint inhibitor therapy. First Author: Samp R. Master, Louisiana State University Health Sciences Center, Shreveport, LA

Background: Cardiac toxicity has largely been underestimated toxicity of checkpoint inhibitors. There have been several cases of myocarditis and fatal heart failure reported in patients treated with checkpoint inhibitors. We did a retrospective analysis of data of adverse effects of drugs that has been made available to public by the FDA. Methods: The FDA has made the data on adverse effects of various treatments available to general public through the FDA Adverse Events Reports System (FAERS) public database. We investigated the cardiac toxicities of various immune check point inhibitor therapies available at FDERS for the years 2017-2018. Results: The reviewed the reported side effects of pembrolizumab, nivolumab, atezolizumab,avelumab,durvalumab and ipilimumab from FDA data. A total of 36,848 toxicities from immunotherapies were reported. Out of that, 2316(6.2 %) were cardiac toxicities and 816 were fatal. The most common cardiac complications were as follows: myocarditis (15%), atrial fibrillation (13%), pericardial disease including pericardial effusion (13%), cardiac failure (17%) and coronary artery disease (19%). Approximately 50%, 43%, 40% 22% and 15% of cases with myocarditis, ischimic heart disease, cardiac failure, atrial fibrillation and pericardia disease were fatal. Conclusions: Out of the reported cases of adverse reaction to check point inhibitor, 6.2% were cardiac toxicities. 35% of cardio toxicities were fatat. Half of the cases who developed myocarditis died. There was no statistical difference in rate of cardio toxicities caused by PD1, PD1L or CTLA 4 inhibitors.

Understanding contribution and independence of multiple biomarkers for predicting response to atezolizumab. First Author: Parantu K. Shah, Global Development, EMD Serono Research & Development Inc., Billerica, MA

Background: No biomarker satisfactorily predict response to anti-PD-L1 therapies. Biomarker studies suffer from small sample size, presence of disease subtypes, and lack of simultaneous measurement of multiple biomarkers. The IMVigor210 dataset (Mariathasan et al., Nature 2018) provides baseline measurements for multiple biomarkers of response to atezolizumab (n range: 105-298) coupled with genomewide RNAseq profiles. We examined predictive performance of individual biomarkers and combined information from multiple biomarkers to measure changes in predictive performance. Methods: We built classification models (PR/CR vs. PD/SD) using genes and gene sets that provide information on pathways (mSigDB), immune components (xCell, Cibersort), and predictors of response (IMPres, Immunophenoscope, and TIDE). Prognostic features were removed based on survival association in TCGA. All experiments were done with repeated five-fold double cross validation. Predictions from the gene sets model were used as a single biomarker. PD-L1 expression by IHC in tumor core and immune cells, tumor mutation burden(TMB), neo-antigen burden (NB), location of disease, biomarker type and genomic subtypes were then systematically merged with the gene set based model. Results: NB was the best predictor of response (AUC 0.77), while a model combining NB, TMB, ECOG and expression signatures was marginally better (AUC 0.81) with a chance of over fitting. Chi-square tests for independence suggested that examined biomarkers provide independent predictive information, with lack of increase in AUC. Signatures for TP53 mutations, M1 macrophages, CD8+ T effector cell and DNA repair, among others, were present frequently in classification using gene expression information (AUC 0.71), suggesting their independent contributions to response. Adding gene expression information to NB didn’t improve AUC for response but provided better survival stratification. Conclusions: Integration of examined biomarkers with machine learning did not improve response prediction significantly. We are now examining sizes of subgroups defined by combination of low NB/TMB with these biomarkers.
2570  Poster Session (Board #214), Sat, 8:00 AM-11:00 AM
A phase II clinical trial of ipilimumab/nivolumab combination immunotherapy in patients with rare upper gastrointestinal, neuroendocrine, and gynecological malignancies. First Author: Oliver Klein, Medical Oncology Unit, Austin Health, Heidelberg, Australia

Background: Patients (pts) with rare cancers represent an unmet medical need and have an inferior overall survival compared to patients with more common malignancies. Due to their low frequency, no therapies, including immunotherapies, have systematically been investigated in this population. Ipilimumab (ipii)/Nivolumab (nivo) combination treatment has demonstrated significant clinical activity in pts with advanced melanoma and neuroendocrine carcinoma and response rates with this regimen are higher compared to single agent anti-PD-1 therapy. This phase II study assessed the efficacy and safety of ipii/nivo in rare cancer pts.

Methods: 60 pts with advanced rare upper gastrointestinal (GI), neuroendocrine (NE) and gynaecological (GY) malignancies were enrolled in 3 cohorts. Patients received nivo 3mg/kg and ipii 1mg/kg every 3 weeks for 4 doses, followed by nivo 3mg/kg every 2 weeks. Treatment continued for up to 96 weeks, or until disease progression or the development of unacceptable toxicity. Response (RECIST 1.1) was assessed every 12 weeks. The primary endpoint was clinical benefit rate (CBR), CR, PR and SD. Exploratory endpoints included OS, PFS, PD-L1 status, and immune biomarkers including PDL1 status and tumor mutation burden. Results: 42 pts have so far undergone restaging, 11 pts clinically progressed prior to their first restaging scan. 50 pts have received prior therapy (1-5 lines). Objective responses have been observed in a range of different malignancies. Clinical trial information: NCT02923934. Grade 3/4 immune related adverse events were observed in 28% of pts. 32% of pts achieved CR, PR, ORR, SD and 20% had stable disease. Conclusions: Ipi/Nivo combination treatment has efficacy in a wide range of advanced rare malignancies. Immune related toxicity is in keeping with previously reported clinical trials using the same dosing regimen.

2571  Poster Session (Board #215), Sat, 8:00 AM-11:00 AM
Outcomes after early initiation of nonsteroidal immunosuppressive therapy in patients with immune checkpoint inhibitor-induced colitis. First Author: Yusheng Wang, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Current treatment guidelines for immune-mediated colitis (IMC) recommend 4 to 6 weeks of steroids as first-line therapy, followed by nonsteroidal immunosuppressive therapy (NSIST) (infliximab or vedolizumab) in patients who do not respond to steroids. We assessed the effect of early NSIST introduction and number of NSIST infusions on clinical outcomes.

Methods: We performed a retrospective review of patients with IMC who received NSIST between January and December 2018. Logistic regression analyses were used to assess associations between clinical features and outcomes of IMC (Table).

Results: Of the 1,459 patients who received immune checkpoint inhibitor, 179 developed IMC of any grade; 84 of them received NSIST. Of the 84 patients who received NSIST, 79% were male with mean age of 60. Compared with patients who received NSIST > 10 days after IMC onset, patients who received early NSIST (<10 days) required fewer hospitalizations (P<0.03), experienced steroid taper failure less frequently (P<0.03), had fewer steroid tapering attempts (P<0.01), had a shorter course of steroid treatment (P<0.01), and had a shorter duration of symptoms (P<0.01). Risk factors of IMC recurrence after weaning off steroids included: 1) needing multiple hospitalizations (P<0.01), 2) experiencing steroid taper failure after NSIST (P<0.02), 3) receiving infliximab rather than vedolizumab (P<0.02), 4) receiving fewer than three infusions of NSIST (P<0.02), 5) having lower fecal calprotectin with NSIST detected in 31% of pts. The results of correlative biomarker studies will be presented at the meeting.

Conclusions: Ipi/Nivo combination treatment has efficacy in patients with rare upper gastrointestinal, neuroendocrine, and gynecological malignancies.

2572  Poster Session (Board #216), Sat, 8:00 AM-11:00 AM
Immunomodulation by HDAC inhibition: Results from a phase Ib study with vorinostat and pembrolizumab in metastatic urothelial, renal, and prostate carcinoma patients. First Author: Roberto Pili, Indiana University School of Medicine, Indianapolis, IN

Background: Immunosuppressive factors such as regulatory T cells (Tregs) and myeloid-derived suppressive cells (MDSCs) limit the efficacy of immunotherapies. Histone deacetylase (HDAC) inhibitors have been shown to have immunomodulatory effects. We have previously reported that HDAC inhibitors have synergistic antitumor effects in combination with PD-1/PD-L1 inhibition in tumor models by inhibiting the function of Tregs and MDSCs. Thus, we conducted a Phase Ib clinical study with the HDAC inhibitor vorinostat and the PD-1 inhibitor pembrolizumab in patients (pts) with metastatic urothelial, renal and prostate carcinoma.

Methods: The primary objective was to evaluate the safety and tolerability of this combination strategy. The phase I portion consisted of two dose levels of vorinostat (100 mg and 200 mg, PO daily 2 weeks ON and one week OFF) and a fixed, standard dose of pembrolizumab (200 mg IV every 21 days). Patients were assigned to three cohorts: Cohort A (previously treated, anti-PD-1/PD-L1 naïve urothelial and renal cancer pts = 15), Cohort B (previously treated, anti-PD-L1/PD-1 resistant urothelial and renal cancer pts = 14), and Cohort C (prostate cancer pts = 14).

Results: Dose levels 1 (4 enrolled, 3 evaluable) and 2 (4 enrolled, 3 evaluable) were completed without DLTs and 200 mg was the Phase II recommended dose for vorinostat. The most common resolved grade 3/4 toxicities were acute kidney injury (n = 1), anemia (n = 1), diarrhea (n = 1), and hypothyroidism (n = 1) in the dose expansion cohorts. We have enrolled 43 pts (37 evaluable) in the dose expansion cohorts. For Cohort A, B, and C the median PFS was 2.8 months, 5.2 months, and 3.5 months. Two PR were observed including the dose escalation phase. Two PCA pts have achieved undetectable PSA. We have performed several correlative studies including flow cytometry and gene expression analysis on peripheral blood mononuclear cells, PDL-1 staining and PSMA PET scans in a subset of pts.

Conclusions: The results from this phase Ib suggest that the combination of vorinostat and pembrolizumab is relatively well tolerated and may be active in a subset of immunotherapy refractory pts and immune checkpoint naïve PCA pts. Clinical trial information: NCT02619253.

2573  Poster Session (Board #217), Sat, 8:00 AM-11:00 AM
Efficacy and a novel clinicopathologic-genomic nomogram of atezolizumab in patients with non-small cell lung cancer (NSCLC): A combined analysis of two multicenter, randomized, phase II/III trials. First Author: Yunfang Yu, Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Department of Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

Background: Atezolizumab, a programmed death ligand 1 (PD-L1) inhibitor, prolonged overall survival (OS) compared with docetaxel among patients with previously treated non-small cell lung cancer (NSCLC). This analysis combines two independent multicentre, randomized trials (POPLAR and OAK). We conducted a combined analysis of the two trials to evaluate its efficacy and genomic biomarkers, and to further developed a novel predictive clinicopathologic-genomic nomogram of immunotherapy in NSCLC.

Methods: Patients (N = 1,137) with stage IIIIB/IV NSCLC and disease progression after previously platinum-based chemotherapy were randomly assigned (1:1) to receive atezolizumab (12,000 mg/m2 every 3 weeks) or docetaxel (75 mg/m2 every 3 weeks). The primary endpoint was OS. We applied a two-stage meta-analysis of pooled individual patient data in the intention-to-treat population. In OAK trial, patients treated with atezolizumab were randomly assigned (1:1) to the training group or the validation group to develop a predictive clinicopathologic-genomic nomogram of immunotherapy. POPLAR and OAK were registered with ClinicalTrials.gov, numbers NCT020068227 and NCT01903993.

Results: In the pooled analysis, the median overall survival (OS) was 12.4 months (95% confidence interval [CI], 11.95 to 15.22) with atezolizumab versus 9.66 months (95% CI, 8.73 to 10.70) with docetaxel. The risk of death was 28% lower with atezolizumab than with docetaxel (hazard ratio [HR], 0.72; 95% CI, 0.62 to 0.83; P < 0.001). The race, sex, tumor histology, Eastern Cooperative Oncology Group performance status, PD-L1 expression, and especially pretreatment mutation (TP53, DNM3TA and KEAP1) were significantly associated with OS, and were used for the development of the predictive nomogram. The clinical use of the nomogram showed a greater association with 3-year OS than the blood-based tumor mutational burden (tMB) or PD-L1 expression alone (nomogram, AUC = 0.818; tMB, AUC = 0.701; PD-L1, AUC = 0.526) among NSCLC patients who had received atezolizumab. The superior predictability of the nomogram was further confirmed in the validation and entire OAK cohorts. Conclusions: Among patients with advanced, previously treated, non-small cell lung cancer, atezolizumab was significantly superior than with docetaxel. Furthermore, we constructed a novel and powerful clinicopathologic-genomic nomogram for personalized immunotherapy options.
2574 Poster Session (Board #218), Sat, 8:00 AM-11:00 AM
Neoadjuvant presurgical PD-1 inhibition in oral cavity squamous cell carcinoma. First Author: Joshua Dean Horton, Medical University of South Carolina, Charleston, SC

Background: Oral cavity squamous cell carcinoma (OCSCC) is a highly prevalent surgically-treated subset of head and neck cancer with frequent recurrence and poor survival. Immunotherapy has demonstrated efficacy in recurrent/metastatic head and neck cancer, but has not been validated in the neoadjuvant presurgical setting. Methods: A Simon two stage design was used in this single-arm, Phase II clinical trial with a preplanned analysis after completion of stage one. The first stage included 9 patients with stage II-IVA OCSCC who received 3-4 biweekly doses of 3mg/kg Nivolumab (anti-programmed death 1 (PD-1)) followed by definitive surgical resection for cure. The primary endpoint was overall response rate to treatment. Secondary endpoints were safety and feasibility. Results: Presurgical Nivolumab therapy resulted in an overall response rate of 44% (95% CI: 14-78%) with four patients having >30% reduction in tumor size consistent with partial response. An additional patient had stable disease while the remaining four patients progressed through treatment. Neoadjuvant Nivolumab was not associated with delays in definitive surgical treatment. There were no grade 3-4 adverse events and no treatment interruptions. At median follow up of 10 months (2-16), there were 4 recurrences in 3 patients and one death. Objective response by RECIST 1.1 criteria on interval imaging predicated 3-4 adverse events and no treatment interruptions. At median follow up of 33 days after start of immunotherapy) with no unexpected wound healing problems. In both groups, 4 patients (67%) experienced immune-related toxicity. Overall, in these 12 patients, neoadjuvant ipilimumab + nivolumab resulted in an overall response rate of 44% (95% CI: 14-79%) with 30% reduction in tumor size consistent with partial response. No patients with nCR had a recurrence at follow-up of 11 months. Preliminary data (mutational load will be added) show increased H7-B3 gene expression in non-responders before treatment, and increased endothelial cell and NK cell gene expression in responders post-treatment. Overall, in these 12 patients, neoadjuvant ipilimumab + nivolumab resulted in a significant increase in responder-related gene expression when compared to nivolumab only, irrespective of treatment response.

Conclusions: Neoadjuvant presurgical PD-1 blockade is associated with encouraging response rate and demonstrates feasibility and safety for OCSCC. Clinical trial information: NCT03021993.

2575 Poster Session (Board #219), Sat, 8:00 AM-11:00 AM
Feasibility and toxicity of neoadjuvant nivolumab with or without ipilimumab prior to extensive (salvage) surgery in patients with advanced head and neck cancer (the IMCISION trial, NCT03003637). First Author: Charla L. Zuur, Netherlands Cancer Institute (NKI-AVL), Amsterdam, Netherlands

Background: surgery w/o adjuvant radiotherapy (RT) for (recurrent) advanced head and neck squamous cell carcinoma (HNSCC) results in 30-50% 5-year OS, indicating the need for novel treatment options. In recurrent metastatic HNSCC nivolumab nearly tripled the 2-year OS. Aiming at improving clinical outcome in advanced HNSCC in a curative setting, we tested the feasibility of nivolumab ± ipilimumab neoadjuvant to salvage surgery w/o RT. Methods: investigator-initiated phase-II/II trial to assess feasibility of neoadjuvant nivolumab monotherapy (240 mg in week 1 & 3: arm-A) or in combination with ipilimumab (1 mg/kg in week 1: arm-B) before surgery (± week 5) w/o RT for advanced HNSCC. Results: 12 patients were included (3-design, both arms) in phase-II of this study; 71/10 patients had pre-existent moderate-to-severe comorbidities (ACE-27). All patients were HPV negative. All patients received surgery as planned (25-33 days after start of immunotherapy) with no unexpected wound healing problems. In both groups, 4 patients (67%) experienced immune-related toxicity. Overall, in these 12 patients, neoadjuvant ipilimumab + nivolumab resulted in an overall response rate of 44% (95% CI: 14-79%) with 30% reduction in tumor size consistent with partial response. No patients with nCR had a recurrence at follow-up of 11 months. Preliminary data (mutational load will be added) show increased H7-B3 gene expression in non-responders before treatment, and increased endothelial cell and NK cell gene expression in responders post-treatment. Overall, in these 12 patients, neoadjuvant ipilimumab + nivolumab resulted in a significant increase in responder-related gene expression when compared to nivolumab only, irrespective of treatment response.

Conclusions: neoadjuvant ipilimumab + nivolumab can safely be administered prior to major surgery for advanced HNSCC. Efficacy is promising and will be further evaluated in the phase-II trial continuation. Clinical trial information: NCT03003637.

2576 Poster Session (Board #220), Sat, 8:00 AM-11:00 AM
Effect of exonic microsatellite instability of B2M on the predictability of MSI/dMMR for immunotherapy. First Author: Jia Wei, The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China

Background: Microsatellite instability/mismatch repair deficiency (MSI/dMMR) are the main biomarkers for immunotherapy. Cases of acquired resistance to ICI treatment caused by the inactivation of microsatellite genes such as β-2-macroglobulin (B2M) whose product is critical to antigen presentation. MSI instability/mismatch repair deficiency (MSI/dMMR) for immunotherapy. Effect of exonic microsatellite instability of B2M on the predictability of MSI/dMMR for immunotherapy

Methods: NGS test confirmed concurrent mutation in B2M for a MSI-H CRC patient with primary resistance to forth-line anti-PD1 treatment. In addition, NGS test confirmed concurrent mutation in B2M for a OCSCC who received 3-4 biweekly doses of 3mg/kg Nivolumab (anti-programmed death 1 (PD-1)) followed by definitive surgical resection for cure. The primary endpoint was overall response rate to treatment. Secondary endpoints were safety and feasibility. Results: Presurgical Nivolumab therapy resulted in an overall response rate of 44% (95% CI: 14-78%) with four patients having >30% reduction in tumor size consistent with partial response. An additional patient had stable disease while the remaining four patients progressed through treatment. Neoadjuvant Nivolumab was not associated with delays in definitive surgical treatment. There were no grade 3-4 adverse events and no treatment interruptions. At median follow up of 10 months (2-16), there were 4 recurrences in 3 patients and one death. Objective response by RECIST 1.1 criteria on interval imaging predicated 3-4 adverse events and no treatment interruptions. At median follow up of 33 days after start of immunotherapy) with no unexpected wound healing problems. In both groups, 4 patients (67%) experienced immune-related toxicity. Overall, in these 12 patients, neoadjuvant ipilimumab + nivolumab resulted in an overall response rate of 44% (95% CI: 14-79%) with 30% reduction in tumor size consistent with partial response. No patients with nCR had a recurrence at follow-up of 11 months. Preliminary data (mutational load will be added) show increased H7-B3 gene expression in non-responders before treatment, and increased endothelial cell and NK cell gene expression in responders post-treatment. Overall, in these 12 patients, neoadjuvant ipilimumab + nivolumab resulted in a significant increase in responder-related gene expression when compared to nivolumab only, irrespective of treatment response.

Conclusions: neoadjuvant ipilimumab + nivolumab can safely be administered prior to major surgery for advanced HNSCC. Efficacy is promising and will be further evaluated in the phase-II trial continuation. Clinical trial information: NCT03003637.

2577 Poster Session (Board #221), Sat, 8:00 AM-11:00 AM
Immune-mediated colitis after resumption of immune checkpoint inhibitor therapy. First Author: Hamzah Abu-Sbeih, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Immune checkpoint inhibitor (ICI) therapy is often suspended because of immune-mediated diarrhea and colitis (IMDC). We examined the recurrence rate and risk factors for IMDC after ICI resumption. Methods: This retrospective multicenter study examined patients who resumed ICI therapy after improvement of IMDC between 1/2010 and 11/2018. Univariate and multivariate logistic regression analyses assessed the association of clinical covariates and IMDC recurrence. Results: Of the 167 patients in our analysis, 32 resumed an anti-CTLA-4 agent and 135 an anti-PD-1/L1 agent. The median duration from IMDC to restart of ICI treatment was 49 days (IQR, 23-136). IMDC recurred in 57 (34%) patients overall (44% of those resuming an anti-CTLA-4 agent and 32% resuming an anti-PD-1/L1 agent); 47 of these patients (82%) required immunosuppressive therapy for recurrent IMDC (Table). The median duration from ICI resumption to IMDC recurrence was 53 days (IQR 22-138). On multivariate logistic regression, patients who received anti-PD-1/L1 therapy at initial IMDC had a higher risk of IMDC recurrence (odds ratio (OR), 3.45, 95% CI, 1.59-7.69; P=0.01). Risk of IMDC recurrence was higher for patients who required immunosuppression for initial IMDC (OR, 3.22, 95% CI, 1.08-9.62; P=0.02) or had longer duration of IMDC symptoms in the initial episode (OR, 1.01; 95%CI, 1.00-1.03; P=0.03). Risk of IMDC recurrence was lower for those who resumed anti-PD-1/L1 therapy than for those who resumed anti-CTLA-4 therapy (OR, 0.30, 95% CI, 0.11-0.81; P=0.02). Conclusions: One-third of patients who resumed ICI treatment after IMDC experienced recurrent IMDC. IMDC recurrence was less frequent after resumption of anti-PD-1/L1 than after anti-CTLA-4. Characteristics of current IMDC based on resumed ICI therapy.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: ICIs targeting PD-1/L1 and/or CTLA-4 have activity against many different cancers. We and others have previously shown that a higher TMB, a surrogate for an increased number of expressed tumor neoantigens, is an important biomarker for response to anti-PD-1/L1 monotherapy. Whether the relationship between the TMB and response to ICIs extends beyond anti-PD-1/L1 is unknown. Methods: TMBs for 9801 PDAC and 1030 CRC tumor types for which TMB has been described using a genomic profiling assay performed by Foundation Medicine. We conducted searches of MEDLINE (from Jan 1, 2010 to Jan 20, 2019), as well as abstracts presented at ASCO, ESMO, AACR Annual Meetings 2010-2018 to identify the objective response rate (ORR) for anti-PD-1/L1, anti-CTLA-4 and combination anti-PD-1/L1 plus anti-CTLA-4, in each of these cancer types. We pooled the response data from the largest published studies that evaluated the ORR. We excluded studies that; enrolled < 10 evaluable patients, investigated ICI therapies in combination with other agents, and studies that selected patients based on immune-related biomarkers. Across tumor types, enrolled in 4 dose escalation cohorts (P 400, 600 and 800mg/d: 3 pts each; P 1200mg/d: 2 pts) and expansion cohorts was completed in January 2019. Results: Statistical significance (n = 1377, r²= 0.2606, p = 0.1086). The additional ORR benefit of adding a CTLA-4 inhibitor to anti-PD-1/L1 therapy increased with increasing TMB. In tumor types with a lower TMB (< 10 mutations/MB), combined ICI therapy led to an average improvement of 5.5% in ORR over PD-1/L1 monotherapy, versus 21.8% ORR improvement in high TMB tumors (≥10 mutations/MB). Conclusions: A strong relationship exists between TMB and clinical activity of both PD-1/L1 monotherapy and combination ICIs with PD-1/L1 plus CTLA-4. The clinical benefit of adding anti-CTLA-4 to PD-1/L1 is greatest in high TMB tumors and limited to low TMB tumors.

Background: There have been important changes in early drug development units with an unprecedented increase of immune-oncology (IO) trials. Currently at the Vall d’Hebron Institute of Oncology (VHIO) close to 50% of our Phase 1 trials (Ph1t) portfolio includes IO drugs, while from 2011 to 2015 most (80%) of our Ph1t assessed targeted agents (TA). We wanted to investigate whether this shift had a positive impact on patient (pts) outcome. Methods: We performed a retrospective analysis of the pts treated with IO and TA at VHIO Ph1t Unit from Jun’11 to May’18. Only pts treated with IO in ≥ 28d line were included (and without an approved IO therapy as per standard-of-care) and those with TA classified as tiers II-III by the ESMO scale for clinical actionability of molecular targets ESCAT (which also represents unapproved indications). The aim of this study was to compare overall survival (OS) for the two cohorts. Given the non-randomized nature of the study a propensity score weighting (PSW) was used to control for selection bias in treatment effect estimation. Results: Out of 545 eligible pts, 281 (51.5%) received IO and 264 (48.5%) IO, with unadjusted median OS (mOS) of 7.7 months (m) and 9.2m, respectively. In univariate analysis, OS was associated with tumor type, number of previous treatment lines, regimen (monotherapy vs combination), and clinical-laboratory prognostic factors (Vioscore: albumin < 3.5 g/dL; LDH > upper limit of normal; neutrophil [leukocytes minus neutrophils] ratio (dNLR) > 3; more than 2 sites of metastasis; and presence of liver metastasis) (p < 0.05). After adjusting for these factors in a PSW model, the IO group showed statistically significant longer OS with HR = 0.75 (95%CI 0.65 – 0.86. p = 0.0001). The In a stratified analysis by tumor type we found no significant heterogeneity in the relative benefit of IO over TA. Conclusions: In real world data from our Ph1t population, treatment with IO was associated with longer OS than treatment with TA, even after adjusting for known prognostic factors and treatment selection biases. These results suggest that the likelihood of patient benefit with IO therapies in Ph1t is increasing.

Background: Targeting tumor associated macrophages is an emerging strategy to increase the responsiveness of PDAC and CRC to anti-PD/L1. Pexidartinib (P) is an orally active, small-molecule kinase inhibitor that targets the colony-stimulating factor-1 receptor (CSF1R) on macrophages. Methods: Adult pts with advanced/ metastatic PDAC or CRC were treated with a fixed dose of D (1500mg q4w, IV) and ascending doses of P (200, 600, 800 and 1000mg/d, orally). Dose escalation was conducted according to a Likelihood Continual Reassessment Method with a 28-day window to evaluate dose-limiting toxicity (DLT), a stopping rule adverse dose escalation termination in case of a high probability (> 90%) for the next 6 pts to be assigned to the same dose. Following the determination of RP2D, 14 pts with PDAC and 14 pts with CRC who consented to serial tumor biopsies were enrolled in expansion cohorts to assess preliminary anti-tumor activity and biomarkers. Results: 19 pts (12M, 7F, median age, 56 y [range, 43-76y]) were enrolled in 4 dose escalation cohorts (P 400, 600 and 800mg/d: 3 pts each; P 1000mg/d: 1 pt). Pharmacokinetic analyses showed dose-dependent increase in the exposure of P from 400 to 1000 mg. Two DLTs (AST/ALT elevations including one with bilirubin increase) were seen at dose level P 1000mg/d. The most frequent (> 2pts) AEs were: fatigue, maculopapular rash/pruritus/dry skin, hair color changes, arthralgia, edema (periorbital), limanparesis, chills/fear. P has potential to be used as a bridge in non-responders. Conclusions: The additional ORR benefit of adding a CTLA-4 inhibitor to anti-PD-1/L1 therapy increased with increasing TMB. In tumor types with a lower TMB (< 10 mutations/MB), combined ICI therapy led to an average improvement of 5.5% in ORR over PD-1/L1 monotherapy, versus 21.8% ORR improvement in high TMB tumors (≥10 mutations/MB). Conclusions: A strong relationship exists between TMB and clinical activity of both PD-1/L1 monotherapy and combination ICIs with PD-1/L1 plus CTLA-4. The clinical benefit of adding anti-CTLA-4 to PD-1/L1 is greatest in high TMB tumors and limited to low TMB tumors.
2582  Poster Session (Board #226), Sat, 8:00 AM-11:00 AM
High prevalence of IBD-associated genetic variants in patients (pts) with immune checkpoint inhibitor (ICI) enteritis/colitis. First Author: Shilpa Grover, Brigham and Women’s Hospital, Boston, MA.

Background: IBD is a frequent toxicity of ICI therapy but there is paucity of data on risk factors. Specific serological markers and genetic polymorphisms have been associated with inflammatory bowel disease (IBD) (ulcerative colitis, Crohn’s disease). However, the prevalence of these markers in pts with ICI colitis is unknown. We performed a pilot study to determine the prevalence of IBD-associated genetic and serologic biomarkers in pts with ICI colitis.

Methods: Cancer pts with histologically confirmed ICI enteritis/colitis and no history of IBD underwent commercial IBD panel testing. The panel included 4 genetic markers (ATG16L1, NXXK2–3, ECDM, STAT3), 8 serological markers (anti-A4-IgA, anti-A4-IgA-X, anti-CbIr1, anti-OmpC, ASCaIgA, ASCa-IgG, PANCA, ANCA), and 5 inflammatory markers (vaso- endothelial growth factor (VEGF), intracellular adhesion molecule 1 [ICAM-1], vascular cell adhesion molecule 1 [VCAM-1], C-reactive protein, serum amyloid A [SAA]). Clinical testing on serum samples was performed by Prometheus Laboratories (San Diego, CA). Results: Of 15 cancer pts with biopsy confirmed ICI colitis, 10 (67%) were homzygous for 1 or more of 4 genetic markers. The remaining 5 pts were heterozygous for 1 or more of the genetic markers. One or more serologic markers associated with IBD were elevated in 7/15 (47%) pts. Serum reactivity was noted for ASCa-IgA (1/15, 7%), ASCa-IgG (1/15, 7%), anti-OmpC (3/15), 20%, anti-CbIr1 IgG (2/15, 13%), anti-A4-IgA (1/15, 7%), and ANCA (2/15, 13%). One or more inflammatory markers were elevated in 13/15 (88%) pts. Elevations in VEGF, VCAM-1, ICAM-1, and SAA were noted in 2 (13%), 8 (53%), 8 (53%), and 11 (73%) pts, respectively. Only 6 (40%) pts had elevations in CRP levels despite the presence of active inflammation on biopsy. The IBD panel was reported as being consistent with Crohn’s disease in 2 pts, ulcerative colitis in 1 pt and indeterminate colitis for type with IBD.

Conclusions: In this pilot study, all pts with ICI colitis, were either homzygous or heterozygous for two or more high risk IBD alleles. If validated, such testing may prospectively identify pts at risk for developing ICI colitis.

2583  Poster Session (Board #229), Sat, 8:00 AM-11:00 AM
Measuring the long-term “tail of curve” survival benefits in oncology trials: A comparison of the ASCO Value Framework and the ESMO Magnitude of Clinical Benefit Scale. First Author: Louis Everest, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada.

Background: Recently, anti-cancer agents have generated excitement due to their capacity to preserve long-term survival in some patients, represented by a “tail of the survival curve”. However, as traditional measures of clinical benefit may not accurately capture long-term survival, amendments to frameworks was poor (kappa: 0.01; p = 0.50). The ASCO-VF v2 bonuses more often than ESMO-MCBS version 1.1 (v1.1) and 45 did not have irAEs after a minimum of one year of treatment. In this pilot study, all patients with ICI colitis, were either homzygous or heterozygous for two or more high risk IBD alleles. If validated, such testing may prospectively identify pts at risk for developing ICI colitis.

2584  Poster Session (Board #228), Sat, 8:00 AM-11:00 AM
Overcoming genetically based resistance mechanisms to PD-1 blockade. First Author: Davis Yun Toorejian, University of California Los Angeles Jonsson Comprehensive Cancer Center, Los Angeles, CA.

Background: Mechanism-based strategies to overcome resistance to anti-PD1 therapy are urgently needed. Using CRISP/RCaSt genome editing tools, we developed acquired resistant models through JAK1/2 and B2M loss of function (LoF) mutations in human melanoma cell lines and in the murine MC38 colon carcinoma, known for high mutational load and good response to anti-PD-1. We hypothesized that the downstream activation of the IFN-e receptor pathway or the activation of natural killer (NK) cells would overcome this resistance.

Methods: We studied signaling changes in four human cell lines (parental and LoF) exposed to IFN-gamma using RNAseq. In addition, we analyzed the in vivo antitumor activity in MC38 variants with anti-PD1 and characterized the tumor microenvironment (TME) using CyTOF (Cytometry by Time-of-Flight). Finally, we tested strategies to overcome resistance mechanisms with SD-101 (TLR-9 agonist) and bempegaldesleukin (NKT-214, CD-122 biased agonist) with the extent of CD8 and NK1.1 depletion. Results: RNAseq differential gene expression analysis showed that the IFN-gamma-induced expression of antigen presenting machinery, IFN-gamma signaling and chemokines (CXCL9/10) was lost in JAK1/2-LoF human melanoma cell lines. The significant antitumor activity of anti-PD-1 against MC38 parental cell line was lost in JAK1/2 and B2M LoF sublines, and CyTOF analysis revealed that anti-PD-1 therapy was unable to increase tumor CD8+ T-effectors in these LoF tumors. The intratumoral administration of SD-101 (50 μg/injection qdx3wks) was able to overcome local resistance even in non-injected sites in JAK1/2 and IFNAR-type-I LoF tumors, and systemic administration of bempegaldesleukin (0.8 mg/kg, qdx2, i.v.) was able to overcome resistance in B2M LoF with significantly increased survival (Table). Depletion studies showed complete abrogation of antitumor responses in mice with anti-NK1.1, anti-JAK1 LoF and B2M LoF, and partial abrogation with anti-NK1.1. our findings support the testing of these rational mechanistic strategies in patients with a PD1 resistance.
2587 Poster Session (Board #231), Sat, 8:00 AM-11:00 AM
Real-world outcomes of underrepresented patient populations treated with immune checkpoint inhibitors (ICIs): African American descent, poor ECOG performance status (PS) or chronic viral infections

**Background:** ICIs have now become standard of care for treatment of multiple malignancies. However, patients (pts) who are African American descent (AA), have a poor ECOG performance status (PS) or chronic viral infections (human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C (HCV)) were underrepresented in early clinical trials. Despite these gaps in data in these pt populations is not well reported.

**Methods:** We performed a retrospective analysis of pts treated with ICIs (anti-PD(L)-1, anti-CTLA-4, or combination ICIs) across five MedStar Health hospitals from January 2011 to April 2018. Investigator-assessed best responses were noted. CTCAE v4.03 was used to capture immune-related adverse events (irAEs).

**Results:** We identified 765 pts treated with 829 unique ICIs therapies across different malignancies. A total of 203 AA pts, 178 pts with a pre-treatment ECOG PS ≥2, 213 pts with HIV, and 50 pts with HBV/HCV were noted. Any grade and grade ≥ 3 irAEs in the HIV cohort were 24% and 10% with an ORR of 29%. Any grade and grade ≥ 3 irAEs in the HBV/HCV cohort were 20% and 4%. Similar trends were seen in the subset of patients with grade 3 irAEs in the AA cohort were 27% and 8%, respectively. The ORR in pts with ECOG PS ≥2 was 14%. Any grade and grade ≥ 3 irAEs in this cohort were 30% and 4%. Smoking and gender were both in the ORR. In the HIV cohort, the NSCLC treated with anti-PDL1 monotherapy (Table). Outcomes of NSCLC pts treated with anti-PDL-1 monotherapy. **Conclusions:** ICI therapy was not associated with any new safety signal in the above underrepresented populations. Prospective studies are needed to validate this data.

<table>
<thead>
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<th>Cohorts (N)</th>
<th>ORR (N)</th>
<th>Any grade irAEs (N)</th>
<th>Grade ≥ 3 irAEs (N)</th>
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<td>Entire cohort (232)</td>
<td>21% (44/214*)</td>
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<td>10% (22)</td>
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<tr>
<td>African American (102)</td>
<td>19% (18/94*)</td>
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<td>16% (10/64*)</td>
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</tr>
</tbody>
</table>

*Response evaluable patients.

2587 Poster Session (Board #233), Sat, 8:00 AM-11:00 AM

**First Author:** Xiaodong Jiao, Department of Medical Oncology, Zhejiang Hospital, Second Military Medical University, Shanghai, China

**Background:** Tumor mutation burden (TMB), calculated by whole-exome sequencing (WES) or large NGS panels, has an important association with immunotherapy responses. Elucidating the underlying biological mechanisms of high TMB might help develop more precise and effective means for therapy and immunotherapy response prediction. Meanwhile, the landscape of TMB across different cancer types and its association with other molecular features have not been well investigated in large cohorts in China.

**Methods:** Cancer patients whose fresh tissue (n = 1556), formalin-fixed, paraffin-embedded (FFPE) specimen (n = 1794), and pleural fluid (n = 84) were profiled using 295- or 520-gene NGS panel. The association of the TMB status with a series of molecular features and biological pathways was interrogated using bootstrapping.

**Results:** TMB, measured by 295- or 520-cancer-related gene panels, were correlated with WES TMB based on in silico simulation in the TCGA cohort. We compared the TMB landscape across 11 cancer type groups, were found the highest average TMB in lung squamous cell carcinoma, whereas the lowest TMB was established in sarcoma. High microsatellite instability, DNA damage response deficiency, and homologous recombination repair deficiency indicated significantly higher TMB. The independent predictive power for TMB of twenty-six biological pathways was tested in 10 cancer groups. Cox signaling pathway most commonly correlated with low-TMB, significant association was identified in four cancer groups. In contrast, no pathway was significantly correlated with high-TMB in more than two cancer groups. Overall, we discovered that the underlying pathways which may be the main drivers of TMB status varied greatly and sometimes had an opposite association with TMB across different cancer types. Moreover, we developed a 14- and 22-gene signature for TMB prediction for LUAD and LUSC, respectively, with only 10 genes shared by both signatures, indicating a histology-specific mechanism for driving high-TMB in lung cancer. **Conclusions:** The findings extended the knowledge of the underlying biological mechanisms for high TMB and might be helpful for developing more precise and accessible TMB assessment panels and algorithms in more cancer types.

2588 Poster Session (Board #232), Sat, 8:00 AM-11:00 AM
Intra and perinodular CT delta radiomic features associated with early response to predict overall survival (OS) in immunotherapy-treated non-small cell lung cancer (NSCLC). A multi-site multi-agent study

**First Author:** Prateek Prasanna, Case Western Reserve University, Cleveland, OH

**Background:** None of the current biomarkers for predicting response to checkpoint inhibitors (ICI) for advanced NSCLC are associated with long-term benefits, such as improved OS. In this multi-agent (nivolumab, pembrolizumab, or atezolizumab) multi-site study (Cleveland Clinic, Univ. of Pennsylvania), we demonstrate that changes in computer-extracted textural parameters from within and around 30 mm outside the nodules, between baseline and post-treatment CT following ICIT correlare with RECIST-derived responses, and are prognostic of OS. **Methods:** CT scans from 139 NSCLC patients both pre- and post- 2-3 cycles of ICIT were acquired from 2 sites. Patients with objective response/stable disease per RECIST v1.1 were defined as ‘responders’, and those with progressive disease were ‘non-responders’. The cohort was divided into a discovery (D1 = 50) and two validation sets (D2 = 62, D3 = 27), 454 intranodular texture (IT) features, and 7426 perinodular features (PT) were extracted from the temporalscans. Relative differences were computed to yield a set of ‘delta-radiomic’ descriptors. In D1, 8 features that evolved the most between baseline and post-treatment CT, and performed the best in in silico responders, were determined. These were then used with a Linear Discriminant Analysis classifier to identify the responders from the non-responders. We then computed a radiomic risk score (RRS) system and tested its prognostic ability in assessing differences in OS. **Results:** A combination of 5 IT, 3 PT delta radiomic features yielded an AUC of 0.88 (0.78 in D1 and a corresponding AUC = 0.85 and 0.81 in D2 and D3, respectively. Multivariable survival metrics are shown in Table. **Conclusions:** Delta-radiomic features, both from inside and outside the nodules, could be used to identify patients likely to derive clinical benefit from ICIT (eg. OS) beyond anatomic response.
Background: Overall response rates to immune checkpoint inhibition (ICI) are <50% even in TMB-high patients (e.g. Checkmate-227), suggesting other mechanisms of immune escape exist beyond expressing checkpoints. At least 18% of somatic-specific exonic DNA variants are not expressed in mRNA (Rabizadeh, 2018), yet the selection criteria for which variants to silence remains unclear. We sought to determine if immunogenicity of variants affects their suppression. Methods: Somatic-specific single-nucleotide variants (SNVs) were identified from paired tumor/normal whole-exome sequencing (WES), and annotated as expressed if observed in >2 RNAseq reads. MHCI binding affinity for 9-mer neoepitope peptides resulting from said SNVs were predicted using NetMHC within presented HLA-types. Cases with >200 non-synonymous exonic mutations were designated as TMB-high in accordance with Rizvi et al, 2015. Tumor immune activity was inferred by RNAseq expression of 6 checkpoint/TME markers, as well as by estimating immune infiltration using RNAseq deconvolution of immune genesets (Binda et al 2013). Significant association between TMB, neoantigen-load, expressed neoepitope binding affinities, and immune activity were analyzed. Results: Within a clinical database of 1,363 cases with T/N/R sequencing, a total of 147,015 potential neoepitopes were identified. A small but significant enrichment was observed for silencing neoepitopes that are predicted to bind MHCI (OR = 1.22, p = 2.4e-78 one-sided Fishers test). The silencing rate was similar between the 17% of patients with high TMB vs others, but was increased in 35% of all patients with high inferred immune infiltration (N = 490, OR = 1.30, p = 1.8e-31). A further silencing enrichment was observed in 19% of all patients displaying high immune activity but low PD-L1 expression (N = 263, OR = 1.44, p = 4.0e-45). Conclusions: We observe significant preferential silencing of MHCI binding neoepitopes. Specifically, when tumor infiltrating immune cells are activated, silencing neoepitopes may be an alternative to checkpoint expression for avoiding an immune cascade. Patients with TILs and silenced neoepitopes may benefit from epigenetic priming therapy prior to ICI therapy.

Association of an inflammatory gene signature with CD8 expression by immunohistochemistry (TIA-GEP) in multiple tumor types. First Author: Peter M Szabo, Bristol-Myers Squibb, Princeton, NJ

Background: A multiparameter tumor inflammation assay based on gene expression profiling (TIA-GEP) can extend the utility of IHC to interrogate the tumor microenvironment (TME). Using CD8 expression assessed by IHC (CD8-IHC) as a surrogate for inflammation, statistical modelling was used to develop a specific gene signature on the TIA-GEP panel to predict CD8-IHC. The correlation between TIA-GEP and CD8-IHC and the prevalence of inflammation were explored across multiple tumor types. Methods: Levels of inflammation were measured by CD8-IHC and TIA-GEP on 1778 procured samples across 12 tumor types. Quality control metrics involved sample input quality, technical errors, and inter-variability. Generalized linear models were used to identify an inflammation score that predicts the CD8-IHC score in melanoma and SCCHN tissue. The predictive accuracy of this signature was also examined in 10 additional tumor types. Results: Assessment of TME inflammation by CD8-IHC was consistent with that observed by TIA-GEP in multiple tumor types. The range of inflammation varied across different tumor types, with relatively lower inflammation range and scores in SCLC, ovarian, and prostate cancers, and higher values in NSCLC, melanoma, SCCHN, and gastric cancers. \( R^2 \) x 100 values reflecting percent variation in CD8-IHC associated with TIA-GEP ranged from 62.4% to 79.2% (\( P < 0.0001 \)) for all tumor types except prostate cancer (32.5%). Low correlation in prostate cancer may be a result of low prevalence of inflammation by CD8-IHC. Estimated linear regression slopes between CD8-IHC and TIA-GEP ranged from 0.74 in SCLC to 1.27 in gastric cancer. Conclusions: The results suggest that the inflammation signature is a robust potential diagnostic tool predicting inflammation in the TME. The inflammation signature not only correlates with CD8-IHC for multiple tumor types, but also leverages the alternative benefits associated with TIA-GEP, which include information related to tumor inflammation-associated biomarkers and flexibility in exploring the value of other genomic signatures.

Can serum IL-6 levels predict sarcopenia and poor outcome in relapsed/refractory gynecologic cancer patients? First Author: Tomoyuki Yoshikawa, Department of Clinical Oncology, National Defense Medical College Hospital, Tokorozawa, Japan

Background: Cancer cachexia occurs in more than half of cancer patients and can be the primary cause of death for at least 20% of all patients. Cancer cachexia also lowers quality of life in cancer survivors due to a severe loss of skeletal muscle mass. Although a multitude of cytokines have been implicated in facilitating a cachectic state, the correlation of serum IL-6 and cancer-induced muscle wasting in gynecologic cancer patients has not been elucidated. Methods: The correlation between serum level of IL-6 and skeletal muscle volume in the patients with gynecologic cancers that received multiple lines of therapy was retrospectively evaluated. We used the psoas muscle index (PMI: cm2/m2), the psoas major muscle area at the fifth lumbar level divided by the height squared, measured using digital axial CT images, for the value of skeletal muscle volume. The level of IL-6 cut-off for elevation was defined as more than 12.0 pg/mL. The comparison of the survival distributions from the day of IL-6 measurements was made using a log-rank test. Results: A total of 74 cases were assessed for the serum IL-6 and PMI. 32 cases with different cancers, 24 cases with endometrial cancers, 13 cases with cervical cancers, and 5 patients with others. The group with elevated IL-6 were associated with the lower PMI (t-test, \( p = 0.0154 \)). The patients with IL-6 elevation had significantly worse survival compared with those with normal IL-6 (1y-OS; 31% vs. 80%, \( p < 0.0001 \)). In 28 patients with more than two point measurements of IL-6, the patients with the decrease to the level of IL-6 cut-off had favorable survival compared with those without the decrease (6m-OS; 100% vs. 52%, \( p = 0.0069 \)). Conclusions: Serum level of IL-6 could be a sentinel biomarker for cancer-induced sarcopenia in the patients with gynecologic cancers. Additionally, IL-6 could be a biomarker to determine further continuation of aggressive chemotherapy for the patients that had received multiple lines of chemotherapy.
2595 Poster Session (Board #239), Sat, 8:00 AM-11:00 AM
Evaluation of tumor microenvironment and biomarkers of immune check- 
point inhibitor (ICI) response in metastatic renal cell carcinoma (mRCC).
First Author: Jason Zhu, Department of Medicine, Duke University School of Medicine, Durham, NC

Background: ICIs are now standard of care for mRCC; however, there are few biomarkers to predict ICI response. Recent data from atezolizumab/ bevacizumab trials in mRCC suggest tumors with high T\text{\textsuperscript{IL}}/PD-L1+are more likely to respond to ICI. Here, we use two gene panels as well as other inflammation markers in the tumor microenvironment to correlate with ICI responses. Methods: This multicenter study evaluated 86 patients (pts) with mRCC treated with ICIs. FFPE tumor samples were evaluated by RNA sequencing for T\text{\textsuperscript{IL}} status. Two gene panels were analyzed: a T\text{\textsuperscript{IL}} Gene Panel (CD8, CD27, IFNG, GZMA, GZMB, PRF1, EDME, CXL9, CXL10, CXL11, CD274, CTLA4, FOXP3, TIGIT, IDO1, PSMB9, TAF1) and a 5-Gene panel (FOXP3, CCR4, KLRR1, ITK, and TIGIT) based on the gene expression pattern of tumors in our cohort. Objective response rates (ORRs, defined as CRs and PRs) were correlated with PD-L1 status (positivity was defined as \geq 1% TPS based on Dako 22C3 IHC assay), and TMB (0-10, 10-20, >20 mut/MB), and tumor inflammation (high CDB expression compared to a large reference population). Best responses to ICI was determined by an expert radiologist using RECIST 1.1 criteria. Inflamed tumor status, T\text{\textsuperscript{IL}} gene panel, 5-gene panel, PD-L1 status, and TMB were associated with ORR and tested using a chi-squared test with Yates’s continuity correction. Results: ORR was 50% (4/8) for PD-L1 positive pts and 14% (9/65) for PD-L1 negative pts (p = 0.042). The majority of tumors (9/12, 76%) with TMB >10/MB, 43% (5/12) were classified as T\text{\textsuperscript{IL}}+. ORR was 23% (10/43) in the T\text{\textsuperscript{IL}}+ cohort and 12% (5/43) in the T\text{\textsuperscript{IL}}- cohort (p = 0.256). ORR was 31% (14/45) in the 5-gene high cytokine and 2% (1/41) in the 5-gene low cytokine cohort (p = 0.001). Conclusions: TMB and tumor inflammation based on CD8 and inflammatory cytokines have the potential to influence objective response rates (ORRs) in mRCC treated with ICIs. Gene expression signatures provide a more comprehensive evaluation of the tumor microenvironment and may lead to better predictive biomarkers for ICI response than individual biomarkers such as PD-L1, TMB, or CDB expression.

2598 Poster Session (Board #242), Sat, 8:00 AM-11:00 AM
Application of artificial intelligence to predict a new class of novel synthetic lethal targets. First Author: Spyro Mousses, Systems Oncology, Scottsdale, AZ

Background: Synthetic lethal targets are proteins that are contextually vulnerable. Inhibitors of PARP1, for example, selectively produce a lethal phenotype in the context of cancer cells which have lost BRCA1 or BRCA2 function. As a high mutation rate is a hallmark of many cancers, targeting synthetic lethal interactions to selectively inhibit cancer cells with altered genetic backgrounds may increase the specificity and efficacy of therapeutics. Recently, clinical trials have targeted synthetic lethal pairs such as EGFR and BRAF, TP53 and BCL2, and PTEN and CHD1. Previous attempts to identify synthetic lethal targets have relied on empirical results from published studies of biological pathways perturbed in cancer cells. Developing strategies to rapidly identify synthetic lethals by combining multiple experimental and computational approaches would result in a new class of potential cancer drug targets beyond the existing efforts that rely on single experimental or computational methods alone. Methods: Here we present Expansive AI, an artificial intelligence augmented knowledge network that enables rapid hypothesis generation for accelerated discovery research. Using a purpose-built, hypergraph database of massive, integrated genomic and biomedical data, we can query all synthetic lethals and their component genes, as well as a wealth of data related to these genes. The database of biomedical data includes 11,000+ cancer genomes from TCGA, prior knowledge resources such as gene ontology and pathway resources, and experimental data including chemical and protein interaction and patient data. The hypergraph’s architecture allows for linking and nesting data, enabling efficient extraction of biologically-relevant features. Results: Using these features, a neural network classified 540 new candidate pairs that have previously not been reported. The candidate pairs were filtered to include only known oncogenes and least-studied genes. This produced a list of gene pairs which may represent the most novel class of synthetic lethal target candidates identified to date. Conclusions: We highlight the results of this AI-based approach and discuss validation efforts of the predicted interactions in specific cancer contexts.

2599 Poster Session (Board #243), Sat, 8:00 AM-11:00 AM
A dose-finding study of the SMAC mimetic Debio 1143 when given in combination with avelumab to patients with advanced solid malignancies. First Author: Rosalyn A. Juergens, Juravinsky Cancer Centre, McMaster University, Hamilton, ON, Canada

Background: Second mitochondria-derived activator of caspase (SMAC) mimetics regulate apoptosis and modulate NFkB signaling which drives the expression of genes involved in immune and inflammatory responses. In patient (pt) tumors, Debio 1143 increased PD-1/PD-L1 expression and stimulating lymphocytes. In pre-clinical models, it synergizes in vitro and in vivo with PD1/PD-L1 checkpoint inhibitors (CPis). Methods: In a phase I study, using a mCRM model, avelumab (10 mg/kg i.v. on D1&15 q4w) was combined with escalating doses of Debio 1143 (100 mg/d to 250 mg/d orally, D1-10 & D15-24 q4w) to define the RP2D. Consenting adult pts with advanced solid tumors, normal organ function, and PS-ECOG = 0-1 were treated with N or P. Between Aug. 2015-Dec. 2018 were analyzed. Laboratory results were collected at baseline, 6 weeks (6-wk), and 12 weeks (12-wk) and correlated with the outcome. NLR and PLR were defined as absolute neutrophil and platelet count divided by lymphocyte count, respectively. NLR >5, PLR >200, and LDH levels > upper normal limit were considered high. Overall survival (OS) was defined as time from ICI start to death and Progression Free Survival (PFS) as time from start to progression disease or death for any cause. OS and PFS curves were estimated using the Kaplan-Meier method and compared with the log-rank test. Results: We included 71 consecutive NSCLC pts treated with N (75%) or P (25%). Baseline characteristics: median age 69 years (range 46- 
80), sex male 76%, squamous histology in 39%. PD-L1 expression (39/71): <1% in 20%, 1-49% in 45%, and \geq 50% in 35%. NLR >5 was associated with lower PFS and OS, with an increased predictive value over time (p =0.01 and p =0.009 at baseline and p =0.007 and p =0.001 at 12-wk, respectively). In contrast, NLR \leq 5 was associated with shorter PFS and OS (p =0.05 and p =0.004, respectively). Conclusions: Baseline evaluation of NLR, PLR and LDH levels is significantly associated with outcome in NSCLC treated with single agent ICIs. Moreover, dynamic changes of LDH levels at 12-wk significantly predicted outcome. These easy to determine parameters may have a place in the selection process of pts candidate for immunotherapy.

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2600 Poster Session (Board #244), Sat, 8:00 AM-11:00 AM

First-in-human (FIH) trial evaluating immune activation and safety of PIN-2 administered intravenously to patients with advanced solid tumors. First Author: Gary Bird, PhD, Incyte, Inc., Palo Alto, CA

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment; however, combining ICIs often results in increased immunosuppression and disease progression. PIN-2 is a novel immunomodulating agent derivatized from a transactivator (Tat) protein that stimulates innate immunity in vivo by promoting differentiation of peripheral blood monocytes into activated APCs linking the innate and adaptive immune systems resulting in endogenous T-cell priming against a multitude of tumor associated antigens untargeted by ICIs.

Methods: A FIH clinical trial was conducted in patients (pts) with extensively pretreated solid tumors to evaluate the pharmacodynamics (PD) and safety of PIN-2. 8 pts (2 men), mean age 62.7 (±7.9) years, and a median of 4.5 prior treatment lines, were enrolled in 2 Australian centers. 2 pts received 1 cycle of treatment and 6 received 2 cycles. Pts were given 300 μg of PIN-2 IV 3 times/wk for 2 wks followed by a 1 wk rest period. A 2nd cycle of treatment was offered based on pt and investigator preference. Plasma was collected at 6 and 24H post-infusion to evaluate immune activation. Th1 cytokines (TNF-α, IFN-γ, IL-12, CSF-2) were analyzed to assess PD activity. Results: A significant increase in TNF-α was seen 6H following PIN-2 infusion (p = 0.0142), demonstrating rapid onset of immune activation. There were no clear changes in the other parameters evaluated. PIN-2 was rapidly cleared from plasma, with mean T1/2 = 24.0 (8.07) min, Tmax = 1.06 (±0.66) min, Cmax = 77,500 (61,600) pg/mL, and AUC0-24H = 960,000 (493,000) pg/mL. 3 pts received treatment to ≥3 cancer types; 1 pt (a med/ped) exhibited transient infection (1, unrelated SAE of abdominal pain) and 1 for disease progression on day 12. Treatment related AEs were grade 1 and 2, and readily managed. There was a single unrelated gr 3 event (anemia) and no AEs > gr3. 2 pts developed anti-drug antibodies; however, these did not result in changes in PK. No post-treatment blood tests abnormal (≥2 months). Conclusions: PIN-2 was well tolerated and managed. There was a single unrelated gr3 event (anemia) and no AEs > gr3. 2 pts developed anti-drug antibodies; however, these did not result in changes in PK. No post-treatment blood tests abnormal (≥2 months). Conclusions: PIN-2 caused an early increase in TNF-α consistent with PD activity predicted by preclinical data. Further study alone and in combination with other agents in pts with advanced solid tumors is warranted. Clinical trial information: ACTRN12617001597381.

2602 Poster Session (Board #246), Sat, 8:00 AM-11:00 AM

Safety profile of INT230-6, a novel intratumoral (IT) formulation, during injection into a variety of refractory deep and superficial tumors with evidence of tumor regression and immune activation. First Author: Anthony B. El-Khoueiry, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA

Background: INT230-6 is comprised of cisplatin (CIS), vinblastine (VBL) and an amphiphilic penetration enhancer which facilitates dispersion throughout tumors and diffusion into cancer cells. In preclinical experiments, INT230-6 led to necrosis and recruitment of immune cells with high rates of complete responses of injected and bystander tumors. This abstract highlights the safety and early pharmacodynamic activity of this approach.

Methods: Patients with solid tumors that progressed on all standard treatments were enrolled. Dose escalation occurred by increasing number of tumors injected, loading per tumor, and total dose. INT230-6 was injected once every 2 weeks in multiple lesions for 5 sessions. Patients were monitored for safety and tolerability weekly. Pharmacokinetic (PK) samples and peripheral blood were collected for flow cytometry and circulating cytokines. Pre and on study biopsies are ongoing. Results: 28 patients (14 unique cancer types) received a median of 3 prior treatments were enrolled. Doses from 0.3 ml up to 80 ml of INT230-6 were given in single lesions with some patients receiving a total of 1.20 l (9.7mg VBL exceeding the IV VBL dose) without significant systemic absorption or typical cytotoxic adverse events. Ph analysis suggests that systemic exposure of VIN or CIS is ~10% of injected. No DLT’s or drug-related SAE’s reported. The most frequent adverse event was grade 1 or 2 pain at injected site. Superficial tumors showed signs of response including flattening, areas of necrosis and ulceration. Tumor reduction, apparent in in both injected and bystander tumors, may indicate an ablative effect. An increase > 30% in CTD T-cells was seen in the blood of 3/9 PD-IV patients. Conclusions: INT230-6 was safe and well tolerated in > 100 injections (28 patients) with encouraging activity and pharmacodynamic effects in advanced refractory tumors. Additional analysis of immune cells from on study biopsies will be presented. A new cohort will evaluate combination with an anti-PD1 antibody to understand if local tumor delivery can increase systemic antigen load, increase imnologic cell recognition and initiate a systemic immune response. Clinical trial information: NCT03585289.

2603 Poster Session (Board #247), Sat, 8:00 AM-11:00 AM

THOR-707: Using synthetic biology to reprogram the therapeutic activity of interleukin-2 (IL-2). First Author: Marcus E Milla, Synthorx Inc. Research & Development, La Jolla, CA

Background: Recombinant interleukin-2 (rIL-2) is approved immunotherapy in melanoma and renal cell carcinoma based on complete durable remissions. The anti-neoplastic properties of IL-2 are mediated by interactions with the beta-gamma chain (IL-2Rβγ) on naive CD8+ T cells, which lead to their expansion and differentiation into T effector and T memory cells directed against the tumor. However, the widespread use of IL-2 in oncology is limited by interaction with the high affinity IL-2 receptor alpha chain (IL-2Rα) on regulatory CD4+ T cells (Tregs), which leads to immunosuppression, and on innate lymphoid cells in the vascular endothelium, which leads to eosinophilic recruitment and activation, and the sometimes fatal complication of vascular leak syndrome (VLS). A rIL-2 biased toward IL-2βγ affinity with no IL-2Rα interaction could fill unmet needs in oncology. Methods: Using a synthetic biology platform, we have engineered THOR-707, a rIL-2 that contains a novel amino acid encoded in the IL-2 gene via a new DNA base pair (X-Y). The novel amino acid serves as a hook for site specific peptidoglycan that extends half-life, blocks IL-2Rα engagement and binds to the IL-2Rβγ. Results: In non-human primates, THOR-707 can be dosed to maximize the level of cytotoxic CD8+ T lymphocytes without elevation of VLS-inducing eosinophils. In murine tumor models, THOR-707 induced the expansion of peripheral and intratumoral CD8+ T cells without expansion of suppressive Tregs. Single-agent dose-dependent antitumor efficacy was observed in two syngeneic mouse models. In combination with a PD-1 inhibitor, survival of tumor-bearing mice was longer than either agent as monotherapy. Efficacy in tumor models was durable, suggesting activation of CD8+ memory T cell populations. Conclusions: THOR-707 is a reprogrammed, site-directed, single-regulated rIL-2 that changes the pharmacologic profile of IL-2, potentially providing a favorable risk-benefit profile. First-in-human studies are expected to begin this year evaluating THOR-707 as monotherapy and in combination with a PD-1 inhibitor. Based on preclinical evidence to-date, THOR-707 may potentially address existing and emerging unmet needs across multiple solid tumors.

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AB928, a novel adenosine receptor antagonist, combined with chemotherapy or AB122 (anti-PD-1) in patients (pts) with advanced tumors. Preliminary results from ongoing phase I/II studies. First Author: John D. Powery, Carolina BioOncology Institute, Huntersville, NC

Background: AB928, a selective, small-molecule A2A/A2B antagonist, potentially blocks the immunosuppressive effects of high adenosine concentrations in the tumor microenvironment. Preclinically, combining adenosine receptor inhibition with either chemotherapy or anti-PD-1 resulted in greater tumor control, suggesting AB928 may have additive activity when paired with either of these agents in cancer pts.

Methods: Three dose-escalation (3+3 design) studies are assessing the safety, pharmacokinetics (PK), pharmacodynamics, and clinical activity of increasing doses of AB928 (75, 150, 200 mg orally once daily) in combination with: standard pegylated liposomal doxorubicin in triple-negative breast cancer (TNBC) and ovarian cancer (OC), standard mFOLFOX in gastroesophageal cancer (GEC) and colorectal cancer (CRC), and AB122 (240 mg every 2 weeks) in various advanced tumors. Following identification of the recommended phase 2 dose of AB928 in combination with chemotherapy or AB122 in dose escalation, the following tumor cohorts may be expanded (15–40 pts/cohorts) to further test the combinations: TNBC and OC, GEC and CRC, and renal cell carcinoma. Results: As of 1 Feb 2019, 9 pts were treated across the 3 studies, and time on treatment ranged from 1-182 days (table). Overall, AB928 combination therapy was well-tolerated. Two pts underwent post-baseline disease assessment; both had stable disease. Preliminary data indicate that AB928 PK and adenosine receptor coverage in cancer pts are similar to what was previously assessed in healthy volunteers. AB122 PK and PD-1 coverage are equally unaffected by AB928 co-administration. Updated data, including biomarker data, will be presented at the meeting. Conclusions: Early results showed a favorable safety profile of AB928 combination therapy. All 3 studies are actively recruiting pts. Clinical trial information: NCT03719326; NCT03720678; NCT03629756.

Study in TNBC & OC (NCT02719326) Study in GEC & CRC (NCT03720678) Study in various tumors (NCT03629756)

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AB206

Bалцикафторида (a CXCR4-антигонд) + eribulina в HER2-негативной метастатической гормон-чувствительной рака молочной железы (МБС): Свойства выживаемости в процессе I фазы клинических исследований. Первый автор: Peter A. Kaufman, Breast Oncology, Division of Hematology/Oncology, Burlington, VT

Background: Bалцикафторида (B) является потенциальным антителом против CXCR4. Preclinische evidence suggests that disrupting CXCR4 dependent pathways prevent development of breast cancer metastases, increases the cytotoxic effect of chemotherapy and immunotherapy, and consolidates tumor cell evasion of the immune system. Encouraging preclinical and efficacy data were published recently from the ongoing Phase 1 trial investigating B + eribulina (E) in patients with HER2 negative MBC (Perenas S. et al. Lancet Oncol. 2018; 19: 812–24). The objective response rate, median progression free survival and median overall survival (OS) for the expanded cohort (EC) and the overall efficacy population (OEP) were 37.5% and 29.6%, 6.2 months and 4.5 months, and 18 months and 16.8 months, respectively. Here we report the 18 and 24 months landmark OS data from this trial.

Methods: This trial enrolled 56 patients with HER2-negative, CXCR4-positive MBC, previously treated with 1–3 chemotherapy regimens for MBC. A 3+3 dose escalation design was used, followed by an FC. All cohorts received E on days 2 and 9, and B on days 1–3 and 8–10 of 21 day cycles. The association between various baseline biomarkers and treatment outcomes including OS is currently being investigated in a multivariate analysis (MVA). Results: Landmark survival data for the trial are shown in the table. Clinical trial information: NCT03400985. Conclusions: As of 1 Feb 2019, 9 pts were treated across the 3 studies and time on treatment ranged from 1-182 days. Overall, B + eribulina combination therapy was well-tolerated. Two pts underwent post-baseline disease assessment; both had stable disease. Preliminary data indicate that B + eribulina PK and adenosine receptor coverage in cancer pts are similar to what was previously assessed in healthy volunteers. B + eribulina PK and PD-1 coverage are equally unaffected by B co-administration. Updated data, including biomarker data, will be presented at the meeting. Conclusions: Early results showed a favorable safety profile of B + eribulina combination therapy. All 3 studies are actively recruiting pts. Clinical trial information: NCT03719326; NCT03720678; NCT03629756.

Study in TNBC & OC (NCT02719326) Study in GEC & CRC (NCT03720678) Study in various tumors (NCT03629756)

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AB207

Салливартин метастатического рака молочной железы, используя масс-спектрометрию. Первый автор: David Roumanes, Immunoscape, Cambridge, MA

Background: Immunotherapy recent successes have opened new avenues for the treatment of cancer and the presence of tumor-specific CD8+ T cells in tumor-bearing individuals offer a promising therapeutic target. However, the detection and profiling of such T cells are challenging due to the need to detect rare antigen-specific T cell subpopulations in patient samples that are limited in size thus making it difficult to exploit these parameters for predictive signatures of clinical response. Moreover, the identification and analysis of neoantigen-specific CD8+ T cells in tumor-bearing individuals is challenging due to the small pool of such cells. Methods: In order to identify therapy-relevant tumor antigens and to facilitate a concurrent in-depth characterization of cells directed towards these targets, immunoSCAPE leverages the high-dimensional immune profiling capabilities of cytometry by time of flight (CyTOF) combined with a unique technology allowing the identification rare antigen-specific T-cell subsets. Results: We applied this technology to patient tumor-infiltrating lymphocytes from human cancer samples and tumor-derived neoantigens recognized by T-cells were identified and characterized. Interestingly, the majority of patient-derived tumor infiltrates consisted of tumor-unrelated T-cells characterized by a diverse phenotype. Strikingly, the expression of CD39 was absent from these bystander cells, suggesting that CD39 could be a useful biomarker for the identification of putative tumor-reactive T cells. Conclusions: Simultaneous immune profiling revealed that tumor-unrelated, bystander CD8+ T-cells are phenotypically different in human tumor infiltrates and identified CD39 as a putative marker of neoantigen-specific T-cells. By providing insights into the nature, frequency and phenotype of antigen-specific T-cells, immunoSCAPE’s unique target discovery and high-dimensional immune profiling platform is a valuable tool for the development of novel diagnostic and therapeutic strategies.
2608 Poster Session (Board #252), Sat, 8:00 AM-11:00 AM
Phase I study of KN035, the first subcutaneously administered, novel fusion anti-PD-L1 antibody in patients with advanced solid tumors in China. First Author: Jian-Ming Xu, 302nd Hospital of PLA, Beijing, China
Background: KN035 is a novel fusion protein of humanized anti-PD-L1 single domain antibody and human IgG1 Fc fragment, formulated for subcutaneous (SC) injection. Methods: The escalation phase followed a modified 3+3 design with a 28-day DLT evaluation period and 8 dose levels were planned at 0.1, 0.3, 1.0, 2.5, 5.0, and 10 mg/kg SC weekly. One patient each was enrolled at 0.1 and 0.3 mg/kg dose levels. Additional dose levels followed traditional 3+3 design. Response was assessed using RECIST 1.1 every 12 weeks. Results: As of 11/2/2018, 17 patients were enrolled in the escalation phase (urothelial carcinoma = 2), hepatic cell carcinoma = 2, intrahepatic cholangiocarcinoma = 2, thymic carcinoma = 2, colorectal cancer = 2, renal epithelial cell carcinoma (RCC, n=3), Squamous-cell lung carcinoma (n=1) and ovarian cancer (n=1). The majority of subjects had advanced disease stage, stage IV (15/17) and stage III (2/17). A total of 7 subjects received radiotherapy, 16 subjects received surgery, and 13 subjects received systemic anti-cancer therapies from previous treatment. None had received prior checkpoint inhibitor treatment. Planned maximum dose of 10 mg/kg reached was (n=3) without DLT. A phase I study one Grade 3 drug related Treatment Emergent Adverse Event (TEAE) occurred at 0.3 mg/kg dose level, which was immune related dermatis and resolved later. All other drug related TEAEs were either Grade 1 or 2, with the most common events as elevated ALT (5/17) and elevated AST (4/17). Among all enrolled subjects, the most common TEAE was Grade 1 PR, including one RCC subject at 2.5 mg/kg and one Intrahepatic cholangiocarcinoma subject at 5 mg/kg, and one cholangiocarcinoma subject at 10 mg/kg. Conclusions: KN035 exhibits a favorable safety profile and promising preliminary anti-tumor activity in patients with advanced malignancies. Clinical trial information: NCT03101488.

2610 Poster Session (Board #254), Sat, 8:00 AM-11:00 AM
Immunological impact of canerpaters (C-REV, formerly HF10), an oncolytic virus with or without ipilimumab (Ipi) for advanced solid tumor patients (pts). First Author: Takayuki Nakayama, Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan
Background: C-REV, an oncolytic, spontaneous mutant of Herpes Simplex Virus type 1 (HSV-1), is a cancer immunotherapy agent that combine direct tumor cell killing with immune modulation. A phase I study for solid tumors with cutaneous and/or superficial lesions treated with C-REV monotherapy and a phase I study for unresectable or metastatic melanoma treated with C-REV and Ipi combination therapy were conducted. Immune status of cancer pts before and after administration of C-REV with/without Ipi has been unclear. Methods: A phase I study (n = 6) included solid tumor pts with cutaneous and/or superficial lesions treated with C-REV monotherapy (1 x 10^6), and Ipi (10 mg/kg weekly) for advanced melanoma pts. Four Ipi injections q2wk was injected into each tumor for advanced melanoma pts. For the QW schedule, the starting dose was 1 mg/kg (n=3) with escalation to highest dose level of 5 mg/kg QW. No maximum tolerated dose (MTD) was reached. Among evaluable treated subjects (n=14), there were two confirmed partial responses. Preliminary PK analysis suggested that after SC administration, KN035 was slowly absorbed (Tmax ~ 4 d) and the mean residual time (MRT) was 13 days after reaching the peak concentration post SC administration. Results: KN035 increased approximately proportionally with dose. Trough concentrations were maintained above 15 μg/mL post administration of 5 mg/kg Q2W. No apparent exposure-body weight relationship was observed. Conclusions: KN035 exhibits a favorable safety profile in patients with advanced malignancies and preliminary results demonstrate encouraging anti-tumor activity. Based on PK data from the Q2W schedule, a fixed dose with less frequent dosing schedule of every 3 or 4 weeks is presently being evaluated. Clinical trial information: NCT03248843.

2611 Poster Session (Board #255), Sat, 8:00 AM-11:00 AM
A phase 1/2a study of GEN-009, a neoantigen vaccine based on autologous peptide immune responses. First Author: Roger B. Cohen, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA
Background: Tumor-specific neoantigens provide individualized targets for immunotherapy. In silico selection methods are sub-optimal at predicting immunogenic targets, missing up to 70% of true neoantigens. ATLAS is a powerful tool that screens all candidate neoantigens for pre-existing patient-specific CD4 or CD8 responses in an HLA alognic assessment. ATLAS also identifies inhibitory peptides that may suppress tumor immunity and accelerate tumor progression. The GEN-009 vaccine contains stimulatory but no inhibitory peptide antigens. Methods: GEN-009-101 is a first-in-human phase 1/2a study testing platform feasibility, safety, immunogenicity and clinical activity in selected solid tumors. After next-generation tumor sequencing and cytokine-based ATLAS assessment using autologous T cells and APCs, up to 20 stimulatory synthetic long peptides are used in each personalized vaccine. GEN-009 is administered with poly-ICLC on weeks 0, 3, 6, 12 and 24. Part A, safety and immunogenicity pilot, has completed target enrollment of patients without evidence of disease to receive GEN-009. Part B has 6 tumor-specific cohorts of up to 15 pts naive to PD-1 blockade who will receive GEN-009 with a SOC immunotherapy; Part C: up to 15 pts refractory to PD-1 inhibitors will receive GEN-009 monotherapy. Results: GEN-009 has been successfully generated for patients. Repeated dosing has been well tolerated with mild local discomfort and no DLT. ATLAS screening results below show notable interpatient variability; one subject had only CD4 neoantigens, one had only CD8, another had a strong CD8 bias, and one patient had prominent inhibitory peptides. Conclusions: GEN-009 is a neoantigen vaccine that personalizes tumor specific targets and the individual patient’s capacity to respond. Immunogenicity data will assess CD4 and CD8 T cell responses to each vaccine neoantigen. Clinical trial information: NCT03633110.

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A donor-dependent in vivo model for single agent and drug combination cytokine release syndrome safety evaluation. First Author: James G. Keck, The Jackson Laboratory, Sacramento, CA, USA

Background: Although antibodies and CART cells therapies have been successfully used for cancer therapy, they can have lethal adverse effects such as cytokine release syndrome (CRS). The animal models and in vitro human PBMC assays presently in use can’t reliably predict the CRS in patients. A predictive marker for identifying patients at risk for developing CRS upfront would improve the safety of immune-oncology drug development.

Methods: We have developed a sensitive, consistent and rapid in vivo humanized mouse model for quantitating CRS. The NSG mouse and its derivatives are engrafted with human PBMCs. On day 6 we induced cytokines release with pembrolizumab, avelumab, atezolizumab, ipilimumab, anti-CD28, ATG and OKT3 in single dose; as well as combination treatments involving pembrolizumab, lenalidomide, ATG and anti-CD28. Furthermore, we compared our method versus the in vitro PBMC assay.

Results: The cytokine levels were also compared to the dose response. Results: There are about 10-15% CD4+ human cells on day 5 of engraftment; and among of them, there were approximately 70% CD5 T cells and 25% CD56 NK cells. All tested cytokines, human IFN-γ, IL-10, IL-6, and TNF were upregulated after 2 and 6 hours of OKT3, ATG, anti-CD28, pembrolizumab, avelumab and atezolizumab drug treatment. Mouse’s rectal temperatures dropped from 37-38 °C to about 36 °C at 6 hours’ time point in the treated groups. There is various cytokines release levels, low to high response in different donors with anti-CD28 treatment. All donors showed high response to OKT3. The cytokine release levels were consistent with a dose response or variable PBMC engraftment. The cytokine levels were also higher in some drug combination studies such as pembrolizumab combined with lenalidomide or ATG; anti-CD28 combined with ATG. Our in vivo method was able to detect cytokine CRs similar to the in vitro testing method and response to OKT3. The cytokine release levels were consistent with a dose response or variable PBMC engraftment.

Discussion: Gut microbiota affecting responses to immune checkpoint inhibitors (ICIs) against non-small cell lung cancer (NSCLC) has been investigated in western population. However, considering genetic variation, this phenomenon remains in vague in east-asian NSCLC population. The study is designed to explore the relationships between gut microbiome and clinical outcomes treated with anti-PD-1 blockade in Chinese patients.

Methods: 37 NSCLC patients received the treatment of Nivolumab were enrolled in the study from the clinical trials CheckMate870 (NCT03195491). Fecal samples were collected at the starting point, every time point performing clinical evaluation and that with disease progression. 16s sequencing was applied to assess the gut microbiota characteristics. Peripheral immune profiles were determined by multi-color flow cytometry in parallel. Results: When subgrouping patients into responders (R) and non-responders (NR) groups according to the clinical response assessed by RECIST1.1, patients in R group harbored higher diversity of gut microbiome at the starting point with consistent composition along the treatment. Analyzing progression-free survival (PFS) according to RECIST 1.1, patients with higher microbiome diversity had significantly prolonged PFS when compared to those with low diversity. Compositional difference was observed between two groups as well with the enrichment of Akkermansia muciniphila, Biﬁdobacterium logum, Prevotella copri in R group whereas Ruminococcus_unclassified in NR group. Analysis of systemic situational difference was observed between two groups as well with the significantly prolonged PFS when compared to those with low diversity. Compositional difference was observed between two groups as well with the significantly prolonged PFS when compared to those with low diversity.

Conclusions: Our results report the strong correlation between the gut microbiome diversity and the responses to anti–PD-1 immunotherapy in Chinese NSCLC patients regardless of genetic variation between Western and Chinese population. Patients with a favorable gut microbiome (such as high diversity) have enhanced immune responses mediated by effector T cell function in the periphery. These findings provide important implications for the prediction and the enrichment of anti-pD-1 therapy in Western population.
Interleukin-6 is potential target to de-couple checkpoint inhibitor-induced colitis from antitumor immunity. First Author: Daniel M. Johnson, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: A deep understanding of the immunobiology of checkpoint inhibitor (CPI) induced immune related toxicities, such as immune related enterocolitis (irEC), and how these compare to the immune signatures in tumors could lead to the development of strategies that de-couple autoimmunity from anti-tumor immunity. Methods: Total RNA from patient-matched irEC and normal colon FFPE tissue from patients [n = 12] receiving CPIs were profiled with the 770 gene NanoString nCounter PanCancer Immune Profiling Panel (NanoPCIP). The mean fold change in gene expression from normal vs. irEC inflamed colonic tissue and baseline vs. on-treatment tumor samples from patients responding or non-responding to ipilimumab based therapy were analyzed. C57BL/6 mice with B16. BL6 melanoma tumors were treated with systemic anti-IL-6 + anti-CTLA4 vs. anti-CTLA4 alone vs. placebo and tumor size was measured. Results: In patients with irEC, the highest significantly upregulated differentially expressed gene (DEG) in inflamed colon tissue encoded for IL-6 (Fold change +24.1). None of the significant and highest upregulated DEGs in the colitis group, including IL-6, were significantly upregulated in responding tumors. Interestingly, IL-6 was also the highest upregulated DEG in non-responding tumors numerically. When comparing mean fold changes across these analyses, the gene with the largest difference in upregulation between colitis and responding tumors was IL-6; the other highest upregulated genes in colitis encoded for neutrophil and monocyte chemotactic proteins. In mouse models, the addition of IL-6 blockade to anti-CTLA4 therapy significantly improved tumor shrinkage compared to anti-CTLA4 alone. Conclusions: Our data demonstrates that IL-6-mediated inflammation may be more prevalent in irEC and tumors not responding to CPIs than in tumors responding, and blocking IL-6 enhances CPI anti-melanoma activity. Targeting IL-6 may ameliorate irEC without hindering anti-tumor immunity.

Pan-tumor prognostic value of multiple immune protein expressions. First Author: Stéphane Lambert, Drug Development Department (DITEP), Villejuif, France

Background: Using multiple immune-checkpoint proteins (ICP) screening in clinical routine could improve the evaluation of patients’ prognosis and ultimately tailor their treatment choice. We have evaluated this hypothesis in the context of early drug clinical trials. Methods: Patients included in MOSCATO-02 trial had refractory cancers and were candidate for phase 1 study. They were proposed to have a biopsy on an accessible tumor site for the analysis of four proteins by immunohistochemistry (IHC) and RNAsq: PD-L1, CD3, CD8 and FOXP3. Quantification of IHC staining was separated between intratumoral, interstitial and stromal by semi-quantitative method. Their relations to prognosis have been evaluated by survival Random Forest and compared to classical prognosis clinical variables, such as age and RMH score (calculated by the number of metastatic sites, lactate dehydrogenase (LDH) and serum albumin). Results: From April 2016 to September 2017, 228 patients included in MOSCATO-02 had a successful biopsy procedure with available IHC expression analysis. The main tumor subtypes were gastro-intestinal, urological, head and neck, breast and lung. RNAsq analyses were performed for two thirds of the patients (N=170). Median overall survival was 8.1 months (CI95% 7.79 – 10, 65). We found that, in a cohort of phase I patients, RMH score was the most important variable used to estimate prognosis. Prognosis value of immune proteins were considerably inferior compared to clinical criteria. Among those proteins, the percentage of PD-L1 low score (1+) and average staining intensity of CD3 were the most valuables for prognosis evaluation. Variables with very few importance to prognosis estimation were CD8 and FOXP3 IHC scores, biopsy site and cancer types, subsequent treatments by immunotherapies or targeted therapies. Conclusions: In this cohort of patients with refractory cancers, the RMH score is confirmed as highly prognosis. Immune proteins could be used as a support to guide patient’s selection but does not constitute effective prognosis criteria.

Onalespib, a potent and selective heat shock protein (HSP)-90 inhibitor, for the treatment of refractory solid tumors. First Author: Susumu Kiyuna, Department of Medical Oncology, Keio University School of Medicine, Tokyo, Japan

Background: HSP90 is the major target of onalespib (SB-719915) a gamma-secretase inhibitor (GSI), and is involved in the activation of protein kinase B (AKT), and nuclear factor-kB (NF-kB). Methods: The 90kDa heat shock protein (HSP90) participates in the cellular processes that contribute to the growth and survival of cancer cells. HSP90 inhibition leads to degradation of these aberrant proteins through the ubiquitin-proteasome pathway, allowing for simultaneous suppression of multiple pathways. Inhibition of HSP90 alone stimulates a compensatory upregulation of HSP70 expression. Patients enrolled to the expansion phase underwent optional paired tumor biopsies for assessment of proof-of-mechanism demonstration of modulation of client proteins. Results: Twenty-eight patients have been treated, 10 of whom were enrolled to the expansion cohort with optional tumor biopsies. The combination of onalespib and AT7519 is tolerable, although the doses of both agents were below the monotherapy MTDs. Prolonged disease stabilizations were observed. Pharmacokinetic and pharmacodynamic analyses are ongoing, including assessment of HSP70 expression in plasma and tumor. Clinical trial information: NCT02503709.
Non-small cell lung cancer (NSCLC) next generation sequencing (NGS) using the Oncomine Comprehensive Assay (OCA) v3: Integrating expanded genomic sequencing into the Canadian publicly funded health care model. First Author: Kirstin Perdrizet, University of Toronto, Toronto, ON, Canada

Background: Standard of care (SOC) molecular diagnostics for stage IV NSCLC patients in Ontario, Canada includes publicly reimbursed EGFR/ALK, and selected BRAF and ROS-1 testing. Other genomic alterations are not tested routinely; however, enhanced molecular testing may broaden treatment options for patients. This study evaluated costs, identified actionable targets, and determined clinical trial eligibility as a result of using the OCAv3 NGS in stage IV NSCLC patients. Methods: In a prospective study of stage IV NSCLC out-patients at Princess Margaret Cancer Centre (Toronto) without EGFR/ALK/KRAS/BRCA mutation (unless failure of prior targeted therapy), diagnostic samples were tested by OCAv3 (ThermoFisher; 161 genes: hotspots, fusions, and copy number variations). Primary endpoints were incremental actionable targets and clinical trial opportunities as a result of broader OCAv3 testing. Secondary endpoints include feasibility and cost from the Canadian public healthcare perspective, and treatment outcomes. Results: Of 65 enrolled patients (Feb 2018-Jan 2019; 40 (62%) completed/14 (21%) screen fail/11 (17%) pending), median age of completed cohort was 65, 60% (N = 24) female, never/light smokers 68% (N = 27), Asian 38% (N = 15), previously treated 33% (N = 13). Actionable targets beyond SOC were identified in 33% (N = 13): ERBB2 (N = 8), BRAF V600E (N = 3), NRG fusion (N = 1), MET exon 14 (N = 1). New clinical trial options were identified in 70%. Failure of NGS secondary to insufficient tissue (91% (N = 10) of screen failures; usually due to tissue exhaustion from prior SOC molecular testing). Incremental costs per case beyond beyond EGFR/ALK are estimated at $540 CAD. If ROS-1 and BRAF testing were publicly reimbursed at current rates, the incremental profiling cost with OCAv3 would be $90 CAD per case. Conclusions: Although a key barrier to implementation is lack of funding for NGS in the Canadian publicly funded system, the OCAv3 consolidates genomics testing, identifies additional actionable targets, and substantially increases clinical trial eligibility for patients at a small incremental cost. Clinical trial information: NCT03558165.

Baseline tumor-immune signatures associated with response to bempedaglesuin (NKTR-214) and nivolumab. First Author: Michael E. Hurwitz, Yale School of Medicine, New Haven, CT

Background: PIVOT-02 is an ongoing phase 1/2 study of bempedaglesuin (NKTR-214), a CD122-preferential IL-2 pathway agonist, plus nivolumab in patients with advanced solid tumors. Bempedaglesuin (NKTR-214) increases proliferative tumor infiltrating lymphocytes (TIL) and cell surface PD-1 on immune cells and PD-L1 on tumor cells, demonstrating potential synergistic activity with anti-PD-1 therapy. Pre-treatment baseline genetic, genomic, and immune microenvironmental factors were systematically assessed in patients with a broad spectrum of cancers (N = 159). Methods: Whole-exome sequencing data, RNA-Seq data and clinical data of 1096 breast tumors from The Cancer Genome Atlas (TCGA) database were used to analyze the pattern of indels in breast cancer. Next generation sequencing (NGS) data of 81 metastatic breast tumors from clinical dataset were also used to validate the indels mutation pattern in different molecular subtype. Results: 81.7% (895/1096) of breast tumors in TCGA dataset harbored at least one indels mutation. Hormonal receptor (HR) negative tumors were associated with higher burden of indels mutations than HR positive tumors in both TCGA dataset (P = 0.05) and NGS-clinical dataset (P = 0.003). Indels were significantly correlated with higher TMB and neoantigen level in TCGA cohort (P < 0.0001). In addition, tumors with at least eight indels mutations (cut off at 80% percentile) exhibited even higher TMB (P < 0.0001) and neoantigen (< 0.0001) level. Among 45 immune related genes, the mRNA expression of 22 genes were significantly higher in tumors with indels mutations, such as LAG3, IL18, IL6, CTLA4 and PDCD1. Indels group also showed a high levels of genome instability in terms of HRD-LOH (P = 0.004), NAH (P = 0.000), wGini (P = 0.001) and LST (P = 0.014). Conclusions: Breast tumors with indels mutations exhibited the immunogenic phenotype. Further studies are warranted to investigate the potential value of indels as a predictive biomarker for immunotherapy in breast cancer.
Tumor mutational burden (TMB) is a predictive biomarker of response to immune checkpoint inhibitors across multiple cancers. In Phase 1 of the Friends of Cancer Research TMB Harmonization Project, we demonstrated a robust correlation between TMB estimated using targeted next-generation sequencing (NGS) gene panels and whole exome sequencing (WES) applied to TCGA data. These findings demonstrated variability in TMB estimates across different panels. Phase 2 evaluates sustainable TMB reference standards according to genes represented in their respective panels (panel-TMB). The association between WES-TMB and each panel-TMB was investigated using regression analyses. Bias (relative to WES-TMB) and variability in TMB estimates across panels were rigorously assessed. All analyses were blinded. Results: The set of reference standards spanning minimum mutational range (4.3 to 31.4 mut/Mb) preliminary data from 12 laboratories shows a good correlation between panel-TMB and WES-TMB in this empirical analysis. Across panels, regression $R^2$ values range 0.77-0.96 with slopes ranging 0.60-1.26. Calibration analyses that seek to minimize variability of TMB estimates across panels using the established set of reference standards are ongoing, as well as investigating cancer type dependence on the relationship between panel-TMB vs. WES-TMB, which will be available at the time of presentation. Conclusions: Preliminary findings demonstrate feasibility of using sustainable reference control cell lines to standardize and align estimates of TMB across different targeted NGS assays. Future studies aim to validate reference standard materials as a reliable alignment tool by using formalin-fixed paraffin-embedded human tumor samples.

Tumor mutational burden (TMB) profile of K-RAS/TP-53 co-mutation in metastatic non-small-cell lung cancer (m-NSCLC). First Author: Sushma Jonna, Georgetown University Medical Center.

Background: Early data suggests that co-occurring genetic events define biological heterogeneity in K-RAS mutant NSCLC, with K-RAS/TP-53 (KP) co-mutated subset having potential therapeutic vulnerabilities to immune checkpoint blockade (ICB). To explore the immunological basis for these findings, we evaluated the immune biomarker profile (TMB/PD-L1) in KP compared to TP-53 or K-RAS mutated and -normal tumors. Methods: Caris life sciences NGS dataset consisting of 1317 m-NSCLC tissue samples from 2016-18 was queried. PD-L1$^\text{H}$ was defined as $\geq 1\%$ staining using 22c3 Dako assay. TMB was measured by counting all somatic non-synonymous missense mutations using targeted NGS (592 genes). TMB-high (H) was defined as $\geq 10$ mutations/Megabase (mut/Mb). $p$-values were calculated using Chi-square and Mann-Whitney test. Results: K-RAS mutations were identified in 28.7% (378/1317). Within this K-RAS mutant group, KP subset constituted 49.4% (187/378), remaining were K-RAS mutated/TP-53 wild type (K-Pwt). 72.2 % ($135/187$) of KP had PD-L1$^\text{H}$ with 51.9% (97/187) having PD-L1$^\text{H}$ with $\geq 50\%$. KP had higher median TMB vs. K-Pwt (14.5 vs. 9.0 mut/Mb, $p<0.001$) and higher % of TMB-H vs. K-Pwt (79.9 vs. 45.1%, $p<0.001$; Table). Even in the PD-L1$^\text{neg}$ group, KP had higher % of TMB-H vs. K-Pwt (86.5 vs. 41.5%, $p<0.001$). K-RAS or TP-53 exon-subtypes had no difference in median TMB or % of TMB-H. Across metastatic sites, brain tissue had the highest % of KP subset (38.3%, 68/187) followed by bone (28.9%, 54/187). Within KP subset, brain tissue had higher median TMB vs. bone (16 vs. 11 mut/Mb, $p<0.001$) as well as greater % of TMB-H vs. bone (86.5 vs. 68.5%, $p=0.01$). Conclusions: This is the largest dataset to date highlighting the unique immune profile of KP mutant m-NSCLC. Our results show that KP subset has a significantly higher TMB than K-Pwt, especially in the PD-L1$^\text{neg}$ subgroup. Metastatic site-specific variations in TMB were also observed for the KP subset. These findings could have therapeutic implications in guiding patient selection for ICB and merit prospective investigation.

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The consensus Immunoscore adapted to biopsies in patients with locally advanced rectal cancer: Potential clinical significance for a “Watch and Wait” strategy. First Author: Canne El Siassy, Hopital Européen Georges Pompidou, Paris, France

Background: We investigated whether an adaptation to rectal biopsies of the recently validated consensus Immunoscore, could predict the response to neoadjuvant treatment and delineate clinical responders that could benefit from a “Watch and Wait” (W&W) strategy with acceptable outcomes. Methods: Initial biopsies from 273 patients with locally advanced rectal cancer (LARC) treated by neoadjuvant chemoradiotherapy (nCRT) followed by Total Mesorectal Excision (TME), were immunostained for CD3+ and cytotoxic CD8+ T cells and quantified by digital pathology to determine the Immunoscore within pre-treatment Biopsy (ISB). Expression level of 44 immune related genes post-neoadjuvant treatment was investigated by Nanostar technology (n = 64 patients). Results were correlated with response to neoadjuvant treatment, disease free survival (DFS) and time to recurrence (TTR). Prognostic performance of ISB was finally assessed in 73 LARC treated by W&W strategy. Results: ISB Low, Intermediate and High were respectively observed in 23.3, 50.4 and 26.3 % of the cohort. ISB was positively and significantly correlated with the response to nCRT, as evaluated by Dvorak classification (P = .0034), ypTNM (P = .0003), downstaging (P = .0014), and neoadjuvant rectal (NAR) score, (P < .0001). ISB status was also positively associated with the degree of local immune activation post-neoadjuvant treatment. ISB High patients were at lower risk of relapse, with 5-year event-free survival of 81.1 % (95% CI: 73.1 - 89.0) and 5-year DFS of 57.8 % (CI, 45.9-72.9 %) in ISB Low patients. In multivariate analysis, ISB was the only significant parameter at presentation associated with DFS (High vs Low: P = .001). Among W&W patients, significant difference was observed for TTR according to ISB status (High vs Low: P = .029). Conclusions: ISB could provide a reliable estimate of the response to nCRT and risk of recurrence in LARC patients treated by TME or W&W strategy.

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A multiplex immunofluorescence assay to assess immune checkpoint inhibitor-targeted CD8+ activation and tumor colocalization in FFPE tissues. First Author: Tony Nayar, Clinical Pharmacodynamics Biomarker Program, Applied/Developmental Directorate, Frederick National Laboratory for Cancer Research, Frederick, MD

Background: Immune checkpoint inhibitors promote antitumor immune responses by enhancing T-cell activity. Measuring the pharmacodynamic effects of these drugs is challenging, as it requires assessing both immune cell and cancer cell populations. To evaluate T-cell activation in tumor tissue from patient biopsies, we developed a robust multiplexed immunofluorescence assay. Methods: Our assay uses novel oligo-conjugated antibodies (UltiVue) for simultaneous quantitation of TCR activation (phospho-CD3delta), immune checkpoint signaling via PD-1 (p-3SH1/p-SHP2), and the net stimulation/inhibition resulting from the integration of these two pathways in CD8 cells (p-ZAP70), while also providing the proximity of CD8 cells to tumor tissues, identified by β-catenin. The method was clinically validated using custom tissue microarrays (TMA) containing tumor biopsies of 3 different histologies (CRC, NSCLC, and breast). Results: From a total of 192 tumor core biopsies, 2064 NSCLC, 964 CRC, and 365 breast TMA cores were individually analyzed to have a significant number of CD8 tumor infiltrating lymphocytes (TILs) at baseline (≥ 50 cells in the examined section). In 18 of the 20 NSCLC cores, ≥50% of CD8 cells both inside and outside of the tumor were activated (CD3d-py142+). In 6/9 CRC cores, ≥50% of CD8+ cells inside tumor tissues were activated, and in 4/9 CRC cores, ≥50% of CD8+ cells in stroma were activated. In 2/3 breast tumor cores, 90% of CD8+ cells inside tumor tissues were activated; in the remaining core, 90% of CD8+ cells in stroma were activated. Interestingly, all 192 cores had minimal to no expression of activated Zap70 (pY493) in CD8+ cells. Conclusions: Depending on tumor histology, baseline biopsy samples may contain variable numbers of activated CD8+ TILs which may reside inside or outside of tumor tissue and express very low levels of Zap70-pY493. Anti-PD-1 therapy is predicted to enhance T-cell cytotoxic activity, as demonstrated by an increased number of TILs and elevated Zap70-pY493 expression. This assay is being used for pharmacodynamic evaluations in ongoing immunotherapy clinical trials. Funded by NCI Contract No HHSN261200800001E.
Evaluation of TMB estimates for the prediction of response to immune checkpoint blockade. First Author: Jan Budczies, Institute of Pathology, University of Heidelberg, Heidelberg, Germany

Methods: We analyzed TMB as predictor of IO response in a multi-cancer cohort published by Miao et al. The performance of three large panels (Illumina TSO500, Qiagen TMB [QIAseq] and Oncomine TMB [OTMB]) and two small panels (Illumina TST170 and Oncomine Comprehensive Assay [OCAv3]) was compared to WES by in silico simulations. Separation of responders (PR/CR) from non-responders (PD) was analyzed in the melanoma (n = 125) subcohort. We also simulated PS in the simulations. Separation of responders (PR/CR) from non-responders (PD) was compared to WES by in silico simulations. Oncomine Comprehensive Assay [OCAv3] was compared to WES by in silico simulations. Separation of responders (PR/CR) from non-responders (PD) was analyzed in the melanoma (n = 125) subcohort. We also simulated PS in the simulations. Separation of responders (PR/CR) from non-responders (PD) was compared to WES by in silico simulations. Oncomine Comprehensive Assay [OCAv3] was compared to WES by in silico simulations. Separation of responders (PR/CR) from non-responders (PD) was analyzed in the melanoma (n = 125) subcohort. We also simulated PS in the simulations. Separation of responders (PR/CR) from non-responders (PD) was compared to WES by in silico simulations. Oncomine Comprehensive Assay [OCAv3] was compared to WES by in silico simulations. Separation of responders (PR/CR) from non-responders (PD) was analyzed in the melanoma (n = 125) subcohort. We also simulated PS in the simulations.

Results: In lung cancer, TMB was strongly predictive for IO response (area under ROC curve [AUC] 0.78-0.94). WES performed (borderline)-significantly better than PS for all five panels (OCAv3: p = 0.011, TST170: p = 0.001, QIAseq: p = 0.048, OTMB: p = 0.063, TSO500: p = 0.11). For the cut-point of 199 mutations, misclassification rates compared to WES (16.7%) were borderline-significantly higher in the small panels OCAv3 (33.3%, p = 0.087) and TST170 (36.1%, p = 0.054), but not for the large panels. In melanoma, TMB was moderately predictive (AUC 0.58-0.63) and WES performed (borderline)-significantly better than the OCAv3, TST170, QIAseq and TSO500 panels. In the multi-cancer cohort, WES did not perform better than PS. TMB estimates from PS include an inherent fuzziness originating from the definition of the coding sequence. Based on a random mutation model, we derived a mathematical formula for the coefficient of variation (CV) of TMB: The CV decreases inversely proportional with both the square root of the TMB level and with the square root of the panel size. We showed that the mathematical law of the coding mutation density is realizable with large sequencing data. Our results (H. R. 1989, C. T. 0.97) and the corresponding equation (Mpb) performed impermeable in diagnostic TMB estimation. Even using the largest commercially available panels it can be challenging to capture the full predictive information of TMB. The detrimental effect of small panel size can be addressed by using larger panels, but halving the CV of TMB necessitates quadruplication of the panel size.

Conclusions: Our results provide the first evidence that polymorphisms within TMB were generally higher than WES-based TMB with a mean increase in TMB. The detrimental effect of small panel size can be addressed by using larger panels, but halving the CV of TMB necessitates quadruplication of the panel size.

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Results: clinical and immunological correlations were made using multivariate areas with tumor activity according with the CT or PET every week 10 times. LN area one week apart. Afterwards we treated S.C. as well but now in the microenvironment were performed to detect Granzyme B by ELISPOT, containing-protein (VCP) and EGFR were analyzed by IHC, Th1 and CD8 were enrolled after the local IRB ethic committee approved the pilot clinical with increased levels of IL-12 production lungs (p = 0.004) and hepatic tissue (p = 0.001) disappeared and correlated 0.0001) and this correlated with the scans post-treatment. The patients were lost to follow up; all surviving patients were followed 5 years. Toxicity was minimal. Median overall survival (OS) for all 72 patients was 49.4 mos; 5-year OS 46%. There was no correlation between survival and the number of DC or ITC in the first three injections. Patients with recurrent stage 3 disease that had not recurred (n=18) had a 72% 5-year OS; patients with non-measurable stage 4 (n=30) had a 53% 5-year OS. Patients with measurable stage 4 (n=14) had received an average of four prior therapies. They had a median OS of 18.5 months, and 2-year OS of 46%. Conclusions: This patient-specific DCV was associated with encouraging survival in all three clinical subsets. Because of its mechanism of action and absence of toxicity, it should be evaluated further. Clinical trial information: NCT00948480, NCT00436930.

2639 Preliminary results of a phase I clinical trial using an autologous dendritic cell cancer vaccine targeting HER2 in patients with PET every week 10 times operated high-risk bladder cancer (NCT01730118). First Author: Hoyoung M. Maeng, National Cancer Institute, Bethesda, MD

Background: We developed a HER2 targeting autologous dendritic cell (DC) vaccine transduced with an adenovirus expressing the extracellular and transmembrane domains of HER2 (AdHER2). In mice, the homologous vaccine cured virtually all mice with established or metastatic tumors. Protection was dependent on antibody binding against HER2 but was ADCC independent. We translated these findings into a clinical trial. Methods: This is an open-label, phase I study in patients with 1) metastatic cancer that progressed after ≥ 1 standard therapies, or 2) history of high risk bladder cancer with definitive treatment, whose tumor is HER2 immunohistochemistry (IHC) score ≥ 1+ or FISH HER2/CEP17 ratio ≥ 1.8. Part 1 of the study enrolled patients naïve to HER2-directed therapies and Part 2 enrolled patients who progressed with ≥ 1 anti-HER2 therapy. Results: In Part 1, the lowest dose level (5E+6 viable DCs, N=7, 2 evaluable) showed no benefit. At the second and third dose level (10E+6 and 20E+6, N=7 and N=4; 0 and 1 evaluable in each), 1 CR (ovarian), 1 PR (stomach), and 3 SD (1 ovarian carcinosarcoma and 2 colon) were observed. Two bladder cancer patients who received vaccine as an adjuvant did not recur for +24 and +36 month each. In Part 2 (N=6, 2 evaluable), 1 male breast cancer patient showed SD. Response assessed using US-Fingerprint Related Response Criteria. 1 pt with CR is summarized in the Table. Injection-site reactions occurred in all patients and were self-limited. Echo, EKG and troponin follow up to 2 years showed no cardiac toxicity. Dose expansion cohort (40E+6) is enrolling. Conclusions: We have translated a cancer vaccine from a mouse to a clinical trial. Preliminary results of a phase I trial of an autologous AdHER2 DC vaccine show potential clinical benefit in select patients with HER2 expressing tumors with no cardiac toxicity. Clinical trial information: NCT01730118.

2640 Phase I trial of a modified vaccinia ankara (MVA) priming vaccine followed by a fowlpox virus (FPV) boosting vaccine modified to express brachyury and costimulatory molecules in advanced solid tumors. First Author: Julie Marie Collins, National Cancer Institute, Bethesda, MD

Background: Brachyury, a transcription factor, plays an integral role in epithelial-to-mesenchymal transition, metastasis, poor prognosis, and resistance to chemotherapy. It is expressed in many tumor types, and rare in normal tissue, making it an ideal immunologic target. BN-Brachyury composes heterogeneous vaccination with recombinant MVA priming followed by FPV boosting, each encoding transgenes for brachyury and three costimulatory molecules (B7-1, ICAM1, and LFA-3). Heterologous prime boost approach is intended to optimize immunogenicity, as previously observed. Methods: Pts with metastatic solid tumors were treated with 2 monthly doses of MVA-brachyury SC at the previously tested dose, 2.2 x 10^7 infectious units (IU), followed by FPV-brachyury SC, 1 x 10^7 IU, for 6 monthly doses and then every 3 months for up to 2 years. The primary objective was to determine safety and tolerability and establish the RP2D. Immune assays were conducted to evaluate immunogenicity. Results: in 10 pts (3 chordoma, 6 GI, 1 papillary thyroid), no dose-limiting toxicities or serious treatment-related adverse events (TRAEs) were observed. The only Grade 3 TRAE was sedation associated with fever, which resolved spontaneously and did not recur with subsequent cycles. All other TRAEs were Grade 1 or 2; the most common was injection-site reaction in all patients. Five pts had stable disease for > 24 wks (per RECIST v1.1) and remain on treatment. One pt with chordoma, for which BN-Brachyury was granted orphan drug designation, has had an 13.2% reduction in tumor size. As previously demonstrated, brachyury-specific T cell responses were observed, as were responses against cascade antigens (non-encoding antigens) CEA and MUC-1. Conclusions: Heterologous MVA- and FPV-brachyury is well tolerated and inducible, 11 immune responses against brachyury and cascade antigens, suggesting induction of immunologically relevant tumor cell destruction. These data have informed combining BN-Brachyury with checkpoint inhibition (NCT03493945) and radiation (NCT03595228) to evaluate potential for synergistic activity in selected populations. Clinical trial information: NCT03349983.
2641 Poster Session (Board #285), Sat, 8:00 AM-11:00 AM
A phase I study (E011-MEL) of a TriMix-based mRNA immunotherapy (ECI-006) in resected melanoma patients: Analysis of safety and immunogenicity. First Author: Ana Padrón, Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Barcelona, Spain

Background: ECI-006 is a combination of TriMix (mRNAs encoding for dendritic cell [DC] activating molecules [CD40L, CD70 and catTLR4]), and mRNAs encoding for melanoma-specific tumor-associated antigens (TAAs): tyrosinase, gp100, MAGE-A3, MAGE-C2, and PRAME. DCs transfected ex vivo with TriMix and TAAs mRNAs showed significant cytokine production in combination with ipltumimun in metastatic melanoma without increasing toxicity. This study aims to assess the safety and immunogenicity of ECI-006 vaccine administered intranodally (i.n.) in an adjuvant setting for patients with resected melanoma. Methods: Twenty patients who underwent resection of stage IIIC/IV cutaneous melanoma received 5 administrations of ECI-006 (either 600 μg or 1800 μg [n = 10, each]) i.n. on Day 1 and after 2, 4, 6 and 14 weeks. Treatment-emergent adverse events (TEAEs) were graded using CTCAE version 4.0.3. Blood samples for immune monitoring (ELISPOT and intracellular cytokine staining [ICS]) were collected pre-dose and at weeks 4, 7, 14 and 15. Results: Nineteen patients completed the treatment. One patient in the low dose group discontinued the study after 4 doses due to disease relapse. Administration of ECI-006 was well tolerated. No serious adverse events or TEAES Grades 3 or higher were reported. Of all TEAEs, myalgia and fatigue were the most reported in 3 (15%) and 5 (25%) patients, respectively. ELISPOT analyses were on T cells pre-stimulated in vitro for 12-10 days, using a previously in-house validated protocol. Vaccine-induced immune responses according to predefined criteria were detected in 4/10 and 3/9 patients treated with the low and high dose, respectively. Samples from these patients are currently being submitted to T-cell receptor repertoire analysis. Among patients undergoing resection of stage IIIC/III/IV melanoma, i.n. administration of ECI-006 at 600 or 1800 μg was generally well tolerated. ECI-006 demonstrated to be immunogenic in a proportion of patients. These results warrant further development of ECI-006 in combination with anti-PD1 therapy in melanoma patients. Clinical trial information: NCT03394937.

Conclusions: Our data show that such a personalized mRNA vaccination is feasible and can elicit antigen-specific T cell responses. Combination of vaccines with checkpoint inhibitors or adoptive T cell therapy can open the possibility to develop a personalized immunotherapy, but further studies in the context of clinical trials are needed. Clinical trial information: NCT03480152.

2642 Poster Session (Board #286), Sat, 8:00 AM-11:00 AM
Final results of a phase I study evaluating INVAC-1, a novel DNA vaccine expressing an inactive form of human telomerase reverse transcriptase (hTERT) in patients with resected solid tumors. First Author: Gal Cafri, National Cancer Institute Surgery Branch, Bethesda, MD

Background: INVAC-1 is an optimized DNA plasmid encoding an inactive form of human Telomerase Reverse Transcriptase (hTERT), a universal tumor antigen expressed in most of human tumors with little or no expression in somatic cells. We report here the final results of a First-In-Human Phase I study evaluating INVAC-1 as a single agent in patients (pts) with advanced solid tumors, ended in June 2018. Methods: A two-center Phase I trial evaluated INVAC-1 given monthly for a minimum of 3 cycles and up to 9 cycles by intradermal injection followed by electroporation (n = 20) or using a needle-free injection system (n = 6). Primary objectives included safety, tolerability and dose limiting toxicities to identify the maximum tolerated dose and recommended phase 2 dose. Secondary objectives included immune response (assessed by IFN-γ ELispot) and anti-tumor activity. Immuno-monitoring included detection of autoantibodies, lymphocyte phenotyping and inflammatory cytokine levels in blood. Anti-tumor activity was evaluated through RECIST 1.1 adapted to immune response, and plasma circulating tumor DNA (ctDNA). Results: 26 pts with refractory/progressive tumors were enrolled and treated with 3 escalating doses of 100, 400 and 800 μg. pTs experienced stable disease according to RECIST. For 11 of them, the treatment was extended, up to 9 months. INVAC-1 was well tolerated with no dose limiting toxicities. No immune-related adverse events were observed. No significant modification in inflammatory plasma cytokines levels was observed after INVAC-1 administration. INVAC-1 triggered de novo or enhanced pre-existing CD4/CD8 specific anti-hTERT response in 63% of pts. This specific anti-hTERT immune response was enhanced ex vivo through expanding the immune checkpoint inhibitor nivolumab, ctDNA was evaluated in 17 pts. We observed a ctDNA decrease in 6 cases, a stable level in 5 cases and an increase in 6 cases. Conclusions: Results indicate that INVAC-1 was well tolerated and immunogenic at the doses and schedule tested. Disease stabilization was obtained for the majority of pts (58%) according to RECIST criteria or ctDNA levels. Clinical trial information: NCT02301754.

2643 Poster Session (Board #287), Sat, 8:00 AM-11:00 AM
Immunogenicity and tolerability of personalized mRNA vaccine mRNA-4650 coding for melanoma-specific TAAs in metastatic melanoma patients. First Author: Gal Cafri, National Cancer Institute Surgery Branch, Bethesda, MD

Background: Therapeutic vaccination against cancer has proven very challenging with little clinical benefit. Vaccines against non-viral tumors have mainly targeted differentiation antigens, cancer testis antigens, and over-expressed antigens. However, negative selection in the thymus against these normal non-mutated antigens severely limits the ability to generate high avidity anti-cancer T-cells. The importance of neoantigens to each patient’s unique cancer as targets for immunotherapy has been extensively studied, by our group and others. It is now clear that neoantigen-specific T-cells are present in most cancers and these neoantigens derived from somatic mutations offer a specific and highly immunogenic target for personalized vaccination. We developed a process to identify immunogenic T-cell epitopes derived from tumor-specific mutations using tumor-infiltrating lymphocytes. Methods: We combined, for the first time, validated defined neoantigens, predicted neoepitopes and mutations in driver genes of patients with metastatic common epithelial cancers. Clinical trial information: NCT03480152. Results: Nineteen patients completed the treatment. One patient in the low dose group discontinued the study after 4 doses due to disease relapse. Administration of ECI-006 was well tolerated. No serious adverse events or TEAES Grades 3 or higher were reported. Of all TEAEs, myalgia and fatigue were the most reported in 3 (15%) and 5 (25%) patients, respectively. ELISPOT analyses were on T cells pre-stimulated in vitro for 12-10 days, using a previously in-house validated protocol. Vaccine-induced immune responses according to predefined criteria were detected in 4/10 and 3/9 patients treated with the low and high dose, respectively. Samples from these patients are currently being submitted to T-cell receptor repertoire analysis. Among patients undergoing resection of stage IIIC/III/IV melanoma, i.n. administration of ECI-006 at 600 or 1800 μg was generally well tolerated. ECI-006 demonstrated to be immunogenic in a proportion of patients. These results warrant further development of ECI-006 in combination with anti-PD1 therapy in melanoma patients. Clinical trial information: NCT03394937.

Conclusions: Our data show that such a personalized mRNA vaccination is feasible and can elicit antigen-specific T cell responses. Combination of vaccines with checkpoint inhibitors or adoptive T cell therapy can open the possibility to develop a personalized immunotherapy, but further studies in the context of clinical trials are needed. Clinical trial information: NCT03480152.

TPS2644 Poster Session (Board #288a), Sat, 8:00 AM-11:00 AM
A first-in-human study of KY1044, a fully human anti-ICOS IgG1 antibody as monotherapy in and in combination with anti-PD1-L1. First Author: Sonia Quarantin, Kymab Ltd, Cambridge, United Kingdom

Background: The Inducible T-cell costimulator (ICOS/COD278) is related to the CD28 superfamily and is induced upon T cell activation. There is a hierarchical order of ICOS expression level, in which highly immunosuppressive Treg (CD4*Foxp3*) present in the tumor microenvironment (TME) and the tumor suppressor CD25* T cells are at the bottom level. In addition, ICOS expression on Treg is higher in the TME than in the blood or spleen. Methods: KY1044, a fully human anti-ICOS IgG1 kappa monoclonal antibody, selectively binds to ICOS with high affinity (which is maintained at intratumoral acidic pH) and has a dual mechanism of action: it promotes the preferential depletion of intratumoral ICOS(high) Treg resulting in an increase in the Teff/Treg ratio in the TME; and it stimulates ICOS(low) T eff cells. Preclinical data demonstrate that KY1044 monotherapy or in combination with anti-PD-L1 is associated with immune cell activation and anti-tumor response. In order to validate the dual mechanism of action in vivo, studies in mice and cynomolgus monkeys were conducted. Firstly, KY1044 injected i.v. at doses up to 100 mg/kg weekly were well tolerated in non-human primates. In addition, pharmacodynamic studies in mice and cynomolgus monkey confirm preferential depletion of ICOS(high) cells. KY1044-C01 is an open-labelled first in human Phase I/II study assessing the safety, tolerability, PK, PD and anti-tumor activity of KY1044 administered every 3 weeks (Q3W) as an i.v. single agent infusion and in combination with atezolizumab (1200 mg, Q3W IV) in adult patients with advanced/metastatic malignancies. The primary endpoint of the Phase I dose escalations, designed as sequential but overlapping arms of KY1044 monotherapy and combination with atezolizumab, is safety and tolerability. Secondary endpoints are the characterization of pharmacokinetic, pharmacodynamic and efficacy profiles in all patients. In the Phase II part, the primary endpoint is overall response rate (ORR), and the measure of clinical efficacy will be confirmed as per RECIST 1.1. and immune-related (ir)RECIST. An intensive biomarker profiling is performed as part of the study design to understand the phenotypic and molecular changes in both peripheral blood and tumor. Clinical trial information: NCT03829501.
Phase 1 with expansion cohorts in a study of NEO-201 in adults with chemoresistant solid tumors. First Author: Maria Fara Morelli, NCI, Bethesda, MD

Background: NEO-201 is a novel humanized IgG1 monoclonal antibody (mAb) generated against the Hollinshead allogenic colorectal cancer vaccine platform. Briefly, tumor-associated antigens (TAAs) derived from tumor membrane fractions pooled from colorectal cancer surgical specimens were screened for delayed-type hypersensitivity and evaluated in clinical trials. The original vaccine was used to generate monoclonal antibodies, one of which is NEO-201. In preclinical data generated in our laboratory, we have demonstrated that NEO-201 exerts anti-tumor activity by naturally occurring and antibody-mediated cytotoxicity (ADCC) against several tumor types including colorectal and pancreatic cancer models (Fanti et al., 2018). We have identified NEO-201 antigen as a glycosylated form of CEACAM-5 and -6, which is expressed by tumor tissue but is not present in the surrounding healthy tissue (David et al., 2018). This could result in a specific anti-tumor activity without significant normal tissue toxicity. Nevertheless, toxicity was further assessed in non-human primates and transient neutropenia was the only adverse event observed. Based on this data we designed a first in human phase I trial to evaluate the safety, maximum tolerated dose (MTD), pharmacodynamics (PD) and pharmacokinetics (PK) of the humanized monoclonal antibody NEO-201. Methods: This is a first-in-human phase 1 study with expansion cohort to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of NEO-201 in adults with advanced solid tumors that have high likelihood of expression NEO-201 antigen and have progressed to standard of care treatments and have a PSO-2 ECOG. Study design is a classic Fibonacci (3+3) dose escalation, with a cohort expansion at the MTD. NEO-201 is administered intravenously every two weeks, and four different dose levels will be explored (DL1 = 1mg/kg, DL2 = 2mg/kg, DL3 = 4mg/kg and DL4 = 6mg/kg). No intra-patient dose escalation is allowed. Patients will be evaluated for safety every two weeks, with weekly laboratory testing, according to CTCAEv4.0. and with a DLT window of 28 days (cycle 1). Response will be assessed every 8 weeks (2 cycles of treatment) according to RECISTv1.1. Additionally, biological samples will be collected to understand NEO-201 pharmacokinetic, the effect on the immune system, and their correlation with treatment safety and response. As of February 2019 we have completed enrollment in the first DL and are evaluating for DLT. Clinical trial information: NCT03476681.

Phase 1 clinical trial using armored GPC3 CAR T cells for children with relapsed/refractory liver tumors. First Author: David Henry Michael Steffen, Baylor College of Medicine, Houston, TX

Background: CAR T therapies have been successful against hematologic malignancies, but have benefited only a handful of patients with solid cancers. Glypican 3 (GPC3) is an attractive immunotherapeutic target due to its preferential expression on multiple pediatric and adult solid cancers and lack of expression on non-malignant tissues. GPC3-CAR T cells were tested preclinically in combination with the 4-1BB costimulatory endodomain with IL-15 and IL-21 co-expression enabled CAR T cells to expand and persist the most in vitro and in vivo and led to robust antitumor activity in vivo. We are now testing GPC3-CAR T cells with IL15 and IL21 for the first time in children with relapsed/refractory liver tumors. Methods: In this Phase 1 trial (GAP, NCT02932956), we are evaluating patients in 3 cohorts: 1) GPC3-CAR alone; 2) GPC3-CAR and IL15; 3) GPC3-CAR with IL15 and IL21. We will 1) define the safety and establish the Recommended Phase 2 Dose (RP2D) of GPC3-CAR T cells co-expressing IL15 and IL21; 2) determine persistence and anti-tumor activity of GPC3-CAR cells; 3) examine changes in gene and protein expression in the tumor microenvironment associated with potential immune escape mechanisms. Inclusion criteria are the following: age ≤18; history proven, GPC3-positive tumor; life expectancy ≥12 weeks; Child-Pugh-Turcotte score ≤7; serum AST ≤5 times ULN; total bilirubin ≤3 times ULN for age; INR ≤1.5; absolute neutrophil count >5000µl; platelet count >20,000µl; Hgb >9.0 g/dl. Toxicity will be monitored using the Common Terminology Criteria of Adverse Events v4. The RP2D will be determined by the standard 3+3 dose escalation method using 5 dose levels. Persistence will be quantified using RT-PCR and flow cytometry. Antitumor activity will be defined by 3D imaging using RECIST 1.1 criteria and the immune-related response criteria. Immune-escape will be examined by using single cell RNA sequencing and imaging of paraffin-embedded tissues using codelection by indexing to evaluate candidate proteins. Data will be analyzed via descriptive statistics. Cohort 1 of this study is now open for enrollment. Clinical trial information: NCT02932956.

A phase I/b multicenter study to evaluate the humanized anti-CD73 antibody, CPI-006, as a single agent, in combination with CPI-444, and in combination with pembrolizumab in adult patients with advanced cancers. First Author: Mehrdad Mobasher, Corvus Pharmaceuticals Inc, Burlingame, CA

Background: CD73 expression is elevated in tumors and contributes to increasing levels of immunosuppressive adenosine in the tumor microenvironment. CD73 knockout mice exhibit reduced tumor growth and resistance to experimental metastasis. Inhibition of CD73 activity with an anti-CD73 antibody blocks adenosine production, shown to inhibit tumor growth in syngeneic mouse models. CPI-006 is a humanized IgG1 Fc-y binding-deficient anti-CD73 antibody now being investigated in this Phase I/b multicenter, open label trial as single agent (SA) or combination with CPI-444, an oral, small molecule, selective A2A receptor antagonist or in combination with pembrolizumab, an anti-PD1 indicated for the treatment of patients across a number of malignancies (NCT03454451). Methods: Up to 462 subjects will be enrolled at approximately 35 sites in the US, Canada and Australia. Eligible patients must have: non-small cell lung, renal cell carcinoma, uterine, cervical, colorectal, ovarian, pancreatic, prostate, head and neck, triple-negative breast, endometrial, select sarcomas and non-Hodgkin lymphoma malignancies relapsed, refractory or intolerant to 1 to 5 standard therapies; aged ≥ 18 yo; adequate organ function and measurable disease. The objectives of the study are 1) evaluate the safety and tolerability of SA CPI-006, in combination with CPI-444 and in combination with pembrolizumab, 2) evaluate the pharmacokinetics of each regimen and 3) identify potential biomarkers predictive of response. Study design in table. Study Design. Clinical trial information: NCT03454451.

Dose escalation.

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<th>CPI-006 SA</th>
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<tr>
<td>Dose Expansion Stage 1 (N=11 per cohort)</td>
<td>Dose Expansion Stage 2 (N=17 per cohort)</td>
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<td>CPI-006 + pembrolizumab</td>
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A phase II study of autologous tumor infiltrating lymphocytes (TIL, LN-144/ LN-145) in patients with solid tumors. First Author: Jason Alan Ch'ien, James Graham Brown Cancer Center, University of Louisville, Louisville, KY

Background: Adoptive cell therapy (ACT) with tumor infiltrating lymphocytes (TIL) has demonstrated durable complete responses in immunogenic tumors with high mutational burden in metastatic melanoma patients who had not received prior immune checkpoint inhibitors (ICI); CR rate 24%. Pembrolizumab is an approved agent for the treatment of metastatic melanoma and head & neck cancers among others. Further, ICI have been reported to potentially enhance the efficacy of TIL therapy. One aim of this study is to improve the efficacy response for early line patients by combining TIL with anti-PD-1 in ICI-naive patients with metastatic melanoma (Cohort 1) and head & neck cancers (Cohorts 2). In Cohort 3, TIL therapy alone is offered to NSCLC patients who have received prior systemic therapy, including ICI. Methods: IOV-COM-202 is a prospective, Phase 2 multicenter, open-label study in which 36 patients (12 per cohort) are to be enrolled in one of three cohorts; Cohorts 1 and 2: TIL therapy in combination with pembrolizumab, or Cohort 3: TIL therapy alone. Patients will have tumors resected at local centers and shipped to a central GMP facility to undergo a 22-day manufacturing process that yields cryopreserved infusion product (LN-144/ LN-145) that is shipped back to treating center. All patients receive TIL therapy consisting of 1 week of preconditioning cyclophosphamide/fludarabine, followed by a single infusion of LN-144/LN-145 (Day 0) and up to 6 doses of IL-2 (600,000 IU/kg). Patients in Cohorts 1 and 2 also receive pembrolizumab on Day -1 and then Q3W for up to 2 years or until disease progression or acceptable toxicity. Co-primary endpoints for each cohort are objective response rate (ORR) per RECIST 1.1, and safety (grade ≥ 3 TEAE). Eligibility criteria: Cohorts 1 (melanoma) and 2 (head & neck): patients must not have received prior ICI (eg, anti-PD-1, anti-CTLA-4) and may have received up to 3 lines of prior systemic therapy, Cohort 3 (NSCLC): patients must have received 1-3 prior lines of systemic therapy including ICI. After tumor resection for TIL manufacturing, patients must have additional measurable disease for assessment per RECIST 1.1. Adequate bone marrow/organ function and ECOG PS of 0 or 1 is required. Clinical trial information: NCT03645928.
Intravenous administration of ALKS 4230 as monotherapy and in combination with pembrolizumab in a phase I study of patients with advanced solid tumors.

**Background:** ALKS 4230 is a fusion protein of circularly permuted IL-2 and IL-2 Receptor (IL-2R) α designed to selectively bind the intermediate-affinity (ia) IL-2R, comprised of IL-2Rβ and γc, for activation of CD8 T cells and NK cells, which drive antitumor immune responses. In contrast, unmodified IL-2 activates high-affinity (ha) IL-2R, driving the expansion of immunosuppressive CD4+ regulatory T cells (Tregs) at concentrations below IL-2 Receptor (IL-2R) affinity (ia) IL-2R, comprised of IL-2Rβ and γc, for activation of CD8 T cells and NK cells, which drive antitumor immune responses. In contrast, unmodified IL-2 activates high-affinity (ha) IL-2R, driving the expansion of immunosuppressive CD4+ regulatory T cells (Tregs) at concentrations below those of s.c. activate IL-2R expressing cancer cells. IL-2 to ha-IL-2R on endothelial cells may contribute to capillary leak syndrome seen with high-dose IL-2. Thus, selective activation of the il-2R by ALKS 4230 has the potential to enhance tumor killing and improve tolerability. ALKS 4230 has previously been shown to improve antitumor activity relative to IL-2 in murine models. In this clinical study, ALKS 4230 will be assessed as monotherapy and in combination with anti-PD-1 therapy.

**Methods:** ALKS 4230 is being studied in adults with advanced solid tumors in a phase I first-in-human trial designed primarily to assess the safety of ALKS 4230 alone and with pembrolizumab. The study will also determine a monotherapy recommended phase II dose (RP2D) and characterize its tolerability, immunogenicity, and evidence of anti-tumor activity. It will be conducted in 3 parts: monotherapy dose escalation (Part A), monotherapy dose expansion at the RP2D (Part B), and combination therapy with pembrolizumab (Part C). ALKS 4230 is administered as a 30 minute IV infusion once daily or every other day in each of 3 dose levels in each of the parts in the patient. Eligibility requires ECOG PS 0-1 and adequate bone marrow, liver and kidney function. Part B will enroll 21 patients each in renal cell carcinoma and melanoma cohorts. Part C will enroll up to 79 patients total into 3 cohorts based on tumor type and prior anti-PD-1 therapy; a 4th cohort will enroll patients from Part A and C who receive objective response/progression, or experienced disease progression on monotherapy. The primary PD endpoint is change from baseline in CD8+, T, NK, and Treg cell counts. Inflammatory cytokine levels will also be measured. Parts A and C are currently enrolling. Clinical trial information: NCT02799095.

**TPS2651**

The "INSIGHT" Trial: Two new strata of an explorative, open-labeled phase I study evaluating the feasibility and safety of autologous IMP321 injections (LAG-3 fusion protein, eftilagimod alpha) combined with either standard-of-care drug therapy or PD-L1 inhibition (avelumab) in advanced-stage solid tumor entities.

**Background:** The two new strata of the INSIGHT trial evaluate feasibility and safety of s.c. injections of IMP321 (eftilagimod alpha) in combination with either SOC first/second-line drug therapy (Stratum C) or in combination with a PD-L1 inhibitor (avelumab; Stratum D) in advanced stage solid tumors as well as to generate first efficacy data. This proof-of-concept data could build the basis for further clinical studies exploring the therapeutic potential of combinations of active immunotherapy using IMP321 with SOC drug therapies or immunotherapies targeting the PD-1/PD-L1 axis in various solid tumor entities. IMP321 is a MHC class II agonist that activates antigen-presenting cells (primary target cells) and then CD8 T cells (secondary target cells). Activation of the dendritic cell network and subsequent T cell recruitment at the tumor site with IMP321 may lead to enhanced anti-tumor CD8 T cell responses. Thus, especially combinations with PD-1/PD-L1 inhibitors might display interesting effects by activating immune cells and disabling immune inhibitory mechanisms at the same time. **Methods:** This is a prospective investigator initiated phase I trial consisting of four strata. New stratum D: Patients will receive avelumab i.v. q2w along with s.c. IMP321 injections. This combination is aimed to enhance the immune response against tumor cells compared to chemo-targeted SOC therapy alone. New stratum D: Patients with solid tumors treated with SOC chemotherapy or targeted therapy in first or second line receive concomitant s.c. IMP321 injections. This combination is aimed to enhance the immune response against tumor cells compared to chemo-targeted SOC therapy alone. New stratum D: Patients with solid tumors treated with SOC chemotherapy or targeted therapy in first or second line receive concomitant s.c. IMP321 injections. This combination is aimed to enhance the immune response against tumor cells compared to chemo-targeted SOC therapy alone. New stratum D: Patients with solid tumors treated with SOC chemotherapy or targeted therapy in first or second line receive concomitant s.c. IMP321 injections. This combination is aimed to enhance the immune response against tumor cells compared to chemo-targeted SOC therapy alone.

**TPS2652**

A first-in-human phase I study of FS118, an anti-LAG-3/PD-1 bispecific antibody in patients with tumor infiltrating lymphocytes that have progressed on prior PD-1/PD-L1 therapy.

**Background:** Adaptive cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL) has a long history of efficacy in metastatic melanoma, and is being increasingly considered across other solid tumors. Preclinical data generated at MD Anderson Cancer Center has demonstrated the ability to grow TIL from a variety of tumor types including various types of sarcomas, ovarian and pancreas cancers. We are testing the efficacy of TIL across multiple tumor types using two different manufacturing protocols. **Methods:** We are conducting two ongoing investigator initiated basket TIL therapy trials. The first (NCT03449108) includes cohorts with poorly differentiated soft tissue and bone sarcomas, osteosarcoma, and platinum resistant ovarian cancer. The TIL product used in this trial is an investigational cell product (LN-145, Iovance Biotherapeutics, Inc.). The second trial (NCT03610490) includes cohorts of osteosarcoma, platinum resistant ovarian cancer, and pancreatic cancer (who have progressed on, or received maximal benefit from, front-line therapy). For this trial, TIL are manufactured at MD Anderson Cancer Center using a protocol that includes the use of urelumab (an agonistic anti-CD137 antibody) to potentially deliver superior anti-tumor efficacy while limiting immunotherapy-related adverse effects by dual targeting.

**TPS2653**

Adaptive transfer of tumor-infiltrating lymphocytes in patients with sarcomas, ovarian, and pancreatic cancers.

**Background:** In a small cohort, TIL-LAG-3 expression enriched for TILs with T cell receptor activation during TIL expansion. In both trials eligible subjects undergo tumor harvest using a surgical excisional biopsy of the tumor for TIL manufacturing, receive a modified cyclophosphamide and fludarabine lymphodepletion regimen and up to six doses of IL-2 (600,000 IU/kg) following TIL infusion. No intervening therapy is allowed in between TIL harvest and initial cycles of lymphodepletion. The primary endpoint for each cohort is ORR as assessed by investigators using RECIST 1.1 criteria. The Simon’s two stage design is used to monitor the efficacy of each cohort independently. In the first stage, 10 patients will be treated per cohort. If there is no confirmed response in these 10 evaluable patients, the cohort will be terminated. If the cohort moves forward to Stage II, an additional 8 patients will be treated leading to a total of 18 patients. Three or more responders out of 18 treated patients for the cohort will be considered clinically relevant to justify further investigation. Enrollment is ongoing in all cohorts in both trials. An accrual update will be provided at the annual meeting. Clinical trial information: NCT03449108, NCT03610490.
Background: ATOR-1015 is a human bispecific IgG1 antibody targeting cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and the tumor necrosis factor receptor superfamily member 4,OX40 (also known as CD134). Both in vitro and in vivo, ATOR-1015 induces activation of cytotoxic T cells and depletion of regulatory T cells (1). In syngeneic tumor models, using human OX40 transgenic mice cross-reacting with both targets, ATOR-1015 is demonstrated to localize to the tumor. Further, the effects of ATOR-1015 are shown to occur in the tumor area and not in the spleen (1). Treatment with ATOR-1015 also reduces tumor growth and improves survival in several tumor models in mice, including bladder, colon and pancreatic cancer (1). The non-clinical safety profile and the pharmacokinetics were established in cynomolgus monkeys and the data were used for the dosing schedule.

Methods: This is a multicenter, open-label, dose escalation study enrolling patients with advanced and/or refractory solid malignancies (NCT03782467). The primary objective of the study is to determine the maximum tolerated dose (MTD) or the recommended phase 2 dose (RP2D) and to establish the safety profile of ATOR-1015. ATOR-1015 is administered intravenously biweekly (MTD) or the recommended phase 2 dose (RP2D) and to establish the safety and efficacy evaluation. Study enrollment was initiated in January 2019. A total of up to 53 patients are estimated to be enrolled in the study. (1) Måsson Kvarnhammar et al. Journal for ImmunoTherapy of Cancer; 2018; 6(Suppl 1):115. Abstract P683. Clinical trial information: NCT03782467.

Background: In patients (pts) with locally advanced or metastatic G/GJE cancer, fluoropyrimidine- and platinum (pt)-based combination chemotherapy is first-line standard of care. Despite improvement in chemotherapy regimens, outcomes are poor and survival remains low. Tislelizumab, an investigational anti-PD-1 antibody, was engineered to minimize binding of FcyR on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. Previous reports suggested tislelizumab, as a single agent and in combination with chemotherapy, was generally well tolerated and had antitumor activity in pts with advanced solid tumors, including G/GJE cancer. Methods: This global, double-blind, randomized, phase 3 study (NCT03777657) is designed to compare pt/fluoropyrimidine + tislelizumab versus pt/fluoropyrimidine + placebo as first-line therapy for locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GJE) adenocarcinoma. First Author: Rui-hua Xu, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: ESCC remains the predominant histological subtype of, and accounts for most deaths from, esophageal cancer. PD-1 inhibition has demonstrated antitumor activity and was generally well tolerated in patients (pts) with advanced unresectable or metastatic ESCC. Tislelizumab, an investigational anti-PD-1 antibody, was engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. Results from early phase clinical studies suggest single-agent tislelizumab was generally well tolerated and had antitumor activity in pts with solid tumors, including ESCC. Methods: This phase 3, randomized, placebo-controlled, double-blind study (NCT03783442) is designed to evaluate the efficacy and safety of tislelizumab plus chemotherapy as first-line treatment for unresectable, locally advanced recurrent/metastatic esophageal squamous cell carcinoma (ESCC). First Author: Jian-Ming Xu, The Fifth Medical Center, People’s Liberation Army General Hospital, Beijing, China

Background: Programmed cell death 1 immune checkpoint inhibitors (anti-PD-1, anti-PD-L1) have demonstrated clinical benefit in a subset of patients with manageable safety across a variety of tumor types. T-cell immunoglobulin and mucin-domain-containing molecule-3 (TIM-3) can be co-expressed with PD-1 on exhausted T-cells and may be upregulated in tumor microenvironment (TME) to limit anti-PD-L1 therapy (Koyama et al. 2016). Pre-clinical studies demonstrated that blockade of both PD-1 and TIM-3 improved survival of tumor-bearing mice compared to blocking anti-PD-1 only (Koyama et al. 2016). LY3415244 is a TIM-3/PD-L1 bispecific antibody that has the ability to target and inhibit both TIM-3 and PD-L1 and the potential to overcome primary and acquired anti-PD-L1 resistance by a novel mechanism to bridge TIM-3 and PD-L1-expressing cells. Methods: Study JZDA is a multicenter, nonrandomized, open-label, Phase 1a/1b study of LY3415244 in patients with advanced solid tumors. In Phase 1a, subjects with any tumor type who are either PD-L1 inhibitor-naive or exposed are eligible. In Phase 1b, patients with any tumor type who are either PD-L1 inhibitor-naive or exposed are eligible. In Phase 1a, subjects with any tumor type who are either PD-L1 inhibitor-naive or exposed are eligible. In Phase 1b, patients with any tumor type who are either PD-L1 inhibitor-naive or exposed are eligible. In Phase 1a, subjects with any tumor type who are either PD-L1 inhibitor-naive or exposed are eligible. In Phase 1b, patients with any tumor type who are either PD-L1 inhibitor-naive or exposed are eligible. Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
have been observed in the single pt cohorts. Assessment of pts enrolled into all study objectives will be descriptive and hypothesis generating. No DLTs graded as per CTCAE v4.03, responses as per RECIST v1.1. The analyses of preliminary antitumor activity of COM701. Statistical Considerations: AEs to identify the maximum tolerated dose and/or the recommended dose for vous system metastases. Primary objectives are safety and tolerability of interstitial or inflammatory lung disease, untx or symptomatic central ner-

Defects in DNA damage response genes, including BRCA1/2, ATM (serine/threonine protein kinase) and clear, or BRCA1 (human homolog of the Drosophila mismatch repair gene) and BRCA2 (brca2 breast and ovarian cancer susceptibility), are associated with a predisposition to tumor development. The BRCA1/2 genes are involved in the homologous recombination (HR) pathway, which plays a critical role in the repair of DNA double-strand breaks (DSBs). BRCA1 and BRCA2 act in the HR pathway by recruiting and stabilizing the MRN (mre11, rad50, nbs1) complex, thereby promoting the recruitment of the DNA repair machinery.

TPS2657 Poster Session (Board #294b), Sat, 8:00 AM-11:00 AM
A phase I study evaluating COM701 in patients with advanced solid tumors. First Author: Drew W. Rasco, South Texas Accelerated Research Therapeutics (START), San Antonio, TX

Background: There is a high unmet medical need for the treatment (tx) of patients (pt) who are refractory to or relapse following tx with checkpoint inhibitors. Newer checkpoint therapies with novel mechanisms of action that can activate T cells and demonstrate antitumor activity in this pre-tx pt population are urgently needed. COM701 is a novel first-in-class humanized IgG4 monoclonal antibody that binds with high affinity to PVRIG (poliovirus receptor related immunoglobulin domain containing) blocking its interaction with its ligand, PVRIL2. Both PVRIG and PVRIL2 are part of the DNAM axis as are TIGIT and PD1. Inhibition of PVRIG leads to enhanced activation of T and NK cells, and PVRIG results in tumor growth inhibition in mouse tumor models. We hypothesize that COM701 will demonstrate antitumor activity in pts who are checkpoint inhibitor pre-tx. Methods: NCT03566716 is an ongoing open-label first-in-human phase 1 study in pts with advanced solid tumors. The initial part of this study (Arm A) will evaluate escalating doses of COM701 monotherapy IV Q3 weekly with single pt cohorts for the initial 4 and then 3+3 design. Key Inclusion Criteria: Age ≥ 18 yrs, histologically confirmed locally advanced or metastatic solid tumor, has a Zubrod performance status of 0-2, with absolute neutrophil count ≥ 1,000/mcL, platelets ≥ 75,000/mcL, hemoglobin ≥ 8 g/dL, creatinine clearance ≥ 50 mL/min, total bilirubin ≤ 2.0 x institutional upper limit of normal (IU/L), AST and ALT ≤ 1.2 x IU/L, TSH or free T4 serum ≤ IU/L, and normal adrenocorticotropic hormone (ACTH) ≤ IU/L. The primary endpoint was overall response rate (ORR) by RECIST v1.1 (complete (CR) and partial responses (PR)); secondary endpoints included progression-free (PFS) and, overall survival (OS), stable disease (SD) ≥ 6 months, and toxicity. The objectives of this Phase II trial were to confirm the overall response rate (ORR, confirmed complete and partial responses (CR and PR)) by RECIST v1.1. The analyses of all study objectives will be descriptive and hypothesis generating. No DLTs have been observed in the single pt cohorts. Assessment of pts enrolled into cohort 5 is ongoing at the time of this submission. Clinical trial information: NCT03667716.

TPS2658 Poster Session (Board #295a), Sat, 8:00 AM-11:00 AM
SWOG 1609 (DART): A phase II basket trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors. First Author: Sandip Pravin Patel, University of California San Francisco Cancer Center, San Francisco, CA

Background: Immune checkpoint blockade, in particular anti-CTLA-4 and anti-PD-1-directed approaches, have improved outcomes in various tumor types. However, little is known about the efficacy of these agents in advanced rare solid tumors. We sought to investigate the activity of ipilimumab and nivolumab in previously unstudied rare solid tumors, with planned biomarker evaluation pending including whole exome sequencing, RNAseq, and multiplex immune profiling via the NCI CIMACs.

Methods: We performed a prospective, open-label, multicenter phase II clinical trial of ipilimumab (1mg/kg iv q6weeks) plus nivolumab (240mg iv q2weeks) across 37 cohorts of rare tumors. Eligible patients had incurable rare cancer, defined histo-

Background: The ARETHUSA clinical trial (NCT03519412) is a phase II trial consisting of three different phases. In the initial part of this study (Arm A) will evaluate escalating doses of COM701 monotherapy IV Q3 weekly with single pt cohorts for the initial 4 and then 3+3 design. Key Inclusion Criteria: Age ≥ 18 yrs, histologically confirmed locally advanced or metastatic solid tumor, has a Zubrod performance status of 0-2, with absolute neutrophil count ≥ 1,000/mcL, platelets ≥ 75,000/mcL, hemoglobin ≥ 8 g/dL, creatinine clearance ≥ 50 mL/min, total bilirubin ≤ 2.0 x institutional upper limit of normal (IU/L), AST and ALT ≤ 1.2 x IU/L, TSH or free T4 serum ≤ IU/L, and normal adrenocorticotropic hormone (ACTH) ≤ IU/L. The primary endpoint was overall response rate (ORR) by RECIST v1.1 (complete (CR) and partial responses (PR)); secondary endpoints included progression-free (PFS) and, overall survival (OS), stable disease (SD) ≥ 6 months, and toxicity. The objectives of this Phase II trial were to confirm the overall response rate (ORR, confirmed complete and partial responses (CR and PR)) by RECIST v1.1. The analyses of all study objectives will be descriptive and hypothesis generating. No DLTs have been observed in the single pt cohorts. Assessment of pts enrolled into cohort 5 is ongoing at the time of this submission. Clinical trial information: NCT03667716.

TPS2659 Poster Session (Board #295b), Sat, 8:00 AM-11:00 AM
Pembrolizumab in MMR-proficient metastatic colorectal cancer pharmacologically primed to trigger dynamic hypermutation status: The ARETHUSA clinical trial. First Author: Salvatore Siena, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

Background: Metastatic colorectal cancer (CRC) harbouring genetic defects in the mismatch-repair pathway (MMRd) presents with a high tumor mutational burden (TMB), and is highly sensitive to immune checkpoint blockade. Theoretically, the pharmacological treatment with temozolomide (TMZ) can induce the inactivation of MMR genes, and consequently the pharmacological treatment with temozolomide (TMZ) can induce the inactivation of MMR genes, and consequently the increase of TMB and immunogenic neoantigens, thus suggesting that TMZ could be used to prime MMR proficient (MMRp) tumors for response to checkpoint inhibitors. Accordingly, mCRC patients recruited in previous clinical trials with TMZ as administered, acquired alterations of MMR genes upon treatment and showed remarkable increase in TMB at disease progression (PD). We thus designed the ARETHUSA clinical trial to treat a primary course with TMZ in patients who can sensitize mCRC to the anti-PD-1 inhibitor pembrolizumab. Methods: Arethusa (NCT03519412) is a 2-cohorts, phase II trial consisting of three different phases. In the SCREENING, 348 mCRC RAS-mutated patients will be tested for MMR status. MMRd patients will proceed directly to TRIAL for immediate pembrolizumab treatment (expected 14). MMR-proficient (MMRp) patients will be further tested for expression of O6-methylguanine-DNA methyltransferase (MGMT) by immunohistochemistry and by promoter methylation analysis. IHC-negative, promoter methylation-positive MMRp patients (expected 67) will enter in the PRIMING phase and will be treated with TMZ until PD. TMB will then be assessed on tumor biopsies at resistance. Those patients that will have ≥ 20 mutations/megabase will proceed to TRIAL (expected 20) and will be treated with pembrolizumab. Overall response rate (primary outcome), Progression Free, and Overall Survival, and treatment related toxicities (secondary outcomes) in MMRp pembrolizumab-treated patients will be estimated., while the MMRd cohort will be used for comparison. Tissue biopsies, longitudinal blood and stool collection will be used for discovery of predictive molecular biomarkers and assessment of tumor evolution. Clinical trial information: NCT03519412.

TPS2660 Poster Session (Board #296a), Sat, 8:00 AM-11:00 AM
JAVELIN BRCA/ATM: A phase 2 trial of avelumab (anti-PD-L1) plus talazoparib (PARP inhibitor) in patients with advanced solid tumors with a BRCA1/2 or ATM defect. First Author: David Michael Hyman, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Defects in DNA damage response genes, including BRCA1/2 and ATM, confer sensitivity to PARP inhibitors. Talazoparib is a potent, oral PARP inhibitor with a dual mechanism of action (PARP enzyme inhibition and PARP trapping). Avelumab is a human anti-PD-L1 IgG1 monoclonal antibody with a wild-type Fc region that has shown clinical activity in multiple tumor types. Preclinical and early clinical data suggest that combining a PARP inhibitor with an immune checkpoint inhibitor may provide improved activity. Methods: JAVELIN BRCA/ATM (NCT03565991) is an ongoing, open-label, multicenter, phase 2 trial assessing the combination of avelumab and talazoparib. Enrollment of ~200 patients with a histologically confirmed locally advanced or metastatic solid tumor that has progressed on > 1 line of standard-of-care treatment for locally advanced or metastatic disease and has a germline or somatic defect in BRCA1 or ATM, confer sensitivity to PARP inhibitors. Talazoparib is a potent, oral PARP inhibitor with a dual mechanism of action (PARP enzyme inhibition and PARP trapping). Avelumab is a human anti-PD-L1 IgG1 monoclonal antibody with a wild-type Fc region that has shown clinical activity in multiple tumor types. Preclinical and early clinical data suggest that combining a PARP inhibitor with an immune checkpoint inhibitor may provide improved activity. Methods: JAVELIN BRCA/ATM (NCT03565991) is an ongoing, open-label, multicenter, phase 2 trial assessing the combination of avelumab and talaza-

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
A phase I, first-in-human, open label, dose-escalation and cohort expansion study of MET-4, a bispecific DART protein binding PD-1 and CTLA-4 in patients with recurrent/metastatic solid tumors: A phase 1b study to evaluate the safety, determine recommended phase 2 dose, and evaluate antitumor activity in recurrent/metastatic prostate cancer (mCRPC) and metastatic endometrial cancer (mEC). First Author: Rohit K. Jain, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: Immune checkpoint blockade may induce tumor destruction via both direct antitumor effects and the induction of an antitumor adaptive immune response. The combination of PD-1/PD-L1 inhibitors with other immunotherapeutic approaches, such as radiotherapy and/or chemotherapy, is being evaluated in clinical trials. However, the optimal combinations and clinical benefits that may be achieved for each clinical setting remain unknown. In a previous biomarker-driven clinical study, PD-L1 expression in tumor samples was significantly associated with better response to anti-PD-1/PD-L1 antibodies.

Methods: A phase Ib study to evaluate the safety, determine recommended phase 2 dose, and evaluate antitumor activity in recurrent/metastatic prostate cancer (mCRPC) and metastatic endometrial cancer (mEC). First Author: Raanan Alter, University of Chicago, Chicago, IL

Background: Immune checkpoint blockade (ICB) antibodies have made a major impact in a wide range of cancers. However, only subsets of patients across all malignancies benefit from ICB. In particular, metastatic castrate-resistant prostate cancer (mCRPC) and advanced endometrial cancers (EC) have shown very limited responses to ICB. The central hypothesis of this trial is that the combination of PARP inhibitor (rucaparib) with PD-1 inhibitor (nivolumab) will enhance ICB efficacy in mCRPC and mEC patients. Given that PTEN loss has also been associated with poor response to ICB, a secondary hypothesis of this study is that the combination therapy will have a major impact in a wide range of cancers. However, only subsets of patients across all malignancies benefit from ICB. In particular, metastatic castrate-resistant prostate cancer (mCRPC) and advanced endometrial cancers (EC) have shown very limited responses to ICB. The central hypothesis of this trial is that the combination of PARP inhibitor (rucaparib) with PD-1 inhibitor (nivolumab) will enhance ICB efficacy in mCRPC and mEC patients. Given that PTEN loss has also been associated with poor response to ICB, a secondary hypothesis of this study is that the combination therapy will have a major impact in a wide range of cancers.
TPS2665 Poster Session (Board #298b), Sat, 8:00 AM-11:00 AM
Phase 1/1b multicenter trial of TPST-1120, a peroxisome proliferator-activated receptor alpha (PPARα) antagonist as a single agent (SA) or in combination with pembrolizumab (TPST-0350). First Author: Gina Laport, Tempeste Therapeutics, San Francisco, CA

Background: Tumor cells initially favor glucose metabolism via aerobic glycolysis. As tumors rapidly proliferate and metastasize, glucose stores are depleted and facilitated by a hypoxic tumor microenvironment (TME) and metabolic reprogramming shifts intracellular metabolism (iCM) towards fatty acid oxidation (FAO). Fatty acids support metabolism of suppressive immune cells in the TME to tumor growth (PGPRs). PPARα, a nuclear transcription factor which regulates lipid metabolism and FAO. TPST-1120 is a first in class, oral selective PPARα antagonist that blocks transcription of PPARα target genes leading to an intracellular metabolism shift from FAO to glycolysis. Reduction of fatty acids in the TME leads to direct killing of tumor cells dependent on FAO, skew macrophages from immune suppressive M2 phenotype to an effector M1 phenotype and facilitates the cytotoxicity of immune effector cells. TPST-1120 also restores thymospondin-1, a known natural inhibitor of angiogenesis, to homeostatic levels within the TME. TPST-1120 has an IC50 of 0.04 nM with > 35 fold selectivity over other PPAR isoforms. Preclinical studies in tumor models show efficacy of TPST-1120 as a SA and in combination (combo) with an anti-PD1 monoclonal antibody (mAb) and chemotherapy.

Methods: We have initiated a phase 1/1b multicenter, open label Dose Escalation (DeS) and Dose Expansion (DeX) trial to evaluate TPST-1120 as a SA and in combo with nivolumab, an anti-PD1 mAb, docetaxel, a chemotherapeutic agent and cetuximab, an anti-EGFR mAb. Objectives: 1) evaluate safety and tolerability of continuous dosing of TPST-1120 2) identify a recommended phase 2 dose (RP2D) and 3) evaluate efficacy. Eligibility: 1) patients with selected advanced solid tumors who have failed 1 and up to 5 prior lines of therapies. They are administered with TPST-1120 in nivolumab and 3 combination arms in which TPST-1120 is combined with nivolumab, docetaxel or cetuximab. The RP2D of TPST-1120 to proceed to DeX will be determined by safety and biomarkers during DeS. The DeX arms have 8 histology-specific cohorts, 4 SA arms and 4 combo arms and will follow a 3+3 escalation design. Biomarker analyses include gene expression profiling of PPARα-associated genes, tumor markers of immune modulation and serum lipid profiling. The total sample size is up to 338 pts. This trial is accruing at US sites. Clinical trial information: NCT03829436.

TPS2666 Poster Session (Board #299a), Sat, 8:00 AM-11:00 AM
An open label, multicenter, phase 1b/2 study of rebastinib (DCC-2036) in combination with carboplatin to assess safety, tolerability, and pharmacokinetics in patients with advanced or metastatic solid tumors. First Author: Anthony W. Tolcher, NextOncology, San Antonio, TX

Background: Rebastinib is a potent, orally administered, kinase switch control inhibitor selectively targeting the tumica interna endothelial cell kinase (TIE2). TIE2 is primarily expressed in endothelial cells and has critical roles in angiogenesis. In addition, TIE2 is highly expressed in a subset of macrophages, TIE2-expressing macrophages (TEMs), which are known to have proangiogenic, pro-metastatic, and immunosuppressive properties. Accumulating evidence suggests that chemotherapies, such as carboplatin, increase the recruitment and activity of pro-tumoral TEMs, leading to chemotherapy resistance. Taken together, investigation of rebastinib in combination with a chemotherapy such as carboplatin, one of the most commonly used agents across different tumor types, is warranted in advanced solid tumors. Methods: This study is an open-label, Phase 1b/2, multicenter study in patients with advanced or metastatic solid tumors. The study has two parts: the first part is the 3+3 dose escalation phase designed to evaluate the safety, tolerability and pharmacokinetics of 50 mg and 100 mg rebastinib administered once every three weeks to determine the recommended phase 2 dose (RP2D). Patients who have exhausted all therapies and for whom carboplatin is considered appropriate treatment will be enrolled. The second part is the dose expansion phase with three cohorts: previously treated breast cancer, recurrent, platinum-sensitive ovarian cancer, and malignant mesothelioma to evaluate the safety, tolerability, and efficacy of the RP2D. A Simon’s two-stage design will be used in the second part and initially up to 18 patients will be enrolled into each cohort. If more than 4 responses are observed, then the cohort will be expanded up to 33 patients. This trial is expected to enroll in total, up to 117 patients, approximately 18 patients in the first part and up to 99 patients in the second part. This study is currently open only in the US. Clinical trial information: NCT03717415.

TPS2667 Poster Session (Board #299b), Sat, 8:00 AM-11:00 AM
A multicenter, phase II study of soluble LAG-3 (Eftilagimod alpha) in combination with pembrolizumab (TACT-016). In-patient studies in patients with advanced non-small cell lung cancer (NSCLC) or head and neck squamous cell carcinoma (HNSCC). First Author: Julio Antonio Pegoero, Oncology Consultants PA, Department of Research, Houston, TX

Background: Eftilagimod alpha (efi, IMP321) is a recombinant LAG-3 Ig fusion protein that binds to MHC class II and mediates antigen-presenting cell (APC) activation followed by CD8 T-cell activation. Pembrolizumab binds to the PD-1 receptor and prevents PD-1 from interacting with PD-L1 and PD-L2, from interacting with PD-1 to help restore effector T-cell responses. The rationale to combine efi and pembrolizumab comes from their complementary mechanisms of action. Efi activates APCs and lead to an increase in activated T cells which effect potentially reduces the number of non-responders to pembrolizumab. Combining an APC activator like efi to pembrolizumab is therefore fundamentally different from many other trials combining two checkpoint inhibitors like an anti-LAG-3 mAb with an anti-PD-1 mAb. In a previous phase I study (NCT 02676869) in metastatic melanoma the combination was found to be safe and well tolerable with encouraging signs of clinical activity. Methods: In the course of this multicenter, open label, Phase II study, patients will be recruited for each of three indications: A: 1 line, PD-X (PD-1 or PD-L1) naïve non-small cell lung cancer (NSCLC); B: 2 line, PD-X refractory NSCLC; C: 2 line PD-X naïve head and neck squamous cell carcinoma (HNSCC). The study is designed according to Simon’s optimal two-stage design, with objective response rate as accr as primary endpoint. Secondary endpoints include progression free survival and overall survival. In case there are more responses achieved than a predefined threshold (each part counted separately) in pts recruited in the initial stage (n = 58), additional pts (51) will be recruited in stage 2. Efti will be administered for a maximum of 18 cycles (1 cycle = 3 weeks) as 30 mg subcutaneous injection every 2 weeks for the first 8 and every 3 weeks for the following cycles. Pembrolizumab (200 mg intravenous infusion every 3 weeks) is administered in parallel for up to 35 cycles. Patients are followed up for progression and survival. Clinical trial information: 036255232.

TPS2668 Poster Session (Board #300a), Sat, 8:00 AM-11:00 AM
A multicenter, open label, first-in-human study of an oncolytic viral vector expressing an agonistic anti-CD40 antibody (NG-350A) in patients with epithelial tumors (FORTITUDE). First Author: Aung Naing, University of Texas MD Anderson Cancer Center, Houston, TX

Background: NG-350A is a transgene modified variant of the oncolytic platform virus enadenotucirev (EnAd) which expresses a fully human agonist anti-cluster of differentiation 40 (anti-CD40) antibody. The principal advantage of encoding anti-CD40 within an oncolytic virus is the ability to potentially deliver high levels within the tumor coupled with direct cytotoxicity due to viral lysis and stimulation of the immune-system. NG-350A infects and selectively replicates in tumor cells. The anti-CD40 antibodies are expected to activate the patient’s own dendritic cells, macrophages and B-cells to drive CD4+ and CD8+ T-cell immunomodulatory responses and immune mediated tumor cell killing. EnAd is a tumor-selective chimeric Ad11/Ad3 group B oncolytic adenovirus developed using directed evolution. Phase I clinical studies have identified a well-tolerated systemic dose and regimen for EnAd monotherapy. EnAd shows a high level of selective replication and cell killing for a broad range of carcinoma cell lines (of epithelial origin) with little replication in normal and non-carcinoma cells. Methods: This first in human study will evaluate the safety, tolerability and preliminary efficacy of NG-350A together with virus kinetics, immunogenicity and other pharmacodynamic effects to elucidate the mechanism of action of NG-350A in patients with advanced or metastatic epithelial tumours. In the dose escalation phase up to 33 patients evaluable for dose-limiting toxicity will receive NG-350A by IV infusion on Day 1, 3 and 5 at 6 US sites. The first IV cohort in the dose-escalation phase will utilize the conventional ‘3+3’ design; thereafter dose recommendations will be based on a continual reassessment method. Following determination of the recommended phase 2 dose up to 20 patients will be treated in a dose expansion cohort. In a parallel cohort, up to 12 patients will receive a single dose of NG-350A by intratumoral (IT) injection on Day 1 for direct delivery of high viral titres to tumor. Up to six patients are planned to undergo surgical resection of a tumor lesion to optimize translational research. Clinical conduct of the study was initiated in February 2019.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
An open label, multicenter, phase I/II study of RP1 as a single agent and in combination with PD1 blockade in patients with solid tumors. First Author: Mark R. Middleton, Churchill Hill Hospital, Oxford, United Kingdom

Background: RP1 is an attenuated oncolytic HSV-1 that expresses a fusogenic glycoprotein from gibbon ape leukemia virus (GALV-GP R-) and GM-CSF. RP1 induces potent GALV-GP R-enhanced immunogenic cell death and host anti-tumor immunity in murine tumor models and increases PD-L1 expression. This clinical trial (NCT03767348) was designed to test the hypothesis that RP1 is safe when given alone and together with nivolumab (phase 1) and has efficacy together with nivolumab in four tumor types (phase 2).

Methods: The primary goals of this clinical trial in a total of ~150 patients are to define the safety profile of RP1 alone and together with nivolumab, determine the recommended phase 2 dose (phase 1), and then in four phase 2 cohorts, to determine objective response rate in patients with melanoma, non-melanoma skin cancer, urothelial carcinoma and MSI-H solid tumors. Secondary objectives include duration of response, CR rate, PFS, viral shedding, and immune biomarker analysis. Patients with advanced cancer who failed prior therapy were eligible for the phase 1 component. In Phase 2 patients with histologic diagnoses of the four tumor types (N=30 for each) and who meet safety criteria for nivolumab treatment are eligible. Prior treatment with checkpoint blockade is not allowed except for the melanoma cohort. In the phase 1 portion patients are treated by intratumoral injection every two weeks for 5 total doses followed by 12 patients dosed 8 times at the RP2D in combination with nivolumab. Phase 1 patients were enrolled. Clinical trial information: NCT03767348.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Belvarafenib, a novel pan-RAF inhibitor, in solid tumor patients harboring BRAF, KRAS, or NRAS mutations: Phase I study. First Author: Tae Won Kim, Department of Medical Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: Belvarafenib (HM95573/GDC-5573) is an oral type II pan-RAF kinase inhibitor which demonstrates selective anti-tumor activity in several non-clinical cancer models and in cancer patients with RAS- or RAF- mutation. Here we present overall safety and efficacy findings of two phase I studies, consisting of dose escalation and dose expansion stages.

Methods: Patients with advanced solid cancers harboring deleterious RAS- or RAF mutations were enrolled. In the dose escalation study, patients were treated with Belvarafenib at a starting dose of 50 mg once daily (QD) to 800 mg BID to assess safety and tolerability and to identify the recommended dose (RD). Dose escalation was guided based on pharmacokinetic data and used a traditional 3+3 design. The dose expansion study was comprised of 6 cohorts (according to the type of tumor and RAS- or RAF gene mutation) and patients received the RD of Belvarafenib. The primary objective was to explore anti-tumor activity (per RECIST 1.1) and pharmacodynamic effects.

Results: The dose escalation study included 72 patients in 9 dose cohorts (cut-off date of 18 Jan 2017). Dose dependent increase in exposures observed up to 650 mg BID. The most common treatment-emergent adverse events that occurred in more than 20% of patients were rash, dermatitis acniform and pyrexia. A total of 4 DLTs (different kinds of rashes) were reported and included 2 DLTs at the 800 mg BID level. Therefore, 650 mg BID was considered the RD for Belvarafenib. There were 7 partial responses (confirmed PRs) from 200 mg QD to 800 mg BID in NRAS-mutant melanoma, BRAF-mutant melanoma, KRAS-mutant sarcoma, and BRAF-mutant GIST. Four of nine patients with NRAS-mutant melanoma had a PR (ORR 44%). The dose expansion study included 63 patients in 5 indication-specific and basket cohorts, administered with 450 mg BID Belvarafenib (cut-off date of 6 Oct 2018). No new safety signal was detected. There were 2 PRs each in patients with NRAS-mutant melanoma (2/9), BRAF-mutant melanoma (2/6) and BRAF-mutant CRC (2/7), respectively.

Conclusions: Belvarafenib was well tolerated and exhibited anti-tumor activity in patients with advanced solid tumors harboring RAS or RAF mutations. Belvarafenib is being further investigated in combination with the MEK inhibitor cobimetinib. Clinical trial information: NCT02405065, NCT03118817.

Dabrafenib and trametinib in patients with tumors with BRAF V600E/K mutations: Results from the molecular analysis (MATCH) (MACH) Arm H. First Author: April K. Salama, Duke University, Durham, NC

Background: The NCI-MATCH precision medicine trial assigns patients (pts) with solid tumors, lymphomas, or multiple myeloma with progression on prior treatment to a targeted therapy based on genetic alterations identified in pre-treatment biopsies. Arm H (EAY131-H) evaluated the combination of the BRAF inhibitor (inh) dabrafenib (DAB), and the MEK inh, trametinib (TRM), in pts with BRAF V600E/K mutations. Pts with primary or colorectal cancer were excluded. Pts with NSCLC were excluded after the first 3 dose cohorts (N = 16) and had a median age 55.5 y (8 men, 14 women).

Methods: Patients received at least 1 dose of LY3214996 with a median of 3 cycles (range: 1–650 mg BID). The most common treatment-emergent adverse events that occurred in more than 20% of patients were rash, dermatitis acniform and pyrexia. A total of 4 DLTs were reported and included 2 DLTs at the 800 mg BID level. Therefore, 650 mg BID was considered the RD for Belvarafenib. There were 7 partial responses (confirmed PRs) from 200 mg QD to 800 mg BID in NRAS-mutant melanoma, BRAF-mutant melanoma, KRAS-mutant sarcoma, and BRAF-mutant GIST. Four of nine patients with NRAS-mutant melanoma had a PR (ORR 44%). The dose expansion study included 63 patients in 5 indication-specific and basket cohorts, administered with 450 mg BID Belvarafenib (cut-off date of 6 Oct 2018). No new safety signal was detected. There were 2 PRs each in patients with NRAS-mutant melanoma (2/9), BRAF-mutant melanoma (2/6) and BRAF-mutant CRC (2/7), respectively.

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Methods: In this open-label, multicenter study (NCT03600883) is evaluating the safety, tolerability, pharmacokinetic (PK), and efficacy of AMG 510 in adult patients (pts) with locally-advanced or metastatic KRASG12C mutant solid tumors. The primary endpoint is safety; key secondary endpoints include PK, and with locally-advanced or metastatic KRASG12C mutant solid tumors. The primary endpoint is safety; key secondary endpoints include PK, ORR (assessed every 6 weeks [wks]), DOR, and PFS. Key inclusion criteria: KRASG12C mutation identified through DNA sequencing, measurable or evaluable disease, ECOG PS #2, life expectancy >3 months (mo). Key exclusion criteria: active brain metastases, myocardial infarction within 6 mo. A dose exploration will determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D). A dose expansion will enroll pts with NSCLC, CRC, and other advanced solid tumors carrying the KRASG12C mutation. AMG 510 will be given PO until disease progression, intolerance, or withdrawal of consent.

Results: 22 pts (8 men, 14 women; median age 55.5 y) were enrolled in the first 3 dose cohorts. Tumor types: 6 NSCLC, 15 CRC, 1 other. Most pts (n=17) had ≥3 prior lines of treatment (tx). Median tx duration was 28 d (range: 8–134). 5 pts reported 10 treatment-related AEs (grade 1, n=9; grade 2, n=1); there were no DLTs. Pts with melanoma, thyroid, colorectal cancer were excluded. Pts with NSCLC were excluded after the first 3 dose cohorts (N = 16) and had a median age 55.5 y (8 men, 14 women).

Conclusions: AMG 510 has been well tolerated at the dose levels tested and has shown antitumor activity when administered as monotherapy to patients with advanced KRASG12C mutant solid tumors. MTD has not been determined, and enrollment in the dose expansion is ongoing. Clinical trial information: NCT03600883.
Background: ABBV-085 is an ADC conjugated to monomethyl auristatin E, drug:antibody ratio of 2.11 directed against leucine-rich repeat containing 15 (LRRCL15), a type 1 transmembrane protein highly expressed on the surface of sarcomas and cancer-associated fibroblasts in stroma of many other cancers. ABBV-085 induced antitumor activity in both in vitro and xenograft models of sarcoma. This phase I study assessed the safety/tolerability of ABBV-085 in patients (pts) with advanced solid tumors (NCT02565758).

Methods: Eligible pts (≥18 yr; advanced solid tumors) received ABBV-085 intravenously in a 3+3 dose-escalation (DE) design; 0.3- to 4.8-mg/kg doses every 2 wk (8 cohorts). Pharmacokinetics (PK) were assessed in cycle 1 and cycle 3. Results: As of Dec 2018, 78 pts were enrolled in monotherapy DE and dose-expansion (EXP) cohorts (≥2.7 mg/kg, n = 21; 3.6 mg/kg, n = 45; 4.2 mg/kg, n = 6; 4.8 mg/kg, n = 6); median age: 58 yr (range 21-84); median treatment (Tx) duration: 6.2 wk (range 0.3-54.4). Overall, 77 (98.7%) pts reported ≥1 Tx-emergent adverse events (TEAEs). Fatigue (48.7%) was most common. Dose-limiting toxicities occurred at 3.6 mg/kg (n = 1; anemia), 4.2 mg/kg (n = 1; hypertriglyceridemia), and 4.8 mg/kg (n = 2; ileus). No responses were seen in non-breast tumors; 2 (grade 1/2 blurred vision [reversible on study discontinuation]).

Conclusions: ABBV-085 was well tolerated with durable PR observed in pts with advanced sarcomas. Clinical trial information: NCT02565758.

Talazoparib beyond BCRA: A phase II trial of talazoparib monotherapy in BCRA1 and BCRA2 wild-type patients with advanced first cancer or other solid tumors with a mutation in homologous recombination (HR) pathway genes. First Author: Joshua James Gruber, Stanford University School of Medicine, Stanford, CA

Background: Talazoparib, a PARP inhibitor, is active in germline BCRA1/2 mutant advanced HER2-negative breast cancer, but its activity beyond BCRA1/2 is unknown. We conducted a single institution phase II trial to evaluate talazoparib in single-agent solid tumor (sT) pts with advanced HER2-negative breast or other solid tumors with a germline (g) or somatic (s) alteration in HR pathway genes not including BCRA1/2. Methods: Eligible pts had measurable disease, lacked a germline or somatic mutation in BCRA1/2, received at least one prior therapy for advanced HER2-negative breast cancer or other solid tumor and had a HR pathway gene mutation: PALB2, CHEK2, ATM, NBN, BARD1, BRIP1, RAD50, RAD51C, RAD51D, MRE11, ATR, PTEN, FANCA, FANCc, FANCd2, FANCe, FANCf, FANCg, FANCn. Pts with no progression on or within 8 weeks of their last platinum dose were eligible. Pts were treated with talazoparib 1 mg po daily until disease progression. Response was assessed every 8-12 weeks. If 2 or more responses were observed in 10 pts in stage I, the study would proceed to stage II and enroll 10 additional pts. The null hypothesis of a ≤5% objective response rate would be rejected if at least 3 of 20 respond. Results: Twenty pts were enrolled; 13 breast cancer (12 HR+/HER2-, 1 TNBC) and 7 non-breast cancer (pancreas, colon, uterine, testicular, parotid salivary). Median age was 54 years. Of 12 response evaluable pts with breast cancer, 3 had a RECIST response (ORR = 25%, 2 pALB2, 1 CHEK2g/FANCAp/PTEN) and 3 additional pts (pALB2, sATR, sPTEN) had SD ≥ 6 months (CBR = 50%). No responses were seen in non-breast tumors; 2 (CHEK2 testicular, gATM colon) had SD ≥ 6 months. Talazoparib was well tolerated; 5 patients required dose reduction for hematologic toxicity. Results of tumor HR deficiency status assessment from metastatic biopsies and serial ctDNA profiling will be presented. Conclusions: In this proof-of-concept phase II trial, single agent talazoparib demonstrated activity in HER2-negative advanced breast cancer and other solid tumors with a HR pathway mutation beyond BCRA1/2. Further evaluation of talazoparib in this population is warranted. Clinical trial information: NCT02401347.
Phase 1/2 trial of FF-10502-01, a pyrimidine antimetabolite, in patients with advanced cholangiocarcinoma and solid tumors. **First Author:** Filip Janku, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** FF10502 is a synthetic pyrimidine nucleoside similar to gemcitabine (gem) with a sulfur in the pentose ring. FF10502 is a more potent inhibitor of DNA polymerase Beta than gem with activity in gem resistant patient (pt) derived xenograft models. FF10502 is avidly taken up into DNA and has greater activity against quiescent cells than gem.

**Methods:** Pts > 18 years old with advanced disease who had progressed on standard of care were enrolled into 9 dose levels to determine maximum tolerated dose (MTD) and dose limiting toxicities (DLTs) and subsequently into two expansion cohorts: biliary or solid tumors (ST). FF10502 at doses of 8 to 135 mg/m² was administered iv on days 1, 8, 15 of a 28-day cycle until progressive disease or toxicity. PK/PD evaluations were performed on all pts. Response was assessed by RECIST 1.1. Results: 76 pts were treated; 35 pts in dose escalation, including 7 cholangiocarcinoma pts. MTD was 90 mg/m². DLTs included 2 pts with hypotension at 135mg/m² (G3 and G4) and 1 pt each with G3 fatigue and G2 rash at 100mg/m². In expansion, 19 cholangiocarcinoma, 3 gallbladder and 19 other pts (13 pancreatic, 2 urothelial, and 1 each ovarian, prostate, NSCLC, SCCHN each) were treated. 1 pt with prior rituximab for ITP developed PML. G3 treatment-related low platelets occurred in 3 pts at 90mg/m² after cycle 1. There were 5 partial responses (PRs), including 4 pts who had progressed on prior gemcitabine: 3 of 26 pts with cholangiocarcinoma, 1 urothelial carcinoma and 1 chondroblastic osteosarcoma. 7 cholangiocarcinoma pts stayed on therapy for ≥6 months. FF10502 incorporation into intact or fragmented DNA was observed in 2 urothelial and 1 cholangiocarcinoma pts. 1 pt with metastatic prostatic carcinoma developed a new metastasis at 40 mg/m². The dosing interval was then changed to every 4 weeks (RP2D). All-grade AEs of fever and systolic congestive heart failure occurred in 1 patient each. Grade 3-4 TRAEs were reversible AST elevation at 30 mg/m² on the q4w schedule. Further followup and dose escalation are ongoing. The most common (>10% of patients) dose-limiting toxicities were nausea (24% each), asthenia, vomiting (21% each). Gr 3 AEs of fever, increased alkaline phosphatase, decreased lymphocytes, and vomiting. Grade 3 TRAEs were reversible AST increases in 3 patients and increased GGT, decreased lymphocytes, and myalgia, and vomiting. Grade 3 TRAEs were reversible AST increases in 3 patients and increased GGT, decreased lymphocytes, and vomiting. Grade 3 TRAEs were reversible AST increases in 3 patients and increased GGT, decreased lymphocytes, and vomiting. Grade 3 TRAEs were reversible AST increases in 3 patients and increased GGT, decreased lymphocytes, and vomiting. Grade 3 TRAEs were reversible AST increases in 3 patients and increased GGT, decreased lymphocytes, and vomiting. Grade 3 TRAEs were reversible AST increases in 3 patients and increased GGT, decreased lymphocytes, and vomiting. Grade 3 TRAEs were reversible AST increases in 3 patients and increased GGT, decreased lymphocytes, and vomiting. 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A phase 0 first-in-human study using NU-0129: A gold base spherical nucleic acid (SNA) nanoconjugate targeting BCL2L12 in recurrent glioblas-toma patients.

First Author: Priya Kumthekar, Northwestern Memorial Hospital, Chicago, IL

Background: Glioblastoma is a difficult to treat tumor with therapeutics limited by their ability to cross the blood brain barrier. SNAs, i.e., gold nanoparticles covalently conjugated with a corona of densely packed, highly oriented siRNA oligonucleotides targeted to the GBM oncogene BCL2L12, represent a class of blood-brain and blood-tumor barrier-permeable nanomedical conjugates, for suppressing gene expression in the tumors of GBM patients.

Methods: This is a single-arm, open-label, “window of opportunity” phase 0 first-in-human trial to determine the safety and bioavailability of a novel nanotherapeutic compound, NU-0129. Enrolled patients were treated with intravenous NU-0129 at the dose of 0.04mg/kg. This treatment dosing was considered microdosing defined as 1/50th the NOAEL (no observed adverse event level) from non-human primate studies. Treatment was followed by tumor regression 8-46 hours later. Primary outcome patient safety and toxicity was monitored weekly for 3 weeks post-infusion. Secondary objectives included biodistribution of NU0129 in tissue, evaluation of pharmacokinetics of NU0129 and the feasibility of NU0129 administration. Exploratory objectives included Bcl2L12 expression and post treatment apoptotic markers as well as progression free survival and overall survival rates. Results: 8 patients were enrolled, treated and independently underwent tumor resection. No significant treatment related toxicities were seen. Severe (> grade 3) adverse events were observed in two patients: hypophosphatemia (one grade 3, one grade 4) and one patient with grade 3 lymphopenia, all were considered as “possibly related” by treating oncologists. In 6 of the 8 patients sufficient tumor tissue was preserved for analysis of gold accumulation, M13 ICPs (inducibly coupled plasma-mass spectrometry), and gold accumulation was seen in the tumor tissue of all 6 of these patients. Conclusions: Macrodosing of the nano-therapeutic NU-0129 was well tolerated in glioblastoma patients with no unexpected adverse effects and showed initial evidence of crossing blood brain barrier. Increased accumulation for Bcl2L12 expression, apoptotic markers, and PK and PFS studies are pending. The demonstration of gold nanoparticles in the tumor tissue validates this approach for drug delivery. Clinical trial information: NCT03020017.

Poster Discussion Session: Displayed in Poster Session (Board #4), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

3012

3013

Phase 1, first-in-human study of TRAIL Receptor agonist fusion protein ABBV-621.

First Author: Mark J. Ratain, University of Chicago, Chicago, IL

Background: ABBV-621 is a potent tumor-necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor agonist fusion protein that induces apoptotic cell death, particularly in DR4/5 expressing tumor models. Methods: Patients (pts) with previously treated solid tumors and ECOG 0–2 were administered ABBV-621 (2.5–15 mg/kg IV) over 20 minutes in dose level (DL) 1 or DL18 (DL2 and beyond) of each 21-day cycle. Dose escalation (DE) was guided by a Bayesian continual reassessment method. In addition to PK studies, blood-based PD markers of apoptosis (M30, M65) and drug binding were assessed. Results: As of 14 December 2018, 57 pts were enrolled in the DE portion, of which 30% had pancreatic, 23% colorectal cancer, and 47% other tumor types; 13 were KRAS mutant. Median age was 61 yrs. 60% were male; pts had a median of 4 prior regimens (range 1–10). Pts DL 1.5 (5 on DL 1), 16 on DL18, 3.75 (12), 5 (6), 6.5 (6), 8.5 (4), 11 (4), and 15.9 mg/kg (4). Median duration of ABBV-621 exposure was 2 cycles (range 1–11). Seven pts had dose-limiting toxicities; responses failed depend-ent on dose: Grade 5, the only treatment-related death), blood bilirubin increased (3.75, 6.5 mg/dL), nausea (3.75 mg/kg), fatigue (3.75 mg/kg), increased ALT (2.5, 3.75, 6.5, 15 mg/kg), and increased AST (6.5 mg/kg). Summary of AEs is shown in Table. Clinical trial information: NCT03682509. A partial response (duration 20 weeks) was observed in a pt with pancreatic cancer (2.5 mg/kg D1/D18). 27 pts had stable disease (6 pts for > 12 weeks). ABBV-621 PK was linear (mean ± SD clearance was 1.79 mL/h/kg ± 0.44) with a terminal half-life of 36.7 ± 5.55 hrs (n = 49). ABBV-621 bound to decoy receptors on neutrophils up to 168 h; the duration of binding was dose-dependent. M30 and M65 increased at 8, 24, and 48 h following ABBV-621, but effect was independent of dose. Conclusions: ABBV-621 shows evidence of antitumor activity and effect on blood-based markers of apoptosis, with acceptable toxicity (MTD not reached). NCT03082209.

Poster Discussion Session: Displayed in Poster Session (Board #5), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

3014

Phase 1 trial of IACS-010759 (IACS), a potent, selective inhibitor of complex I of the mitochondrial electron transport chain, in patients (pts) with advanced solid tumors.

First Author: Timothy A Yap, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: A subset of tumors possess genetic or microenvironmental alterations that render cells dependent on mitochondrial oxidative phosphorylation (OXPHOS) for survival. Such tumors are a potential target for complex I inhibitors. IACS, a potent oral selective inhibitor of mitochondrial complex I, showed robust responses in multiple preclinical tumor models, providing strong rationale for clinical testing. Methods: Pts with advanced cancers received IACS in increasing dose levels (DL) using 3+3 dose escalation. 7-day QD induction of IACS was followed by maintenance weekly (QW) or twice weekly (B/W) dosing. Pharmacokinetics (PK), lactate and pH were assessed serially. Paired tumor biopsies were assessed for pharmacodynamic and predictive biomarkers. Results: 18 pts were treated; MF 16/2; ECOG PS 0/1; 3/15. Mean age 49 (23-69 yrs). Tumors comprised advanced colorectal (n = 4), advanced prostate (n = 2), other cancers (n = 9). DL1: 2mg QD 7 days induction/0.5mg QW maintenance (n = 3); DL2: 2.5mg QD 7 days/1mg QW (n = 3); DL3: 3mg QD 7 days/3mg QW (n = 3); DL4: 2.5mg QD 7 days/2.5mg BW (n = 6); DL5: 2mg QD 7 days/2mg BW (n = 5). IACS was well tolerated with 12 (67%) pts reporting G1-2 IACS related toxicities, such as raised lactate (n = 10), nausea (n = 8), fatigue (n = 7), vomiting (n = 5), myalgia (n = 4) and peripheral neuropathy (n = 4). 1 pt in DL3 and 2 pts in DL4 had ≥G3 IACS related toxicities, such as nausea (n = 2), vomiting (n = 1), raised lactate (n = 1), dehydration (n = 1), visual changes (n = 1), and peripheral neuropathy (n = 1). Raised lactate was not associated with acidosis. DL5 is now being expanded to assess the maximum tolerated dose (MTD). Pharmacokinetics showed good oral bioavailability. The Cmax and T1/2, and low intrapatient variability. Cmax = 14nm on Day 7 at the end of DL5 induction phase, confirming biologically active doses. 7 pts had best response of RECIST stable disease. A pt with heavily pretreated CRPC achieved RECIST partial response with resolution of CRPC related pain. Conclusions: IACS is well tolerated with predictable safety; evidence of tumor activity includes tumor shrinkage, TNBC, pancreatic cancer and molecularly selected (EN01 loss; SMARC4 mutation) tumor cohorts. Clinical trial information: NCT03291938.

Poster Discussion Session: Displayed in Poster Session (Board #6), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

3015


First Author: Victor Moreno, START Madrid – FJD, Hospital Universitario Fundación Jimenez Diaz, Madrid, Spain

Background: Bromodomain and extra-terminal (BET) proteins are epigenetic readers that control expression of genes involved in cell growth and onco- genic signaling. CC-90010 is a BET-targeting oral, potent and selective BET inhibitor that showed promising activity in lymphoma and solid tumor cell lines and reduced tumor growth in xenograft models. Methods: CC-90010-ST-001 (NCT03220347; 2015-004371-79) is a phase I, first-in-human study of CC-90010 in patients with advanced solid tumors and R/R NHL. Three schedules and 11 dose levels were evaluated (Table). Primary objectives were to determine safety, maximum-tolerated dose and/or recommended phase II dose (RP2D). Secondary objectives were the identification of early activity signals, pharmacokinetics and pharmacodynamics (PD). Results: As of 10 Dec 2018, 69 pts were enrolled, 67 with solid tumors and 2 with R/R NHL. Data shown are from all pts (N = 69). The median age was 57 yr (range, 21–80), 38 (55%) were male, and the median number of prior systemic anticaner regimens was 3 (range, 1–9). The RP2Ds were dose cohorts 3A and 4B. Dose-limiting toxicities (n = 6) occurred in dose cohorts 3A, 3C, and 4B. Grade 3/4 treatment-related adverse events (TRAES) occurred in 17 pts (25%), most commonly $(\geq$2 pts) thrombocytopenia (7%), platelet count decreased (4%), fatigue (3%), and increased alanine aminotransferase (3%). No deaths from toxicity occurred. Two pts (endometrial carcinoma and astrocytoma) had a partial response (PR); 1 occurred after the data cutoff. Seven pts had prolonged stable disease (SD) > 9 mo. Exposures and PD marker regulation increased with dose in each dosing schedule; terminal half-life was dose-dependent. M30 and M65 observed were mild or moderate in severity, reversible, and manageable by dose adjustments and/or supportive care. Promising ongoing anticance- activity with prolonged SD and PRRs were observed. The preliminary clinical data provide the rationale for dose expansion of CC-90010 in pts with selected advanced malignancies. Clinical trial information: NCT03220347.
**3016** Poster Discussion Session: Displayed in Poster Session (Board #8), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

**Design and development of the molecular analysis for Therapy Choice (NCI-MATCH) Designated Laboratory Network. First Author: James V. Tricoli, National Cancer Institute, Rockville, MD**

**Background:** NCI-MATCH is a precision medicine trial that assigns treatment to refractory cancer patients by tumor mutation profile rather than by histology. After screening fresh tumor biopsies from nearly 6000 patients many treatment arms did not meet accrual due to the low prevalence of the eligible variants. NCIMATCH developed an approach to identify patients for the remaining arms utilizing a network of academic and commercial CLIA-certified labs that perform NGS assays as routine care at MATCH participating sites.

**Methods:** Candidate labs were recruited through a notice in the Federal Register and posted on the NCI and ECOG ACRIN web sites. Twenty-seven labs (17 academic/10 commercial) submitted applications. After acceptance each lab analyzed a common set of 10 DNAs extracted from 8 cell lines and 2 clinical samples for concordance with the central NCI-MATCH NGS assay.

**Results:** For the 17 labs with concordance results, a median of 8 (range 2–58) copy number variants (CNVs) were evaluated by the NGS assay of each DL, with the number evaluated depending on each lab's clinical assay panel content. CNV concordance between central and DL assays, as measured by positive percent agreement (PPA), averaged 98.7% (range 87.5% - 100%) with the central assay as referent and 94.1% (range 77.8% - 100%) with the DL assay as referent. For single nucleotide variants (SNVs) and Insertions/Deletions (Indels) combined, a median of 19 variants (range 2–26) were evaluated by each DL for concordance. PPA between central and DL assays averaged 98.0% (range 87.5% - 100%) and 98.6% (range 90.0% - 100%) with central and DL assay as referents, respectively. Strong correlations were observed between central and DL assays for both CNVs (median \( r = 0.93; 0.33 – 1.00 \)) and SNVs/Indels (median \( r = 0.98; 0.67 – 0.99 \)).

**Conclusions:** Our results suggest that different NGS assay platforms using diverse strategies for target enrichment and data analysis may still achieve high concordance if pre-analytical variables are minimized and the common genomic regions interrogated by each assay are well-understood. The designated lab network allows for a wider search for rare variants in tumors and provides a model for conducting future clinical trials. Clinical trial information: NCT02465060.

**3017** Poster Discussion Session: Displayed in Poster Session (Board #9), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

**Efficacy of entrectinib in patients (pts) with solid tumors and central nervous system (CNS) metastases: Integrated analysis from three clinical trials. First Author: Salvatore Siena, Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, and Department of Oncology and Hemato-Oncology, Università degli Studi di Milano, Milan, Italy**

**Background:** Entrectinib potently inhibits kinases encoded by the NTRK and ROS1 genes. It has shown antitumor activity in the CNS with antitumor activity in intracranial tumor models. We report integrated data (31 May 2018 cut-off) from 3 Phase 1/2 entrectinib trials (ALKA-372-001, EudraCT 2012-000148-88; STARTK-1, NCT02097938; STARTK-2, NCT02568267) for a large cohort of pts with ROS1 fusion-positive NSCLC (ROS1+), or NTRK fusion-positive solid tumors (NTRK+), with/without CNS baseline metastases.

**Methods:** Pts had locally advanced/metastatic NTRK+ or ROS1+ tumors by nucleic acid-based confirmation. CNS baseline metastases were identified by CT/MRI. Tumor assessments were at wk 4, then every 8 wk by blinded independent central review (RECIST v1.1). Primary endpoints: ORR, DOR. Secondary endpoints: CBP, PFS, OS, intracranial efficacy and safety.

**Results:** Most pts had ≥1 prior therapy. Baseline CNS metastases outcomes for the Reportable Pts (N = 53) for NTRK+ or ROS1+ solid tumors with or without CNS disease. Clinical trial information: NCT02097938, NCT02568267.

**3018** Poster Discussion Session: Displayed in Poster Session (Board #10), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

**Genome-wide cell-free DNA fragmentation profiling for early cancer detection. First Author: Alessandro Leal, Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD**

**Background:** Analyses of cell-free DNA (cfDNA) in the blood provide a non-invasive diagnostic avenue for patients with cancer. However, cfDNA analyses have largely focused on targeted sequencing of specific genes, and the characteristics of the origins and molecular features of cfDNA are poorly understood. We developed an ultrasensitive approach that allows simultaneous examination of a large number of abnormalities in cfDNA through genome-wide analysis of fragmentation patterns. **Methods:** We used a machine learning model to examine cfDNA fragmentation profiles of 236 patients with largely localized breast, colorectal, lung, ovarian, pancreatic, gastric, or bile duct cancer and 245 healthy individuals. Estimation of performance was determined by ten-fold cross validation repeated ten times. **Results:** cfDNA profiles of healthy individuals reflected nucleosomal patterns of white blood cells, while patients with cancer had altered fragmentation patterns. The degree of abnormality in fragmentation profiles during therapy closely matched levels of mutant allele fractions in cfDNA as determined using ultra-deep targeted sequencing. The sensitivity of detection ranged from 57% to > 99% among the seven cancer types at 98% specificity, with an overall AUC of 0.94. Fragmentation profiles could be used to identify the tissue of origin of the cancers to a limited number of sites in 75% of cases. Combining our approach with mutation-based cfDNA analyses detected 91% of cancer patients. **Conclusions:** This is the first study to demonstrate genome-wide cell-free DNA fragmentation abnormalities in patients with cancer. Results of these analyses highlight important properties of cfDNA and provide a facile approach for screening, early detection, and monitoring of human cancer.

**3019** Poster Discussion Session: Displayed in Poster Session (Board #11), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

**Multimodality liquid biopsy for early monitoring and outcome prediction in first-line metastatic HER2-negative breast cancer: Final results of the prospective cohort from the French Breast Cancer InterGroup Unicancer (UCBG)—COMET study. First Author: Jean-Yves Pierga, Institut Curie, Paris, France**

**Background:** Circulating Tumor Cells (CTC) are independent markers of progression-free survival (PFS) and overall survival (OS) in patients (pts) with metastatic breast cancer (MBC). Monitoring CTC can detect mutation associated with resistance to treatment and its variations reflect changes in tumor burden. We prospectively monitored CTC, Circulating Endothelial Cells (CEC), serum markers and ctDNA during first line chemotherapy for MBC. **Methods:** The French cohort COMET is a prospective study including first line HER2-negative pts receiving weekly paclitaxel and bevacizumab. Blood samples were obtained at baseline (BL) and before the second cycle of chemotherapy (C2). We present here the final planned analysis. **Results:** From 09/2012 to 11/2014, 286 patients were included: 198 for ctDNA, 251 for CEC and 283 for CTC. Median age was 56 years and 23% of pts had triple negative BC. At baseline, 71% of pts had ≥1 detectable CTC per 7.5 ml of blood (median 4 CTC, range 1-30,000). With a threshold of ≥5 CTC, 49% of pts were positive at baseline and 22% at C2. For ctDNA, out of the first 196 pts analyzed, 147 had at least one somatic mutation (SNV) detected in plasma (75%). The average number of mutations per sample was 2.4 (range 0–9). Most common were KRAS, TP53 and EGFR. Of the 233 cases, 53% with TP53 and QATA3. ESR1 was mutated in 10.6% of the pts and restricted to the ER+ subgroup. PIK3CA was mutated in 23.2% of the pts. Median Allelic Frequency was 9.1%. Only 68 pts (36%) had detectable ctDNA at C2. At baseline, CTC and ctDNA levels were correlated (\( r = 0.40 \), \( p < 0.0001 \)). Despite no complete overlap, 24 pts (12%) had no CTC nor ctDNA detected at baseline. Median follow-up was 53 months and median OS was 32 months. Detectable CTC and ctDNA at baseline and at C2 were significantly associated with decreased PFS and OS. CEC and serum markers level had no prognostic value. At multivariate analysis, triple negative status, detectable CTC at BL and C2, CTC > 2000/mL and grade 3 tumour were independent prognostic factors. **Conclusions:** This is the largest prospective cohort assessing the respective prognostic values of early CTC and ctDNA changes in homogenously treated first line MBC pts. Early decrease of CTC and ctDNA after one cycle of chemotherapy are independent predictive markers of favorable outcome, with a stronger value for ctDNA compared to CTC. Clinical utility of early ctDNA variations monitoring and changes in mutation profile remain to be demonstrated. Clinical trial information: NCT01745757.

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Circulating androgen receptor (AR) gene amplification and resistance to 177Lu-PSMA-617 in patients pts) with metastatic castration-resistant prostate cancer (mCRPC): Results of a phase II clinical trial. First Author: Ugo De Giorgi, Istituto Scienzi Romagnolo per Lo Studio e la Cura dei Tumori (IRST) IRCCS, Melolda, Italy

Background: Plasma AR gain is associated with poor prognosis in mCRPC pts treated with abiraterone/enualutamide, however these pts could benefit from docetaxel (Conteduca et al. Eur Urol 2019). In phase II 177Lu-PSMA-617 in mCRPC pts who progressed after standard survival-prolonging treatments, we aimed to determine if plasma AR gene status enable early assessment of 177Lu-PSMA-617 activity for mCRPC. Methods: Between April 2017 and November 2018, 43 mCRPC pts were treated with 177Lu-PSMA-617 in a phase 2 study. Pts younger than 75 years and not heavily pretreated received 5.5 GBq of 177Lu-PSMA-617, while other pts received 4.2 GBq per cycle, for a total of 4-6 cycles, q8 weeks. We determined AR copy number by droplet digital polymerase chain reaction (ddPCR) on pretreatment plasma samples. We evaluated associations between plasma AR amplification and PSA response (≥50% PSA decline from baseline) and imaging changes (as measured by bone scan, CT, and PSMA PET/CT). Logistic regression was used to estimate the odds ratio (OR) and 95% confidence intervals (95% CI) in order to evaluate the independent relevance of AR status and pts without PSA response and those with early progressive disease defined as treatment interruption occurring within 4 months of the start of 177Lu-PSMA-617. Results: Three patients (8%) received 177Lu-PSMA-617, 7 patients (17 years duration, and one previously PAZ-refractory patient with RCC remains on therapy. The median duration of response was 9.1 months (range 6-36 months). Five treatment-refractory pts achieved durable PRs lasting for 33%, Five treatment-refractory pts achieved durable PRs lasting for 33%, Five treatment-refractory pts achieved durable PRs lasting for 6 years. Higher HDAC2 expression was associated with prolonged progression-free survival (median PFS 5.9 vs. 3.5 months, log-rank p = 0.02). Induction of histone acetylation on ABX lead-in treatment was associated with subsequent time to progression (p = 0.002). On-treatment plasma VEGF levels were inversely correlated with PBMC histone acetylation (p = 0.02). Conclusions: Markedly durable responses with PAZ + ABX are achievable, including in pts with PAZ- and VEGF-refractory RCC and other solid tumor malignancies. Host factors including HDAC expression and acetylation status may identify those most likely to benefit. A randomized phase 3 study is underway of PAZ + ABX as a first- or second-line therapy in pts with locally advanced or metastatic RCC (RENAVIN; NCT033992472). Clinical trial information: NCT01543763.

A phase 1 study of pazopanib with weekly paclitaxel and carboplatin in advanced solid tumors. First Author: Nancy Chan, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Background: Pazopanib (pazo) is an oral tyrosine kinase inhibitor of VEGFR, PDGFR and c-Kit. It is a weak inhibitor of CYP3A4 and CYP2C8 and may decrease paclitaxel (P) clearance. Daily pazo with P and carboplatin (C) every 21 days was not feasible on a previous study. We hypothesized that pazo dosed intermitently and on a different day from P and C may be tolerable. We sought to determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and pharmacokinetics (PK) of pazo with weekly P and C. Methods: Using a 3+3 standard design, a schedule of P 60-80 mg/m2 and C AUC2 on days 1, 8, and 15 with pazo 400-800 mg on days 2-5, 9-12, and 16-26 on a 28-day cycle was evaluated. Pazo alone could be continued if P and C were omitted due to maximal benefit or toxicity. PK was collected during cycles 1 and 2. Results: 34 patients (pts) were treated over 6 dose levels (Table). Mean age 57 (37-79). 9 pts had platinum delay in starting cycle 2 due to grade 3 neutropenia was a DLT at dose level 2 and 5. Pts on 5A missing dosing during C1 and C2 due to neutropenia and required subsequent growth factor, and this was deemed unlikely to be sustainable long-term. Three pts (11%) with neurotoxicity (5%), neuropathy (5%) and thrombocytopenia (56%). Protocol-defined MTD was not determined. PK analysis showed a dose proportional increase in pazo concentration, consistent with previous reports. Pazo did not alter the PK of C. MTD of P was higher C2D1 vs C1D1; mean Cmax ratio between C2D1:C1D1 1.63 (95% CI:1.29-1.96). There were 11 objective responses (10 PR and 1 SD). Pts for PRs without PSA response (decline < 50%) having AR gain was 3.69, 95% CI 0.83-16.6, p = 0.085. The OR for pts with early PD having AR gain was 1.60, 95% CI 3.23-79.27, p = 0.0007. The evaluation of germline alterations in DNA damage repair (DDR) genes is ongoing (i.e., BRCA2, BRCA1, ATM).

Results: 5A

Dose Level

Paclitaxel

Carboplatin

Pazopanib

No. of pts

No. of pts with DLT

60 mg/m2 AUC 2 600 mg 3 400 mg

2

1

60 mg/m2 AUC 2 600 mg 3 800 mg

2

1

70 mg/m2 AUC 2 800 mg 3 600 mg

5

6

70 mg/m2 AUC 2 800 mg 3 800 mg

3

1

80 mg/m2 AUC 2 800 mg 3 800 mg

2

1

5A

80 mg/m2 AUC 2 800 mg 3 800 mg

2

1

Conclusions:

1. Phase 1a study results investigating the safety and preliminary efficacy of ABL001 (NOV1501), a bispecific antibody targeting VEGF and DLL4 in metastatic gastrointestinal (GI) cancer. First Author: Yejun Lee, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: Antiangiogenic therapy has been a successful clinical strategy for the treatment of various cancer types. To date, all approved antiangiogenic drugs primarily inhibit the VEGF/VEGFR pathway. Delta-like ligand 4 (DLL4) has been identified as a potential drug target in VEGF-independent angiogenesis. Anti-DLL4 therapy has shown promise for overcoming anti-VEGF therapy resistance. ABL001 (NOV1501) has been developed as a bispecific antibody to bind and inhibit both DLL4 and VEGF thereby significantly suppressing tumor angiogenesis. Methods: In a classical 3+3 dose-escalation design, ABL001 was administered IV at doses ranging from 0.3, 1, 2.5, 5, and 7.5 mg/kg biweekly (NCT03292783; the next doses of ABL001 are 10 and 12.5 mg/kg). After the first administration of ABL001 in each cohort, DLT (dose limiting toxicity) was observed for 3 weeks. Tumor assessments were performed every 6 weeks and cardiac assessments were performed every cycle. Results: From 2017 November to February 2019, 18 patients were enrolled on this trial. All patients were heavily pre-treated with at least 3 prior lines of chemotherapy. All patients in cohort 4 and 5 were either metastatic colorectal cancer or gastric cancer. Of the 5 cohorts, there was no DLT observed during dose escalation. In addition, there was no maximum tolerated dose identified up to 7.5 mg/kg dose. The most common treatment-related adverse events (AEs) (including all dose levels and all grades) occurred were hypertension, anorexia, general weakness, headache and anemia. Preliminary results of pharmacokinetic (PK) analysis demonstrated slightly shorter mean half-life than conventional monoclonal antibodies due to the bispecifc nature of the ABL-001. In addition, preliminary pharmacodynamic (PD) biomarker data show plasma samples of both VEGF/VEGFR and DLL4/Notch1 pathway modulation after ABL001 administration. One gastric cancer patient at 7.5 mg/kg achieved unconfirmed partial response at the time of this writing. Conclusions: ABL001 therapy has been well tolerated up to 7.5 mg/kg with no significant treatment related adverse events and some preliminary biomarker activity in heavily pre-treated cancer patients. After completion of this ongoing phase 1a study, phase 1b/2a study is planned in combination of ABL001 with chemotherapy or anti-PD-1 antibody. Clinical trial information: 03292783.

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3024  Poster Session (Board #16), Sat, 8:00 AM-11:00 AM
The dynamic detection of drug area under curve (AUC) guides clinical usage of docetaxel in solid tumors. First Author: Yan Zhang, Internal Medicine-Oncology, Jiangsu Cancer Hospital. The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, China

Background: The dosage of most chemotherapy drugs were performed based on the patients’ body surface area (BSA), including docetaxel (DTX). Previous studies showed that this conventional administration of DTX might cause adverse event, such as neutropenia, and neutropenia was proved to associate with DTX area under curve (AUC). This study was designed to evaluate the effect of dose-administration of DTX based on dynamic detection of DTX AUC on clinical outcomes. Methods: A total of 209 patients with DTX chemotherapy (one cycle every 3 weeks) were enrolled, and all patients received 2-6 cycles of treatment. In the first cycle, dosage of DTX based on BSA was administrated in all study population. From the second cycle, one group patients (control group) received DTX according to traditional BSA and the other group patients (experimental group) on the basis of dynamic detection of DTX AUC. The primary outcome was incidence rate of neutropenia and the second outcome was disease control rate (DCR).

Results: Patients with grade 3 or higher neutropenia from the fourth to sixth cycle of DTX chemotherapy were significantly reduced (P= 0.039, 0.012, and 0.001, respectively). In the experimental group, compared with the first cycle, and the number of patients falling within the therapeutic window increased by 27.19% in the sixth cycle after dose adjustment according to the AUC value of previous cycle. The DCR in the experimental and control group was 85.32% and 72.00%, respectively (P= 0.018). Conclusions: The administration method based on dynamic detection of AUC of DTX could significantly reduce incidence rate of neutropenia and received a higher DCR, but the result needed to be confirmed in further studies.

3025  Poster Session (Board #17), Sat, 8:00 AM-11:00 AM
A polymorphism within the mismatch repair gene predicts prognosis and adjuvant chemotherapy benefit in gastric cancer patients. First Author: Daosheng Wang, Department of Medical Oncology, Cancer Therapy Center, Affiliated Hospital of Jiangsu University, Zhenjiang, China

Background: Radical surgery with subsequent adjuvant chemotherapy was effective treatment for early-stage gastric cancer (GC) patients. Unfortunately, after optimal multimodality therapy, up to 30% to 40% of patients undergoing resection will relapse within 5 years. There are no validated prognostic and predictive biomarkers for GC patients who receive adjuvant chemotherapy, and current patient selection is based mainly on post-operative pathological staging. Defective mismatch repair (MMR) or microsatellite instability (MSI) may affect GC outcome. Polymorphisms of MMR genes with a low-penetrant effect can cause heterogeneous MMR capability among individuals. It is not known about the impact of these polymorphisms on GC outcome.

Methods: The polymorphisms rs1800734 in MLH1, rs2303428 and rs3732183 in MSH2, rs735943 in EXO1, and rs11797 in TREX1 were selected and analyzed in independent discovery and validation sets that included 167 and 593 patients, respectively. MSI was determined. Results: In the discovery set, both the rs2303428 TCC+ and the rs11797 GA+AA genotypes significantly correlated with overall survival (OS; P = 0.05). In the validation set, we confirmed the prognostic association for the rs2303428 TCC+ genotype (P = 0.036) but not for the rs11797 GA+AA genotype (P = 0.737). Furthermore, the prognostic role of the rs2303428 TCC+ genotype was observed in non-cardia (P = 0.005) but not in cardia GC (P = 0.934). The multivariate model showed that the rs2303428 TCC+ genotype was an independent predictor for OS in non-cardia patients (HR = 1.54; 95% CI: 1.02-2.32; P = 0.040). Moreover, fluoropyrimidines-based adjuvant chemotherapy significantly improved OS (HR = 0.29; 95% CI: 0.15-0.58; P = 0.001) for non-cardia patients with the rs2303428 TCC+ genotype but not for those with the rs2303428 TT genotype. The rs2303428 genotypes were not associated with MSI frequency. Conclusions: The rs2303428 TCC+ genotype may predict prognosis and adjuvant chemotherapy benefit in non-cardia GC patients independent of MSI. To our knowledge, this study is the first to report the prognostic and predictive roles of MMR genotype in GC. Although prospective validation is necessary, our findings have the potential to improve patient selection for adjuvant chemotherapy and spare large numbers of GC patients’ unnecessary therapy.

3026  Poster Session (Board #18), Sat, 8:00 AM-11:00 AM
A phase I dose-finding and pharmacokinetics study of CPC634 (nanoparticle entrapped docetaxel) in patients with advanced solid tumors. First Author: Florence Atrafi, Erasmus MC Cancer Institute, Rotterdam, Netherlands

Background: CPC634 is a novel product with docetaxel temporarily entrapped within stabilized CnPiPc nanoparticles. We performed the first-in-human study with CPC634 (NCT02442531). Methods: Patients (≥18 years) received CPC634 intravenously either 3-weekly (Q3W) (part 1, 15-100 mg/m²), 2-weekly (Q2W) (part 2, 45 mg/m²) or Q3W with dexamethasone premedication (part 3) following a 3+3 design. Primary objectives were to assess safety, establish the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), and to evaluate the pharmacokinetic (PK) profile of CPC634.

Results: Thirty-three patients (part 1: n = 24, part 2: n = 3, part 3: n = 6) were treated. Skin toxicity was dose limiting at doses > 60 mg/m² in part 1, and at a 45 mg/m² dose in part 2. Skin toxicity was cumulative but resolved after ceasing treatment. The MTD in part 1 was set at 70 mg/m². In part 3, the 60 mg/m² dose was reached at 60 mg/m² with dexamethasone premedication. Grade ≥3 adverse events (CTCAE version 4.03) were skin toxicity (21%), fatigue (8%), neutropenia (6%), peripheral sensory (8%) and motor neuropathy (4%), stomatitis (4%), infections (4%) and hypogammaglobulinemia (3%). Alopecia grade 1 was reported in 15% of patients. CPC634 exhibited a dose-proportional PK profile. One partial response and sixteen cases of stable disease (RECIST 1.1) were confirmed in part 1 and in part 3 as best response. Conclusions: CPC634 could be administered safely but showed cumulative, though reversible skin toxicity at high doses. The RP2D was set at 60 mg/m² Q3W with dexamethasone premedication. Additional studies assessing the intratumoral exposure to CPC634 (NCT0371243) and a phase II efficacy study of CPC634 in patients with platinum resistant ovarian cancer (NCT03742713) is currently ongoing. Clinical trial information: NCT02442531.

3027  Poster Session (Board #19), Sat, 8:00 AM-11:00 AM
Phase I trial of chloroquine (CQ)/hydroxychloroquine (HCQ) in combination with carboplatin-gemcitabine (CG) in patients with advanced solid tumors. First Author: Nagta Faywz Abdel Karim, The University of Cincinnati, Cincinnati, OH

Background: Autophagy is a catabolic process triggered in cells during periods of stress to enable their survival. Established tumors utilize autophagy to survive periods of metabolic or hypoxic stress. Inhibition of early stage autophagy can rescue cancer cells, while inhibition of late stage autophagy will lead to cell death due to accumulation of damaged organelles. The antimalarial drugs CQ and HCQ inhibit late phase autophagy. The goal of our study is to assess the safety, tolerability and activity of combinations of CQ/HCQ in patients with advanced solid tumors who either progressed on other therapies or in whom CQ is a therapeutic option. Methods: This single institution phase I dose-escalation study was designed to evaluate the maximum tolerated dose (MTD) of CQ, later substituted with HCQ, in combination with CG in patients with previously treated advanced solid tumors. Secondary objectives were to determine ORR, PFS and OS. A starting dose of 50 mg of CQ/HCQ was used in conjunction with CG, and increased in increments of 50 mg in each dose cohort. Grade 3 or greater toxicity that is treatment-related, and was not self-limited, or controlled in less than 7 days was considered dose limiting toxicity (DLT). Results: Twenty-three patients were enrolled with a median follow up of 6 months. HCO 100 mg was found to be the MTD in combination with CG with ≥ Grade 3 thrombocytopenia and neutropenia as dose-limiting. Median OS was 11 months, and the 1- and 3-year overall survival rates were 30% and 7%, respectively. Median progression-free survival was 5 months and the 6-, 12-, and 18-months progression-free survivals were 48%, 21% and 14%, respectively (Table). Conclusions: The MTD identified for CG/HCQ was lower than previously reported with concomitant use of chemotherapeutic regimes, likely due to the myelosuppressive nature of CQ. Clinical trial information: NCT02071537.
3028 Poster Session (Board #20), Sat, 8:00 AM-11:00 AM

Prospective cohort study of the impact of hospital-wide dihydrompropyridine dehydrogenase (DPYD) genotype testing for fluoropyrimidine-based chemotherapy on adverse events and hospital cost. First Author: Theodore John Wigle, University of Western Ontario, London, ON, Canada

Background: Fluoropyrimidines remain integral components of modern chemotherapy for solid tumors, and their toxicities can be reduced by pretreatment DPYD genotyping. Our main objective was to demonstrate the feasibility of implementing a hospital-wide pretreatment DPYD testing service based on the CPIC 2013 guideline on fluoropyrimidines and DPYD.

Methods: We enrolled participants prior to the first fluoropyrimidine treatment as well as those who had experienced adverse events (AEs) after initiation of therapy, from December 1, 2013 to November 30, 2018. The primary outcome was the rate of severe global fluoropyrimidine-related toxicity in the pretreatment cohort (grade 3-4; CTCAE v.4.0.3).

Results: Of 1362 patients genotyped for DPYD within the study period 1041 were enrolled pretreatment and included in the primary analysis. The median age was 65 years (19-90), 57% male, 51% 5-FU, and 49% capecitabine. Dose reductions were recommended for 21% of patients tested pretreatment were analyzed as a prospective cohort to assess AEs within 90 days of fluoropyrimidine initiation and associated hospital cost. Of the 1362 patients genotyped for DPYD within the study period 1041 were enrolled pretreatment and included in the primary analysis. The median age was 65 years (19-90), 57% male, 51% 5-FU, and 49% capecitabine. Dose reductions were recommended for 21% of patients.

Conclusion: Pretreatment DPYD genotype guided dosing of fluorouracil and capecitabine is feasible and benefits patients, health care providers, and hospitals. Our data supports adoption of pretreatment DPYD genotyping as a standard of care.

3029 Poster Session (Board #21), Sat, 8:00 AM-11:00 AM

PDX validation of a 3D microtumor platform. First Author: Ellen Sampson, SageMedic Corp, Redwood City, CA

Title: Patient-derived xenograft validation of a 3D microtumor platform

Background: Patient-derived xenograft (PDX) mouse models are thought to most closely reflect the biology of a patient’s cancer. Unfortunately, growing sufficient tumor in a PDX model takes several months and more often than not, the tumor fails to grow at all. The SAGE Direct Platform, an in-vitro model, can create hundreds of live microtumors from virtually every patient’s viable biopsy and test a panel of clinically relevant drugs within no more than 1 week. Thus, concordance of results from a PDX model with results of the SAGE Direct Platform would support a rational for the platform to be potentially useful to predict tumor response in cancer patients.

Methods: A bladder cancer from a 77 year old female was used to establish a PDX model. Mice were divided into three groups receiving either saline (control), cisplatin, or gemcitabine intraperitoneally on the days 1, 8, and 13, and tumor growth was observed. One tumor sample was used to create 3D microtumors and those were tested using the same drugs.

Results: Tumor growth (exceeding 1,000 mm3) was similar after cisplatin compared to control (4.8 vs. 3.7 weeks). After gemcitabine tumors initially shrank and only started growing a couple of weeks after the end of treatment so that tumors reached 10.2 weeks (p<0.001 compared to cisplatin and control). In the SAGE Direct Platform the EC50 of cisplatin was 97.3 μM and thus two orders of magnitudes higher than the EC50 of gemcitabine, which was 0.7 μM.

Conclusions: Both the PDX model and the SAGE Direct Platform have shown this bladder cancer to be virtually resistant to cisplatin with very sensitive to gemcitabine. The next steps of these preliminary data could be to repeat this experimental design with other tumors and/or to start an observational cohort study in patients correlating the SAGE Direct Platform results to patient outcomes.

3030 Poster Session (Board #22), Sat, 8:00 AM-11:00 AM

Anticancer activity in patients with advanced ovarian and biliary tract cancers treated with NUC-1031 in combination with a platinum agent. First Author: Sarah Patricia Blagden, University of Oxford, Oxford, United Kingdom

Background: The inhibition of cellular nucleotide metabolism to promote apoptosis is a key principle of cancer therapy. This, in combination with platinum-induced DNA-damage, is key to promoting anti-cancer activity in a variety of tumors, including ovarian, biliary tract, lung, breast and bladder. NUC-1031, a phosphorimidate transformation of gemcitabine is designed to overcome resistance mechanisms that limit the efficacy of this nucleoside analog. NUC-1031 has shown broad clinical activity across multiple solid tumors as both a single agent and in combination with platinum agents. We show potential synergism between NUC-1031 and a platinum agent in advanced ovarian (OC) and biliary tract (BTC) cancers.

Methods: PRO-002 was a phase Ib study, 25 patients (pts) with recurrent OC who had exhausted all other therapy options received NUC-1031 + carboplatin. 17 pts were considered platinum resistant (10) or platinum refractory (7). ABC-08 is a phase Ib study, 14 pts with advanced BTC treated in the first-line setting with NUC-1031 + cisplatin. Results: In PRO-002, strong efficacy signals were observed in non-platinum-responsive patients. Of the 17 response-evaluable pts with advanced OC who had exhausted all other therapy options received NUC-1031 + carboplatin. 17 pts were considered platinum resistant (10) or platinum refractory (7). ABC-08 is a phase Ib study, 14 pts with advanced BTC treated in the first-line setting with NUC-1031 + cisplatin. Results: In PRO-002, strong efficacy signals were observed in non-platinum-responsive patients. Of the 17 response-evaluable pts with advanced OC who had exhausted all other therapy options received NUC-1031 + carboplatin.

Conclusion: NUC-1031 + Pt show potential synergism between NUC-1031 and Pt, and therefore may have clinical activity in pts with advanced ovarian and biliary tract cancers.
A phase I study of the oral administration of irinotecan in combination with the potent P-glycoprotein (P-gp) inhibitor HM30181A. First Author: Antonio Jimeno, Auriadro CO.

Background: Irinotecan is a prodrug of the potent topoisomerase inhibitor SN-38. In animals, oral administration of irinotecan with the selective minimally absorbed P-gp inhibitor HM30181A increased the bioavailability of irinotecan. Oral administration of irinotecan may also increase the conversion to SN-38. Objectives: To determine the MTD and DLT of orally administered irinotecan in combination with HM30181A 15 mg on day 1 of a 21-day cycle. Additional objectives include determining the PK of irinotecan and SN-38. The PK of irinotecan and SN-38. Methods: This was a phase 1 dose escalation study enrolling cohorts of 3-6 patients with advanced malignancies. Patients had Hb ≥9 g/dL, ANC ≥1.5x10^9/L, platelets ≥100x10^9/L, adequate hepatic and renal function, ECOG 0-1 and were not homogous for UGT1A1*28. Patients were administered HM30181A 15 mg and oral irinotecan 40, 80, 120, 160, 200, 240, 320 and 360mg/m^2. Results: Thirty male and female patients, mean age 60.9 (range 33-78) were enrolled into this ongoing study. The most common cancers were ovarian (6), colorectal (4), breast (4), endometrial (3), and pancreatic (3). The median number of cycles administered was 3 (range 1-9). Treatment-related SAEs were experienced by 6 (20%) patients (nausea or vomiting in 4 subjects). DLTs occurred in 2 patients at the 320 mg/m^2 dose level (neutropenia and C. Difficile diarrrhea) and additional patients are being enrolled at 280mg/m^2. Conclusions: Oral administration of irinotecan may also increase the conversion to SN-38. Confirmation of the MTD when dosed on a 21-day cycle is ongoing.

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DFP-11207 at the dose of 330 mg/m^2/d q12hrs is well tolerated in patients with solid tumors with mild myelosuppressive and gastrointestinal side effects, and generates circulating FEU levels conducive to an anti-tumor effect. DFP-11207 can be explored as monotherapy or substitute for 5-FU, capecitabine or S-1 in combination treatment regimens. Clinical trial information: NCT02171221.

Risk of QTc interval prolongation among cancer patients treated with tyrosine kinase inhibitors. First Author: Anan Abdolmati Abu Rmilah, Mayo Clinic, Rochester, MN

Background: QTc interval prolongation can lead to life-threatening complications such as torsade de points (TdP), ventricular tachycardia (VT), and sudden cardiac death (SCD). It can occur with various tyrosine kinase inhibitors (TKIs) but comparative analyses on the incidence and complication rates are scarce. We thus conducted a comprehensive analysis of TKI use and QTc prolongation in clinical practice. Methods: We retrospectively reviewed the electronic medical records of all cancer patients who were treated with TKI between 01/2005 and 12/2018 at our institution. QTc prolongation was defined as a QTc ≥ 450 ms or 460 ms among male or female patients, respectively. For each type of TKIs, we determined the administration rate and incidence of QTc interval prolongation. We also studied the frequency of QTc prolongation ≥ 500 ms, rate of increase of the QTc interval by ≥ 60 ms, and the development of complications (VT, TdP and SCD). Results: In the present study, we analyzed the data of 685 cancer patients (431 male and 254 female), including 299 patients with RCC, 188 with chronic leukemia, 55 with acute leukemia, 65 with thyroid cancer, 48 with lung cancer and 39 with GIST. These patients received TKI administrations and QTc prolongation was reported in 1/3 of these (289 administrations). The highest frequency was seen with imatinib, nilotinib and dasatinib (30, 40 and 50%). Among cases of QTc prolongation, a QTc interval ≥ 500 ms was documented in 53 (18.3%) and QTc progression ≥ 60 ms in 72 (23%). Complications were found in 14 cases (5%) including VT in 9, TdP in 2 and SCD in 3 administrations. Conclusions: The current findings suggest that TKI therapy leads to QTc prolongation in 1/3 of patients on average and most commonly with the Bcr-Ab1 TKIs, imatinib, nilotinib and dasatinib. While SCD is rare (1%) it can still evolve and in 5% of all QTc prolongations with TKIs are potentially life-threatening. These data support recommendations for serial ECGs in cancer patients undergoing TKI therapy.
Background: Although growth advantage of certain clones would ultimately translate into a clinically visible disease progression, radiological imaging does not reflect clonal evolution at the molecular level. ctDNA, validated as a tool for mutation detection in lung cancer, reflects dynamic molecular changes. Here, we evaluated the potential of ctDNA in monitoring molecular changes and predicting clinical outcomes of EGFR T790M-positive osimertinib treated NSCLC pts. Methods: This prospective multicenter study, enrolled 72 T790M positive osimertinib-treated advanced NSCLC pts who progressed on prior EGFR-TKI to evaluate the potential of ctDNA in monitoring, is part of the ongoing ASTRIS study (NCT02474355). Longitudinal plasma samples, collected from 52 pts, were subjected to sequencing using a panel consisting of 168 lung cancer-related genes. Results: Genomic profile prior to the initiation of osimertinib revealed that mutations participating in cell cycle with an average lead time of 74 days.

With shorter OS (the initiation of osimertinib revealed that mutations participating in cell cycle and more likely to harbor any gene copy number amplification (CNA, p = 0.035), radiological PD had shorter PFS (p = 0.002) and OS (p = 0.022). With a median follow-up of 168 d (ranged from 40 - 550 d), 32 pts experienced radiological disease progression. Among them, 11 (34%) experienced metastatic sites were bone (37%), lymph nodes (29%), lung (27%) and liver (26%).

3036 Poster Session (Board #30), Sat, 8:00 AM-11:00 AM
Can the enumeration of circulating tumor cells (CTCs) and the characterization of circulating tumor DNA (ctDNA) provide insight into organ tropism in metastatic breast cancer (MBC)? First Author: Lorenzo Gerratana, Department of Medicine-Hematology and Oncology, Feinstein School of Medicine, Northwestern University; Department of Medicine (DAME), University of Udine, Udine, Italy.

Background: Liquid biopsy provides real-time data about prognosis and actionable mutations in MBC. The aim of this study was to explore the combination of ctDNA analysis and CTCs enumeration in estimating target organs more susceptible to MBC involvement. Methods: This retrospective study analyzed 85 MBC patients (pts) characterized for both CTCs and ctDNA at baseline. CTCs were isolated through the CellSearch kit (Menarini Silicon Biosystems, PA), while ctDNA was analyzed using the Guardant360 NGS-based assay (Guardant Health, CA). Pts with ≥ 5 CTC/7.5 ml of blood were defined as Stage IV aggressive. Mutations were analyzed using Next generation sequencing (NGS) and targeted next generation sequencing (tNGS) of 523 genes (ESR1, TP53, PIK3CA, PIK3CD, CDK6, and NF1) were associated with lymph node involvement (OR 0.4% VAF). Specificity in HD was 0.86 [0.82-0.90].

Results: Compared to healthy blood donors, progastrin was found at higher concentrations in the plasma of MBC patients (pts) characterized for both CTCs and ctDNA at baseline. CTCs of ctDNA analysis and CTCs enumeration in estimating target organs more susceptible to MBC involvement. Methods: This retrospective study analyzed 85 MBC patients (pts) characterized for both CTCs and ctDNA at baseline. CTCs were isolated through the CellSearch kit (Menarini Silicon Biosystems, PA), while ctDNA was analyzed using the Guardant360 NGS-based assay (Guardant Health, CA). Pts with ≥ 5 CTC/7.5 ml of blood were defined as Stage IV aggressive. Mutations were analyzed using Next generation sequencing (NGS) and targeted next generation sequencing (tNGS) of 523 genes (ESR1, TP53, PIK3CA, PIK3CD, CDK6, and NF1) were associated with lymph node involvement (OR 0.4% VAF). Specificity in HD was 0.86 [0.82-0.90].

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3038 Poster Session (Board #30), Sat, 8:00 AM-11:00 AM
Can the enumeration of circulating tumor cells (CTCs) and the characterization of circulating tumor DNA (ctDNA) provide insight into organ tropism in metastatic breast cancer (MBC)? First Author: Lorenzo Gerratana, Department of Medicine-Hematology and Oncology, Feinstein School of Medicine, Northwestern University; Department of Medicine (DAME), University of Udine, Chicago, IL.

Background: Liquid biopsy provides real-time data about prognosis and actionable mutations in MBC. The aim of this study was to explore the combination of ctDNA analysis and CTCs enumeration in estimating target organs more susceptible to MBC involvement. Methods: This retrospective study analyzed 85 MBC patients (pts) characterized for both CTCs and ctDNA at baseline. CTCs were isolated through the CellSearch kit (Menarini Silicon Biosystems, PA), while ctDNA was analyzed using the Guardant360 NGS-based assay (Guardant Health, CA). Pts with ≥ 5 CTC/7.5 ml of blood were defined as Stage IV aggressive. Mutations were analyzed using Next generation sequencing (NGS) and targeted next generation sequencing (tNGS) of 523 genes (ESR1, TP53, PIK3CA, PIK3CD, CDK6, and NF1) were associated with lymph node involvement (OR 0.4% VAF). Specificity in HD was 0.86 [0.82-0.90].

With shorter OS (the initiation of osimertinib revealed that mutations participating in cell cycle and more likely to harbor any gene copy number amplification (CNA, p = 0.035), radiological PD had shorter PFS (p = 0.002) and OS (p = 0.022). With a median follow-up of 168 d (ranged from 40 - 550 d), 32 pts experienced radiological disease progression. Among them, 11 (34%) experienced metastatic sites were bone (37%), lymph nodes (29%), lung (27%) and liver (26%).

3037 Poster Session (Board #29), Sat, 8:00 AM-11:00 AM
Pregastrin, a novel ubiquitous cancer biomarker for early detection and monitoring. First Author: Benoît You, Institut de Cancérologie des Hospices Civils de Lyon (IC-HCL), CTML, EMR UCBL/HCL 3738, Lyon, GINECO & GINEGEPS, France, Lyon, France.

Background: The successes of recent publications on “multi-tumor” circulating markers highlight the relevance of novel universal diagnostic cancer serum biomarkers. Since the Wnt/β-catenin/Tcf4 pathway, activated in many tumors, induces the GAST Gene encoding progastrin synthesis, we hypothesized that progastrin, easily measurable in the blood, might be a “multi-tumor” diagnostic biomarker. Pregastrin levels were measured in the blood samples of 1,319 patients with 12 different cancer origins, and compared to those of 557 asymptomatic 18-75 years old blood donors. Moreover the longitudinal kinetics of progastrin concentrations were serially assessed during treatments in 168 patients with ovarian cancers enrolled in the randomized CHIVA trial (NCT01983322, GINECO), 191 patients with peritoneal involvement from gastro-intestinal cancers enrolled in BIG-RENAPE trial (NCT03787056), and in 95 HCC patients. The progastrin was measured using an ELISA test developed by ECS Progastrin (Philly, Switzerland). Results: Compared to healthy blood donors, progastrin was found at higher concentrations in the plasma of cancer patients (median 175 pg/ml vs 94 pg/ml; p = 0.0001), diagnostic discriminative power, ROC analysis AUC = 0.86 (95% CI, 0.83-0.89; P < 0.0001). Pregastrin levels were found elevated in all cancer groups, regardless of disease stages, and of pathology origins: ROC AUCs ranged from 0.71 to 0.93, all P < 0.0001 (Table). The longitudinal progastrin changes during treatments, suggest relationship to tumor burden, and potential monitoring value. Conclusions: Progastrin is a novel ubiquitous cancer biomarker, easily detectable in the blood using an affordable ELISA test (CancerRead Lab test(R)). It may change the future paradigms of screening (in particular for populations at higher or lower risks of cancer), cancer diagnostic & monitoring.

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Background: Circulating tumor DNA next generation sequencing (ctDNA NGS) is increasingly being used to detect mutations (MT) in patients (pts) with metastatic (m) NSCLC. Limited data exist on the correlation of baseline ctDNA NGS profile and serial ctDNA NGS monitoring to response to immunotherapy. Methods: We conducted a prospective study in pts with mNSCLC receiving pembrolizumab monotherapy. ctDNA NGS was performed at baseline (T0), 9 (T1), and 18 (T2) weeks. We isolated plasma cfDNA and prepared sequencing libraries for WG sequencing or WG bisulfite sequencing (median cycle of 57 days). Whole-genome cell-free DNA (cfDNA) changes as a dynamic blood-based biomarker can be monitored in patients with advanced NSCLC. First Author: Charu Aggarwal, University of Pennsylvania, Philadelphia, PA

Methods: We conducted a prospective study in pts with mNSCLC receiving pembrolizumab monotherapy. ctDNA NGS was performed at baseline (T0), 9 (T1), and 18 (T2) weeks. ctDNA NGS was performed using a 73 gene panel. Number of MTs and variant allelic fraction (VAF) were determined at baseline, and serially; change in mean VAF was calculated between T1-T0, and T2-T0. Response rate (RR) was assessed using RECIST 1.1. Correlations were made for pt characteristics, RR, progression free survival (PFS), and overall survival (OS). Results: We analyzed 95 samples from 33 pts, 21 female, median age 69 (range 51-89) years, smokers (n = 29), adenocarcinoma (n = 23), 25 pts enrolled at initial diagnosis, majority had high PD-L1 >50% (n = 29, 88%). At T0, 32 pts had detectable MT, median number of MTs was 4 (range 0-21), (non-synonymous MT = 3), most common MT was TP53 (n = 21). Confirmed PR was 27% (n = 9), clinical benefit rate (SD+PR) was 64% (n = 21), and 2 pts were not evaluable for response. Smokers were more likely to have higher number of MT at T0 (4 vs. 1 p = 0.003); there was no correlation with smoking and overall RR (p = 0.12). RR was not related to number of MTs. At T1-T0 (8.9 vs. 5 mos, p = 0.37). A decrease in ctDNA VAF was seen in 6/9 pts with PR (mean VAF change range -0.11 to -0.001); 2/5 pts with PD showed an increase in mean VAF while 3 showed a decrease. At median follow up of 9.26 months (mos), median PFS and OS were 7.4 and 10.5 mos, respectively. Median PFS was longer for pts with a decrease in ctDNA VAF at both T1-T0 (8.9 vs. 5 mos, p = 0.02) and (T2-T0 and 9.1 vs. 5.5 mos, p = 0.006). OS and additional biomarker analyses including correlation of response to a 2mb ctDNA plasma-based NGS panel will be reported at the meeting. Conclusions: Our results demonstrate that it is feasible to serially monitor plasma NSCLC, decline in mean ctDNA VAF correlates with radiographic response and PFS on immunotherapy with pembrolizumab.

A prospective study tracking longitudinal changes in genome-wide cell-free DNA (cfDNA) methylation to identify early non-responders to cancer treatment. First Author: Andrew A. Davis, Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL

Background: Methylation is an epigenetic modification linked to cancer pathogenesis. The aim was to determine if changes in cfDNA methylation patterns before and after initiation of treatment could predict non-response to treatment prior to routine imaging and clinical follow-up. Methods: We prospectively collected clinical data and blood from 28 patients with metastatic malignancies (13 lung, 11 breast, 4 other). Blood was drawn prior to the initiation of therapy, peripheral blood mononuclear cells (PBMC) were isolated and collected at four timepoints (median 18X) on plasma cfDNA to determine methylation levels. By tracking how methylation levels deviate from unaffected individuals, from baseline to subsequent timepoints, we classified patients as either responders (greater deviation) or non-responders. Treatment response at first follow-up imaging (FUI) was determined by RECIST 1.1. Study endpoints were agreement with first FUI and progression-free survival (PFS) by cfDNA methylation classification. Results: The cohort consisted of 68% females and the median age was 70. Main treatment regimens were chemotherapy (N = 12), immunotherapy (N = 18), endocrine (N = 7), or targeted therapy (N = 7). Response was defined as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). At T0, 20/28 (71%) pts had detectable cfDNA. The median number of MTs at T0 was 4 (range 0-15), the common MT was TP53 (n = 30). Confirmed PR was 29% (n = 8), clinical benefit rate (SD+PR) was 64% (n = 21), and 2 pts were not evaluable for response. At T1-T0, 30% (n = 9) of patients showed a decrease in mean VAF, median PFS and OS were 7.4 and 10.5 mos, respectively. Median PFS was longer for pts with a decrease in cfDNA VAF at both T1-T0 (8.9 vs. 5 mos, p = 0.02) and (T2-T0 and 9.1 vs. 5.5 mos, p = 0.006). OS and additional biomarker analyses including correlation of response to a 2mb ctDNA plasma-based NGS panel will be reported at the meeting. Conclusions: Our results demonstrate that it is feasible to serially monitor plasma NSCLC, decline in mean ctDNA VAF correlates with radiographic response and PFS on immunotherapy with pembrolizumab.

Whole-genome cell-free DNA (cfDNA) changes as a dynamic blood-based biomarker for early response assessment of advanced tumors. First Author: Andrew A. Davis, Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL

Background: Liquid biopsies have potential clinical utility as dynamic biomarkers for treatment response. We analyzed serial changes in whole-genome (WG) cfDNA to identify patients with disease progression prior to routine imaging. Methods: We prospectively collected clinical data and blood from 69 advanced cancer patients (28 lung, 25 breast, 16 other). Blood was collected at baseline prior to initiation of a new treatment and at one or two additional timepoints (median 21 and 42 days). We isolated plasma cfDNA and prepared sequencing libraries for WG sequencing or WG bisulfite sequencing (median depth 20X). We quantified changes in the fraction of tumor-derived cfDNA over the initial course of treatment to predict progression vs. no progression. Treatment response at first post-treatment imaging was determined by RECIST 1.1 and clinical assessment. Study endpoints were agreement with first post-treatment imaging and progression-free survival (PFS) by cfDNA prediction. Results: Median age of patients was 70 and 59% were female. Patients were treated with the following therapies: chemotherapy (37), immunotherapy (17), endocrine (9), or targeted therapy (6). Patients with predicted progression by cfDNA (14), indicated by an increase in tumor fraction at either post-treatment blood collection, had shorter PFS (median 63 days) compared to patients without an increase (N = 55; median 255 days), with hazard ratio of 10.3 (95% confidence interval 4.6-23.4, log-rank = 1x10^-10). Positive predictive value was 100% for disease progression and negative predictive value was 78%. These findings were consistent in subset analyses of patients with lung (log-rank = 2x10^-6), breast (log-rank = 3x10^-4), and those treated with immunotherapy (log-rank = 5x10^-4). Conclusions: Our results show the ability to detect early disease progression with high fidelity using WG cfDNA prior to first imaging. These findings were consistent across multiple tumor types and treatments, including immunotherapy patients. Once validated, this dynamic, predictive, blood-based biomarker could aid in clinical decision making for early treatment change as a novel and cost-effective approach.
3044 Poster Session (Board #36), Sat, 8:00 AM-11:00 AM
 Mastocheck: Notable plasma protein biomarker for diagnosis of breast cancer in the real clinical practice by using multiple reaction monitoring-based mass spectrometry. First Author: Yun-Kyeong Kim, Department of Medical and Dental University, Seoul, South Korea

Background: Breast cancer is the most frequently diagnosed cancer and the most leading cause of cancer-related deaths among women worldwide. Although screening mammography is available, there is an ongoing interest in improved early detection and prognosis. And also, serum tumor marker levels, such as CA 15-3 and others, may reflect disease progression and recurrence, they have not proven to be suitable for early-stage detection.

Research investigating biomarkers for early detection, and breast cancer detection and management remains dependent on invasive procedures We aimed to develop biomarker for diagnosis of breast cancer in the real clinical practice by using proteomics technology.

Methods: Based on our previous studies, we performed verification and validation of 124 candidate proteins by using proteomics approach. Among these 124 candidate proteins, the three proteins (neural cell adhesion molecule L1-like protein, apolipoprotein A-1, and metallothionein 1A3) with highest statistical significance were selected. We created the performance algorithm of the 3-protein diagnostic model to predict of the breast cancer.

We performed several experiments for establishment and validation of cut-off value. Furthermore we conducted test for acquisition of sample stability and more experiment to show the retest reliability of evidence compared with other cancers (colon, thyroid, ovary, pancreas and lung cancer) and established effect of anesthesis. Results: Total 1226 samples (532 patients of breast cancer, 562 healthy women and 100 sample of other cancers) was analyzed. The sensitivity, specificity and accuracy from confirmatory experiments were 98%, 85.2% and 85.6% respectively. The result of comparison with other cancers, there are no statistical significant difference and no relevance with effects of anesthesia. With these results, we recently got permission it to use for in vitro diagnostic use from Korea Food and Drug Administration. Conclusions: In this study, we developed a plasma protein biomarker that may help to diagnosis of breast cancer in the real clinical practice. By using MRM approach, the 3-protein biomarker was validated in an independent cohort with acceptable accuracy for early diagnosis of breast cancer.

3046 Poster Session (Board #38), Sat, 8:00 AM-11:00 AM
Comprehensive genomic profiling of circulating cell-free DNA (ctDNA) distinguishes focal amplification (amp) in CO2 in pancreatic anhydrase 11 with highest statistical significance were selected. We created the performance algorithm of the 3-protein diagnostic model to predict of the breast cancer.

We performed several experiments for establishment and validation of cut-off value. Furthermore we conducted test for acquisition of sample stability and more experiment to show the retest reliability of evidence compared with other cancers (colon, thyroid, ovary, pancreas and lung cancer) and established effect of anesthesis. Results: Total 1226 samples (532 patients of breast cancer, 562 healthy women and 100 sample of other cancers) was analyzed. The sensitivity, specificity and accuracy from confirmatory experiments were 98%, 85.2% and 85.6% respectively. The result of comparison with other cancers, there are no statistical significant difference and no relevance with effects of anesthesia. With these results, we recently got permission it to use for in vitro diagnostic use from Korea Food and Drug Administration. Conclusions: In this study, we developed a plasma protein biomarker that may help to diagnosis of breast cancer in the real clinical practice. By using MRM approach, the 3-protein biomarker was validated in an independent cohort with acceptable accuracy for early diagnosis of breast cancer.

3045 Poster Session (Board #37), Sat, 8:00 AM-11:00 AM
Circulating bacterial DNA as a tool towards noninvasive biomarkers for colorectal adenocarcinoma and adenoma. First Author: Ke-Feng Ding, Department of Medical and Dental University, Beijing, China

Background: The gut microbiota is closely associated with the progression of colorectal neoplasia. While most metagenomics studies utilized fecal samples, circulating bacteria DNA in colorectal adenocarcinoma (ADC) or adenoma (ADM) patients remain unexplored. This study aimed to characterize the microbiota DNA in plasma samples and build a machine-learning model for ADC and ADM early detection. Methods: In this proof-of-concept study, we performed whole genome sequencing (~30X) of plasma samples from 25 ADC patients, 10 ADM patients, and 22 healthy controls (HC). Significant biomarkers were identified in the discovery cohort (12 ADC and 11 HC) and built into a random-forest model which was tested in the validation cohort (13 ADC and 11 HC). These biomarkers were further examined in ADM and tested for abundance difference with ADC and HP. Results: In the discovery cohort, 111 species had increased absolute abundance in ADC compared to HC and 165 species had decreased relative abundance. Al- teration in several species (e.g. Flavobacterium and Ruminococcus) were consistent with previously published results in faecal and gut microbiome samples. The random forest-reursive feature elimination model selected 28 significant species from the discovery cohort (mean AUC = 0.98, repeated 2-fold cross-validation) and yielded an AUC of 1 in the validation cohort. Interestingly, most of the species identified by our approach were not previously identified as discriminatory. Conclusion: This study is the first to perform metagenome sequencing for plasma samples with a novel machine-learning approach. Our findings revealed significant difference in relative abundance of several bacterial species between ADC, ADM and HC. A predictive model constructed with selected microbial features accurately distinguished ADC and ADM from HC. Circulating bacteria biomarkers represent potential non-invasive tools for early diagnosis of colorectal neoplasia.

3047 Poster Session (Board #39), Sat, 8:00 AM-11:00 AM
Tumor specific DNA in bronchial lavage as a new diagnostic tool in lung cancer. First Author: Canberk A. Guzergen Thansen, Department of Oncology, Vejle Hospital, Vejle, Denmark

Background: A considerable fraction of lung cancer patients raise diagnostic challenges requiring invasive procedures with a certain risk of complications. Therefore, new diagnostic tools are of major interest. Ablent methylation of the HOXA9 gene occurs in almost all malignant lung tumors and HOXA9 methylated DNA (meth-cDNA) is shed into the circulation. The present study aimed at a prospective investigation of the possible diagnostic value of HOXA9 meth-cDNA in bronchial lavage (BL). Methods: Patients enrolled were referred from the general practitioner suspecting lung cancer. The diagnostic package according to national guidelines includes chest and abdominal CT scan, bronchoscopy, relevant blood tests, and histopathological or cytological verification. Twelve ml liquid was collected at bronchoscopy for analysis of meth-cDNA based on ddPCR technology according to our published method. The analysis was performed blinded to the clinical data and compared to the final diagnosis. Results: Eighty-nine patients were consecutively included from the 1 November 2018 to 31 January 2019. Fifty-six patients (62.9%) were diagnosed with lung cancer and 33 (37.1%) with a variety of benign diseases. Meth-cDNA was found in 42/56 of the patients with a malignant tumor, sensitivity = 75.0% (95%CI=61.8-85.6%), whereas 31/33 of the patients without cancer were negative, specificity = 93.9% (95%CI= 79.8-99.3%). Table summarizes the results. The false negative samples were mainly from patients with peripheral tumors, while false positive patients included one patient with Cryptogenic Organizing Pneumonia and one with unspecific nodule. Conclusions: The presence of meth-cDNA in BL has a high sensitivity and specificity. If validated, the analysis represents a valuable adjunct in the diagnosis of lung cancer. Potentially, it could save the patients from numerous examinations with potential harmful risks and ensure a fast diagnosis. The relation between meth-cDNA and final lung cancer diagnosis (N= 89).

Final lung cancer diagnosis.

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Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Polymorphisms in the dopamine (DA) signaling to predict outcome in patients (pts) with metastatic colorectal cancer (mCRC): Data from TRIBE, MAVERICC, and FIRE-3 phase III trials.

First Author: Minetta C. Liu, Mayo Clinic, Rochester, MN

Background: For multi-cancer detection using cfDNA, TOO determination is critical to enable safe and efficient diagnostic follow-up. Previous array-based studies captured ≤ 2% of genomic CpGs. Here, we report genome-wide fragment-level methylation patterns across 811 cancer cell methylogens representing 21 tumor types (97% of SEER cancer incidence), and define effects of this methylation database on TOO prediction within a machine learning framework.

Methods: Genomic DNA from 655 formalin-fixed paraffin-embedded (FFPE) tumor tissues and 156 isolated cells from tumors was subjected to a prototype 30x whole-genome bisulfite sequencing (WGBS) assay, as previously reported in the Circulating Cell-Free Genome Atlas (CCGA) study (NCT02889978). Two independent TOO models, one with and one without the methylation database, were fitted on training samples; each was used to predict on the test set. A WGBS classifier was used to detect cancer at ≥98% specificity; reported TOO results reflect percent agreement between predicted and true TOO among those detected cancers (166 cases: 81 stage I-III, 69 stage IV, 16 non-informative).

Results: Genome-wide methylation data generated from this database improved TOO performance and coverage of ~30 million CpGs across the genome (~60-fold greater than array-based approaches). Incorrect TOO assignments decreased by 35% (20% to 13%) after incorporating methylation database information into TOO classification. Improvement was observed across all cancer types and was consistent in early-stage cancers (stage I-II). Respective improvements in breast cancer (n = 23) were 87% vs 76% in lung cancer (n = 32) were 85% vs 88%; in hepatobiliary (n = 10) were 70% vs 90%; and in pancreatic cancer (n = 17) were 94% vs 100%. Results using an optimized approach informed by these results in a large cohort of CCGA participants will be reported. Conclusions: Incorporating data from a large methylation database improved TOO performance in multiple cancer types. This supports feasibility of this methylation-based approach as an early cancer detection test across cancer types. Clinical trial information: NCT02889978.

Cohort (n=148)

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**3052 Poster Session (Board #44), Sat, 8:00 AM-11:00 AM**

Cell-free methylated DNA (cfMeDNA) immunoprecipitation and high throughput sequencing technology (cfMeDIP-seq) in patients with clear cell renal cell carcinoma (ccRCC). First Author: Pier Nuzzo, Dana-Farber Cancer Institute, Boston, MA

**Background:** CfMeDNA is a promising biomarker for non-invasive assessment of solid tumors: i) MeDNA is tissue- and tumor-specific ii) cfDNA methylation changes are stable unlike DNA alterations iii) 'methylation target size' is larger than identifying specific genomic alterations and, therefore, more sensitive. CfMeDIP-seq is a sensitive assay for genome-wide bisulfite-free cfMeDNA profiling, that requires 1-10 ng input DNA. We tested the feasibility of cfMeDIP-seq to detect ccRCC across TNM stages.

**Methods:** We evaluated plasma cfDNA collected prior to nephrectomy in 46 pts with ccRCC: 25 stage I, 7 stage II, 6 stage III, 8 stage IV. CfMeDIP-seq involves four steps: 1) cfDNA end-repair, A-tailing, and adapter ligation 2) cfMeDNA immunoprecipitation and enrichment using an Ab targeting 5-methylcytosine (quality control by qPCR to ensure <1% of unMeDNA and >99% reaction specificity) 3) adapter-mediated PCR to amplify cfMeDNA 4) high-throughput NGS for cfMeDNA data. A previously-derived model (Shen et al., Nature, 2018) was used to classify pts as having ccRCC or not based on cfMeDNA. CfMeDIP-seq paired end data was reduced to 300 bp windows of the genome that map to CpG islands, shores, shelves, and ccRCC or not based on cfMeDNA. CfMeDIP-seq paired end data was reduced to 300 bp windows of the genome that map to CpG islands, shores, shelves, and

**Results:** Our data supports a recent study that has shown 100% cfMeDNA methylation false positive rates for detecting ccRCC.

**Conclusions:** cfMeDIP-seq is an invasive, cost-effective, and sensitive assay to detect cancer-specific cfMeDNA in ccRCC pts prior to nephrectomy. With further validation, cfMeDNA may detect minimal residual disease after nephrectomy for 'precision' adjuvant therapy.

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**3054 Poster Session (Board #46), Sat, 8:00 AM-11:00 AM**

Associations between baseline serum biomarker levels and cachexia/prefaecchia in pretreated non-small cell lung cancer (NSCLC) patients. First Author: Gabriela C. Lobato, Rush University Medical Center, Chicago, IL

**Background:** We previously reported associations of pretreatment serum biomarkers with clinical outcomes in a cohort of advanced NSCLC patients that progressed on front-line therapy. This study aims to elucidate mechanisms underlying cancer cachexia/precachexia by evaluating relationships between baseline serum biomarker values and sequential changes in body weight, body mass index (BMI), and neutrophil/lymphocyte ratio (NLR) in NSCLC patients. **Methods:** We used Luminex immunobeads assays to survey 101 protein biomarkers in sera from advanced NSCLC (n = 138) collected prior to their salvage regimen. Serial parameters associated with cancer cachexia included body weight, BMI, and NLR. Outcome variables (progression-free survival (PFS) and overall survival (OS)) were extracted with full IRB approval. Biomarkers were evaluated as continuous variables with the cachexia surrogates using Pearson correlations, whereas associations of PFS and OS were accomplished with the Cox PH test. **Results:** High baseline values of BMI and low baseline NLR were associated with both OS and PFS (each p < 0.05), though weight failed to reach significance. PFS and OS were similarly associated with percent changes (relative to baseline) in weight (p < 0.01), BMI (p < 0.01), and NLR (p < 0.001). Thirteen biomarkers were found to be associated (p < 0.05) with baseline BMI values, including positive correlations with leptin, sol:VEGFR2, and c-peptide and inverse correlations with adiponectin, ferritin, ghrelin, IGFBP-1 and IL-8. Fifteen biomarkers were associated with baseline NLR (all p < 0.05), including positive correlations with visfatin, insulin, and serum amyloid A and inverse correlations with IGF-II. Fifteen biomarkers were found to be associated (p < 0.05) in common with percent weight and BMI changes, including positive correlations with IGFBP-3 and inverse correlations with insulin, FGF-2, TNF-alpha, and resistin. Only prolactin and placental growth factor were found to be associated (p < 0.05) with percent change in NLR. **Conclusions:** A series of circulating protein biomarkers primarily connected with metabolic regulation and systemic inflammation/acute phase response were found to be associated with cachexia/precachexia in NSCLC patients. Additional cohorts are currently being tested to verify these findings.

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**3055 Poster Session (Board #45), Sat, 8:00 AM-11:00 AM**

Training and validation study for sequential monitoring of CAMLs in circulation to predict ongoing progression in lung cancer patients undergoing definitive radiotherapy. First Author: Daniel Adams, Creativ MicroTech, Inc., Monmouth Junction, NJ

**Background:** Cancer Associated Macrophage-Like cells (CAMLs) are a recently described circulating stromal cell common in the peripheral blood of cancer patients that are prognostic for progressive disease. Further, it has been shown that changes in CAML size (i.e. enlargement above 50µm) can predict progression free survival (PFS) in thoracic cancers (e.g. lung). We evaluated plasma cfMeDIP-seq unMeDNA and small cell lung cancer (NSCLC) patients, with an initial training set review of 54 patients, to determine if change in CAML size after radiation therapy was predictive PFS. **Methods:** A 2 year single blind prospective study was undertaken to test the relationship of ≥50µm CAMLs to PFS based on imaging in lung patients before and after induction of chemoradiation, or radiation therapy. To achieve a 2-tailed 90% power (α = 0.05) we recruited a training set of 54 patients and validation set of 50 patients all with pathologically confirmed unresectable NSCLC: Stage I (n = 14), Stage II (n = 16), Stage III (n = 61) & Stage IV (n = 13). Baseline (BL) blood samples were taken prior to start of therapy & a 2nd blood sample (T1) was taken 2-3 weeks later. Blood was filtered by CellSieve filtration and CAMLs quantified. Analysis by CAML size of < 49 µm or ≥50 µm was used to evaluate PFS hazard ratios (HRs) by censored univariate & multivariate analysis. **Results:** CAMLs were found in 95% of samples averaging 2.7 CAMLs/7.5 mL sample at BL, with ≥50 µm having HR (HR = 2.0, 95% CI 1.1-3.6). At T1, 18 patients had increased CAML size ≥50 µm with PFS (HR = 4.6, 95% CI 2.5-8.3, p < 0.001). In total, ≥50 µm CAMLs at BL was 76% accurate at predicting progression within 24 months while ≥50 µm CAMLs at T1 was 83% accurate at predicting progression. **Conclusions:** In unselected NSCLC patients at start of CRT, CAMLs ≥50µm can be an indicator active progression. We identify that a single ≥50 µm CAML after induction of radiotherapy, in our training set and confirmed in our validation set, is an indicator of poor prognosis. We suggest that changes in CAML size during therapy may indicate the efficacy of therapy and could potentially help shape subsequent therapeutic decisions.

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**3056 Poster Session (Board #47), Sat, 8:00 AM-11:00 AM**

Efficacy of tyrosine kinase inhibitors (TKIs) based on the ALK resistance mutations on ampiclox-based TKI rechallenge biopsy in active ALK positive non-small cell lung cancer (NSCLC) patients (pts). First Author: Laura Mezquita, Medical Oncology Department, Gustave Roussy, Villejuif, France

**Background:** Acquired ALK resistance mutations (mut.) are the main mechanism of tyrosine kinase inhibitor (TKI) resistance (30-50%). While next-generation TKIs are more active on mut. than earlier TKIs, compound ALK resistance are associated with failure to next-generation TKIs. We evaluated the clinical utility of detecting ALK resistance mutations in blood to predict TKI efficacy. **Methods:** ALK positive advanced NSCLC pts were prospectively enrolled between Oct, 2015 and Aug, 2018 in 8 French institutions. Prospective samples were collected; ctDNA was analyzed by amplicon-based Innativa InVisionFirst-Lung. **Results:** A total of 101 pts with advanced ALK positive NSCLC were enrolled and 328 samples collected. In samples collected at TKI failure (N=74), we detected 9 simple and 7 complex (≥2) ALK resistance mut. (22%), associated with EML4-ALK variant 3 (38%) vs. variant 2 (13%) vs. variant 1 (none); 30% had other somatic mut. (mainly TP53 and KRAS, PIK3CA, MET, etc.). No mutations were detected in 48% of samples (ctDNA™). ALK mut. were more frequent after 2nd/3rd generation TKI (43% post-lorlatinib (7), 29% post-2nd gen. (31), 11% post-crizotinib (36). ALK/G1202R was the most common, as single (n=3) or complex mut. (n=4). The median overall survival (mOS) was 100.4 mo. (95% CI 41.9-158.9) and the median progression-free survival (mPFS) to subsequent line was 2.8 mo. (0.7-4.9). Patients with ctDNA™ had mOS of 105 mo. (39.3-172.1) vs. 58.5 mo. (33.1-84.0) if ≥1 ALK mut. vs. 44.1 mo. (20.0-68.2) if others (P=0.001). Pts with the complex ALK mut. had worse OS compared to single ALK mut. (mOS 26.9 mo. vs. 58.5 mo., P=0.001); ALK complex mut. were associated with poorer efficacy to subsequent therapy (PFS <3 mo. in 57%; no cases with, P<0.001 vs. single mut., with longer OS (PFS >3 mo. in 56%). Detectable ALK/G1202R mut. were associated with shorter median OS (58.3 mo.; 7.9-109.1) vs. overall population; 86% of cases developed rapid PFS (<3mo) to subsequent therapy with only one durable response to lorlatinib (PFS >6mo.). **Conclusions:** The absence of ctDNA mutations at TKI failure may predict resistance to subsequent therapy. Larger and specifically designed studies should be performed to validate these findings.
3056 Poster Session (Board #48), Sat, 8:00 AM-11:00 AM
Baseline ctdNA characteristics and evolution of ctdNA profile during treatment with selective FGFR inhibitor TAS-120. First Author: Tyler J. Moss, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: There is an increasing role for ctdNA in monitoring response and mechanisms of resistance. We performed ctdNA analysis in a subset of patients enrolled on a Phase I trial with an irreversible, selective FGFR1-4 inhibitor, TAS-120. Methods: 58 plasma samples from 17 patients (13 with cholangiocarcinoma) were analyzed on a 7-gene, next-generation sequencing panel. Selected patients(pts) had longitudinal samples. Results: At least one alteration was detected in 46 ctdDNA samples (6 of 17 patients). No alterations were found in 12 patients. In 7 pts, a second alteration was detected in 46 cfDNA samples, in 16 (94%) of 17 pts on the panel. Selected patients(pts) had longitudinal samples. In 7 pts, a second alteration was detected in 46 cfDNA samples, in 16 (94%) of 17 pts on the panel. Selected patients(pts) had longitudinal samples. In the MAPK pathway progression, cfDNA revealed an increase in gatekeeper mutations in cfDNA at baseline may still respond to TAS-120. FGFR2/3 amplification, and one FGFR4 mutation. 6 pts (35%) had PR, 5 (29%) had SD and 6 (35%) PD as a best response to TAS-120. Four pts had prior FGFR2: 2 had a PR, 1 SD, and 1 PD on TAS-120. Baseline ctdNA mutations became undetectable during treatment in 4/6 pts with PR. 4 of 6 PD pts had other driver mutations at baseline including mutations in PIK3CA, KRAS, IDH1, BRC2, or amplifications in PIK3CA, PDGFR. 9 pts with ctdNA available at progression after SD/PR: 3 had acquired FGFR2 mutations (one each of V564L, V564F, or N549K). Two also acquired alterations in other candidate alterations. The most frequent was PTEN (MAPK/ERK pathway). Another pt had low variant allele frequency (VAF) in NRAS G12D and BRAF V600E (MAPK/ERK pathway). In progression, ctdNA revealed an increase in NRAS VAF and mutations acquired in the MAPK pathway. One pt with prior FGFR4 acquired FGFR2 V564L and V664K detected by ctdDNA prior to initiation of TAS-120, and had a PR on TAS-120. There was a drop in FGFR2 V564I and V664K with response that subsequently increased post progression. The patient also acquired a FGFR2/3 amplification at progression. Conclusions: FGFR alterations can be detected by ctdNA. ctdNA may detect potential resistance mechanisms, including PTEN or MAPK pathway alterations and acquired FGFR2 mutations. Patients with gatekeeper mutations in ctdNA at baseline may still respond to TAS-120. Further study is needed to determine the impact of FGFR2 mutations and alterations on TAS-120 sensitivity.

3057 Poster Session (Board #49), Sat, 8:00 AM-11:00 AM
Analytical validation of a tumor-agnostic integrated multianalyte circulating tumor DNA (ctDNA) assay in early-stage cancer. First Author: Anna Hartwig, Guaranty Health, Inc., Redwood City, CA

Background: ctdNA sequencing has been rapidly adopted for the identification of targetable somatic alterations (alts) in patients with advanced cancers. However, early stage disease detection has been hindered by low levels of ctdNA in circulation and the presence of confounding non-tumor-related somatic alts. We developed and validated a ctdNA assay that combines somatic and epigenomic signals to detect early stage tumors without tumor tissue or white blood cells (WBC). Methods: Using a single input sample, our assay integrates the sensitive detection of genomic alts with quantification of epigenomic signals associated with cancer. Non-tumor alts (e.g., clonal hematopoiesis of indeterminate potential; CHIP) are excluded using a newly developed bioinformatic classifier. To assess analytical sensitivity, specificity, and positive and negative reproducibility, we tested 337 clinical and convired samples. Results: Clinical specificity was determined using 80 plasma samples from 50-75 year old presumpative cancer-free donors, and resulted in a single false positive (99% specificity). Analytical sensitivity (limit of detection) was established using a dilution series of 4 different late stage CRC pts tested in triplicate. Longitudinal ctDNA input (30 ng) across multiple batches. 100% sensitivity was maintained even at the lowest tested level (estimated 0.1% tumor level). Positive/negative reproducibility was assessed by testing triplicates of diluted late stage samples and age-matched healthy donors, respectively, across different ctdNA inputs, and multiple reagent lots. Both positive and negative reproducibility were 90% concordant across cases. Cancer detection across all replicates. In- dependent estimation of tumor levels from epigenomic or genomic signals produced highly concordant results (correlation r-value: 0.82, p-value: 3e-16). Conclusions: We designed and validated a highly specific ctdNA assay that integrates both genomic and epigenomic signals to allow for accurate and quantitative tumor level detection in early stages of the disease without requiring tumor tissue or WBC.

3058 Poster Session (Board #50), Sat, 8:00 AM-11:00 AM
Changes in DNA hydroxymethylation for the detection of multiple cancers in plasma cell-free DNA. First Author: Anna Bergamaschi, Bluestar Genomics, San Diego, CA

Background: Methylation and hydroxymethylation of cytosines enable the epigenomic regulation of gene suppression and activation. 5-hydroxymethylcytosine (5hmC) is globally decreased in tumor tissue. However, genome-wide analysis using precise 5hmC labelling techniques reveals more nuanced changes upon tumorigenesis and raises the possibility that this loss could be exploited for developing a cancer biomarker. This suggests that 5hmC profiles might enable discrete classification of not only tumor tissue but also of tumor cell-free DNA (ctDNA). We sought to identify genome-wide 5hmC changes in plasma based ctDNA from cancer patients representing multiple disease types, stages and clinical characteristics in comparison with non-cancer patients. Methods: ctdNA was isolated from plasma, enriched for the 5hmC fraction using chemical labelling, sequenced, and aligned to the genome to determine 5hmC counts per genomic feature. Regularized regression models were evaluated via cross-validation of out of fold prediction in the training set with 0.84 for all four diseases. The ability to classify non-cancer versus cancer patients was established using a dilution series of 4 different late stage CRC pts tested in triplicate. Baseline cfDNA mutations became undetectable during treatment in 4/6 pts with PR. 4 of 6 PD pts had other driver mutations at baseline including mutations in PIK3CA, KRAS, IDH1, BRC2, or amplifications in PIK3CA, PDGFR. 9 pts with cfDNA available at progression after SD/PR: 3 had acquired FGFR2 mutations (one each of V564L, V564F, or N549K). Two also acquired alterations in other candidate resistance genes (PTEN and MAP2K1). Another pt had low variant allele frequency (VAF) in NRAS G12D and BRAF V600E (MAPK/ERK pathway). In progression, cfDNA revealed an increase in NRAS VAF and mutations acquired in the MAPK pathway. One pt with prior FGFR4 acquired FGFR2 V564L and V664K detected by cfDNA prior to initiation of TAS-120, and had a PR on TAS-120. There was a drop in FGFR2 V564I and V664K with response that subsequently increased post progression. The patient also acquired a FGFR2/3 amplification at progression. Conclusions: FGFR alterations can be detected by cfDNA. cfDNA may detect potential resistance mechanisms, including PI3K or MAPK pathway alterations and acquired FGFR2 mutations. Patients with gatekeeper mutations in cfDNA at baseline may still respond to TAS-120. Further study is needed to determine the impact of FGFR2 mutations and alterations on TAS-120 sensitivity.

3059 Poster Session (Board #51), Sat, 8:00 AM-11:00 AM
Pooled analysis of phase I dose-escalation and dose cohort expansion studies of IMP4297, a novel PARP1/2 inhibitor, in Chinese and Australian patients with advanced solid tumors. First Author: Junning Cao, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Poly (ADP-ribose) polymerase (PARP) enzymes play critical roles in DNA damage detection and repair. IMP4297 is a novel, potent PARP1/2 inhibitor (IC50 6.27nM/1.57nM) and has demonstrated to be 20-fold more potent than Olaparib in anticancer animal models. Two phase I studies were performed to evaluate and characterize the tolerability and safety, pharmacokinetics, and antitumor activity of single agent IMP4297 in Chinese and Australian patients with advanced solid tumors. Methods: Dose escalation used a 3+3 design with a modified Fidencacci escalation. Dose cohort expansion was planned after efficacy was observed at the lowest dose level. Patients received IMP4297 monotherapy orally once a day until disease progression or unacceptable toxicity. Results: As of Jan 12, 2019, 56 patients, including 23 BRCA mutation carriers (BRCA+), had been enrolled at 2-100 mg dose level. No DLT was observed. In these two studies, the most frequent treatment-related adverse events (TRAEs) were leukopenia (20%), followed by anemia (18%), nausea (18%) and thrombocytopenia (14%). The majority of TRAEs were grade 1 or 2. Grade 3 TRAEs occurred in five patients (anemia, n=2; vomiting, n=1; thrombocytopenia, n=1; elevated AST, n=1). Only one patient had a dose reduction due to grade 3 thrombocytopenia. No serious TRAEs were observed. In 15 BRCA+ patients who had measurable lesions, the ORR was 33% and the DCR was 80%. There were 4 BRCA+, platinum-sensitive ovarian cancer patients with an ORR of 75% and a DCR of 100%. One patient with somatic BRCA mutated urothelial carcinoma showed a 75% decrease in tumor size. Conclusions: IMP4297 has been well-tolerated with significant anti-tumor activity. The 100 mg daily dose was selected as the RP2D based on safety, pharmacokinetics and clinical activity, and will be further characterized in dose expansion and phase II studies. Clinical trial information: NCT03508011 and NCT03507543.

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**3060 Poster Session (Board #52), Sat, 8:00 AM-11:00 AM**

**Is the optimal biological dose of oncologic molecular-targeted therapies also clinically effective?**

*First Author: Pauline Corbaux, Université de Lyon, University Claude Bernard Lyon 1, Faculté de Médecine Lyon-Sud, Lyon, France*

**Background:** The determination of the optimal biological dose (OBD) defined as the lowest safe dose associated with biological efficacy, appears to be a promising endpoint for designing the recommended phase 2 trial dose (RP2D) of novel oncologic targeted therapies in early-phase clinical trials. However, the clinical relevance of OBD is still unknown. We conducted a review to assess if the OBDs of molecular targeted therapies defined in early phase trials were useful during subsequent drug development and for oncologic drug approvals.

**Methods:** A systematic review was conducted to identify all the molecular targeted therapies approved by FDA in solid and hematological malignancies, and for which early phase trials defined OBDs. The publications of efficacy trials leading to the first FDA approvals were reviewed, as were the FDA approved doses and dosing schedules, which were compared to OBDs found in the early phase trials. **Results:** OBDs were reported in the early phase trial articles of 39.5% (32/81) FDA approved targeted therapies from 1999 to 2019 (19 small molecules and 13 monoclonal antibodies (mAbs)). The OBDs were not reached for 59.4% (19/32) of these drugs. When both MTD and OBD had been defined, OBD were lower than MTD in 84.6% of cases, and equal for the others. The OBDs were chosen as the RP2Ds for 56.3% of the molecules. In that case, the final FDA approved doses were consistent with the OBDs for 83.3% of the drugs. These observations did not differ between small molecules and mAbs. OBDs mainly relied on indirect effects on the involved signaling pathway elements for small molecules (11/19, 57.9%), and on involved receptor occupancies for mAbs (6/13, 46.2%).

In total, 23.5% of all FDA approved molecular targeted therapies were approved with their OBDs. Although some poorly investigated, OBDs may represent a relevant complementary endpoint in early phase trials of novel anti-cancer targeted therapies, as OBDs are selected as the final FDA approved doses in 83.3% of cases when chosen as the RP2Ds, which is much higher than the previously reported 58.0% when MTDs are chosen as the RP2Ds (Fontes-Jardim et al. JNCI 2015).

**3062 Poster Session (Board #54), Sat, 8:00 AM-11:00 AM**

**Modular phase I-II clinical trial evaluating the selective MET-kinase inhibitor OMO-1 in patients with advanced solid tumors: Safety, and mechanism**

*First Author: Martijn P. Lokkema, University Medical Center Utrecht, Utrecht, Netherlands*

**Background:** MET kinase is a therapeutic target in a range of cancer indications; it is a primary oncoprogenic driver and a mechanism of therapy resistance. OMO-1 is a highly potent, selective oral inhibitor of MET kinase and Organic Cation Transporter 2 (OCT2). It is a primary oncogenic driver and a mechanism of therapy resistance. OMO-1 is a highly potent, selective oral inhibitor of MET kinase and Organic Cation Transporter 2 (OCT2).

**Methods:** This study assesses the safety, tolerability, pharmacokinetics (PK) and preliminary activity of OMO-1 in Chinese patients with advanced solid tumors. Telatinib was administered to Chinese patients with advanced refractory solid tumors as a single agent in 3+3 dose escalation design, starting from 600mg and escalated to 900mg and 1200mg, given orally twice daily. The PK profile, safety, and tolerability were evaluated per protocol. Efficacy was evaluated with RECIST 1.1 criteria every 6 weeks. **Results:** A total of 15 subjects (6 colorectal cancer, 4 lung cancer, 1 head and neck cancer, 1 melanoma, 1 thymic carcinoma, 1 esophageal carcinoma, 1 peritoneal carcinoma) were enrolled per protocol between July 2017 and August 2018, and 13 subjects received at least second line therapies before enrolment. Telatinib was well tolerated in the three dose arms. No dose limiting toxicities (DLTs) occurred during the dose escalation phase. CTC grade 3 AEs observed include hypertension (46.7%, 7/15), fatigue (6.7%, 1/15), transaminase elevation (6.7%, 1/15), hand-foot syndrome (6.7%, 1/15) and neutropenia (6.7%, 1/15), and 3 of 15 subjects (2 colorectal cancer, 1 lung cancer) had grade 5 AEs. No CTCAE grade 4 adverse events were observed. The maximum feasible dose is 900mg bid, which was chosen as recommended phase 2 dose for further development.

**3063 Poster Session (Board #55), Sat, 8:00 AM-11:00 AM**

**First-in-human phase I and pharmacological study of TAS-119, a selective Aurora A (AurA) kinase inhibitor in patients (pts) with advanced solid tumors**

*First Author: Debbie Robbrecht, Erasmus MC, Rotterdam, Netherlands*

**Background:** AurA is a serine threonine kinase regulating cell division and cell cycle progression and has a role in carcinogenesis. This clinical trial investigated safety, pharmacokinetics and -dynamics and antitumor activity of the selective oral AurA kinase inhibitor TAS-119. **Methods:** Pts with advanced solid tumors were enrolled into 6 dose escalation cohorts (70-300 mg Bid 4 days on/3 days off; every 3 out of 4 weeks; or the same schedule in a continuous weekly schedule). In the expansion phase (intermittent schedule), pts with small-cell lung cancer (SCLC), breast cancer, or MYC-amplified/B-catenin mutated (MT) tumors were enrolled, and pts with other solid tumors in a basket cohort. **Results:** Overall, 34 pts were enrolled to the escalation (median age 67 years; 45.3% > 2 prior therapies); DLT was observed in 5 (16.1%) of 31 DLT evaluable pts: 1/10 at 150 mg, 1/6 at 200 mg, 1/5 at 250 mg, and 2/2 at 300 mg Bid (fatigue, nausea, dry eyes, corneal epithelial microcysts). The maximum tolerated dose (MTD) was 250 mg Bid and recommended Phase 2 dose (RP2D) was 200 mg Bid. The most frequent treatment-emergent adverse events were diarrhea (28.3%), eye disorders (27%), fatigue (22.9%), and decreased appetite (14.8%). Grade 3 ocular toxicity were corneal epithelial microcysts in 1 pt (300 mg cohort) and punctate keratitis (expansion breast cancer cohort) in 1 pt. Toxicity grade > 3 in > 10% of pts were diarrhea (escalation part only), and increased lipase. Plasma exposure was dose-proportional and accumulation ratio was low. Pharmacodynamic data demonstrated target inhibition. Overall, 40 pts were enrolled to multiple expansions (10 SCLC, 9 breast cancer, 13 MYC-amp/b-cat MT tumors; 8 other; median age 60 years; 72.5% > 2 prior therapies). Median delivered relative dose intensity was 89.1% (47.9% - 100%). Stable disease was reported in 33/40 patients but no complete or partial responses. **Conclusions:** TAS-119 demonstrated favorable safety and tolerability. Low-grade eye toxicity was a dose-dependent toxicity. Preliminary anti-tumor activity of monotherapy TAS-119 is limited. A Phase 1 trial combining TAS-119 with paclitaxel was conducted in parallel. Clinical trial information: NCT02448589.

### Telatinib multiple doses pharmacokinetic parameters (14-day)

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</table>
Rethinking about the dose limiting toxicities (DLTs): They can be equivocal!  
First Author: Wei Zhong, Pfizer Inc, Cambridge, MA

Methods: To mitigate the risk of dichotomizing and misclassifying DLTs, we proposed a strategy that introduced the new concept of “equivocal” DLT or AE. A novel dose escalation approach is applied to increase the variability associated with less interpretable AEs so that the model recommendations are more weighted towards the unequivocal AEs/DLTs. To evaluate this novel approach, we established a framework incorporating two types of systematic measurement errors on DLT misclassification, one for the misclassified DLT that is not related to the drug treatment while the other for the non-DLT AE that should be considered severe and relevant to dose finding. In our simulation studies, the Bayesian logistic regression model (BLRM) was used to guide dose escalation in simulated trials to compare the novel weighting approach with the traditional approach. A few numerical examples were also included for method illustration. Results: For different types of measurement errors, simulation studies showed that the weighting approach could successfully improve the trial performance, with higher chance of finding the correct MTD and treating more patients at the MTD level. Conclusions: The DLT weighting strategy provides a flexible but powerful tool that may incorporate the clinician’s valuable experience on some specific DLTs/AEs and improve MTD estimation in oncology phase I dose-escalation trials.

Safety and tolerability of veliparib, an oral PARP inhibitor, and M6620 (VX-970), an ATR inhibitor, in combination with cisplatin in patients with refractory solid tumors.  
First Author: Arjun Mitta, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD

Background: M6620 (M), a potent ATR inhibitor, has synergistic activity with cisplatin (C) in multiple preclinical models, resulting in DNA damage and antitumor activity. We hypothesize that inhibition of both homologous recombination and base excision repair through the combination of M6620 and veliparib (V, a potent inhibitor of PARP1/2) would result in accumulation of lethal double stranded breaks induced by cisplatin and increased anti-tumor activity and initiated a phase-1 dose escalation trial of this combination in patients (pts) with advanced solid tumors (NCT02723864). Methods: This is a standard 3+3 dose escalation design with 21-day cycles. M is given IV day 2 (D2) and D9; V orally twice daily D1-3 and D8-10; C IV D1 (and D8 from dose level 3 [DL3] onwards) at 40 mg/m2 (with option of holding after cycle 6). Primary objectives: safety; tolerability; maximum tolerated dose (MTD). Secondary objectives: pharmacodynamic (PD) biomarkers; antitumor activity. Dose-limiting toxicity (DLT) evaluated during cycle 1, response using RECIST 1.1. Results: Thirty-seven patients enrolled, median 5 lines of prior therapy (Range 1-12). MTD: V 200 mg, M 210 mg/m2, C 40 mg/m2 (DL6). DLT: grade (gr) 4 thrombocytopenia (DL4), hypophosphatemia (not resolved in 24 hrs., DL3), infusion reaction (DL7). Common non-DLT AEs (not significantly affect accuracy of determining seriousness (OR, 0.87; 95% CI: 0.31, 2.46) but it did significantly increase accuracy of attributing a serious AE to a drug (OR, 3.60; 95% CI: 1.15, 11.4). Conclusions: The DAT shows promise as a method to reduce errors in attribution of AEs, which may help to ensure the detection of valid safety signals. Many participants were experienced clinical trialists, and the DAT may show greater utility as an educational tool for novice investigators, research staff, and students.
3068 Poster Session (Board #60), Sat, 8:00 AM-11:00 AM
Image-guided surgery for tumor agnostic detection of solid tumors using the pH-activated micellar imaging agent ONM-100. First Author: Floris Jan Voets, ONM, Groningen, Netherlands

Background: ONM-100, a micelle-based polymer imaging agent conjugated to indocyanine green (ICG) and with an exquisitely pH-sensitive binary activation mechanism, may be used for tumor detection. ONM-100 micelles dissociate in acidic environments resulting in activation of the fluorescent ICG tag. As nearly all solid cancer types are acidic, ONM-100 has the potential to act as a broadly indicated tumor agnostic imaging agent. This first-in-human study investigates the safety and feasibility of ONM-100 as a tumor agnostic imaging agent for in-operative fluorescent imaging of various solid tumors. Methods: ONM-100 was iv administered 24±8h prior to surgery in a dose escalation scheme (0.1-1.2mg/kg). Patients with histopathologically confirmed breast cancer (BC), head and neck squamous cell carcinoma (HNSCC), colorectal cancer (CRC) and esophageal cancer (EC) were included. Blood was drawn to assess safety and pharmacokinetic data. Intra-operative fluorescence images were collected before and after tumor excision. Post-excision fluorescence images were obtained from serially sliced specimens and correlated with standard histopathological assessment. Results: 30 patients (11 BC, 13 HNSCC, 3 EC, 3 CRC) were enrolled. No ONM-100 related serious adverse events were observed and the agent was well-tolerated. A strong and sharply demarcated fluorescent signal was observed in all patients with vital tumor tissue (median CNR ranging 1.85-14.05) which correlated with tumor on final histopathology. HNSCC and superficially located BC as well as peritoneal metastases could be clearly visualized in vivo during surgery. In four patients (BC and HNSCC), perioperatively, tumors otherwise unnoticed by the surgeons were detected on the margin or wound bed using fluorescence imaging. Additionally, two BC tumor lesions were detected that were missed by conventional pre-operative imaging and pathological assessment. Conclusions: ONM-100 appears to be safe and enables fluorescent visualization of tumors both in vivo and ex vivo. The first-in-human data demonstrate the feasibility for potential use of ONM-100 for image guided surgery, margin assessment and detection of occult disease. Clinical trial information: NTR 7085.

3069 Poster Session (Board #61), Sat, 8:00 AM-11:00 AM
Radiomics features to identify distinct subtypes of triple-negative breast cancers. First Author: Haruka Itakura, Stanford Univ Medc Ctr, Stanford, CA

Background: We sought to gain new insight into triple-negative breast cancer (TNBC), an aggressive, clinically distinct subgroup of breast cancers, by applying a sequence of computational approaches to tumor segmentation, three-dimensional anatomical characterization, and tumor subtyping. We extracted algorithmically-derived quantitative imaging (radiomics) features from each TNBC lesion in breast magnetic resonance imaging (MRI) to identify underlying subtypes. Methods: We evaluated tumors on pre-treatment, post-contrast MRI from 90 patients with non-metastatic TNBC. We employed active contour segmentation and semi-automated identification of tumor regions-of-interest. We extracted 900 radiomics features from each segmented tumor using an algorithm that characterizes the size, shape, texture, and edge sharpness of tumors at the voxel level. We applied k-means consensus clustering, a statistical tool for unsupervised discovery, and performed 1000 bootstraps with resampling on the feature vectors to examine all resulting clusters from k=2 to 10. Based on two diagnostic metrics of consensus stability, we selected the optimum cluster number. We performed Significance Analysis of Microarrays to identify statistically significant radiomics features for each cluster. Results: Results: A total of 13 distinct image-based clusters in 117 tumors from 90 TNBC patients (multifocal lesions in n=13). Cluster 1 (n=97) was distinguished by 330 radiomics features (False Discovery Rate (FDR)<5%) and Cluster 2 (n=13) by 85 features (FDR<5%), whereas Cluster 3 (n=7) was not significantly associated with features. Clinical characteristics did not differ across the three clusters, with mean age (49.1±11.7) and clinical stage distributions (stage I: 20.7%, II: 55.4%, III: 23.9%) for the cohort mirroring those of individual clusters. Among those who received neoadjuvant therapy, we observed pathologic complete response in 50% (23 of 46, 95% CI, 0.36-0.64) of patients in Cluster 1, 83% (9 of 5, 95% CI, 0.54-1.0) in Cluster 2, and 0% (0 of 3) in Cluster 3. Conclusions: Radiomics features providing voxel-level characteristics of tumor morphology differentiated TNBC into three distinct subtypes. These subtypes, defined by radiomics biomarkers, may be associated with clinical response to neoadjuvant therapy.

3070 Poster Session (Board #62), Sat, 8:00 AM-11:00 AM
[18F] Fluciclatide PET as a biomarker of clinical response to combination therapy of pazopanib and paclitaxel. First Author: Alex Kiesing, Christian Medc, Stuttgart, Germany

Background: Angiogenesis has been shown to be a driver of platinum resistance in ovarian cancer. We assessed the effect of combination pazopanib and paclitaxel followed by maintenance pazopanib in patients with platinum-resistant/refractory ovarian cancer. Integrins αvβ3 and αvβ5 are both upregulated in tumour-associated vasculature. [18F]Fluciclatide is a novel PET tracer that has high affinity for integrins αvβ3, and was used to assess the anti-angiogenic effect of pazopanib. Methods: We conducted an open-label, phase Ib study in patients with platinum resistant/refractory ovarian cancer. Patients received 1 week of single agent pazopanib (800mg daily) followed by combination therapy with weekly paclitaxel 80mg/m2. Following completion of 18 weeks of therapy, patients continued with single agent pazopanib until disease progression. Dynamic [18F]Fluciclatide-PET imaging was conducted at baseline and after 1 week of pazopanib. Response (RECIST 1.1), toxicities and survival outcomes were recorded. Circulating markers of angiogenesis were assessed with therapy. Results: Fourteen patients were included in the intention-to-treat analysis. Complete and partial response was seen in 7 patients (54%). Median progression free survival (PFS) was 7.97 months, and overall survival (OS) was 18.5 months. A reduction in [18F]Fluciclatide uptake was observed following 1 week of pazopanib, and the reduction in uptake was predictive of long PFS. Elevated baseline circulating angiopoietin and FGF were predictive of greater reduction in SUVmax of following pazopanib. Kinetic modelling indicated a reduction in K1 and K3, following pazopanib indicating reduced radiotracer delivery and retention. Conclusions: Combination therapy following maintenance pazopanib is effective and tolerable in patients with platinum resistant/refractory ovarian cancer. We have shown that [18F] fluciclatide-PET uptake parameters alter with pazopanib therapy indicating an anti-angiogenic response. Clinical trial information: NCT01608009.

3071 Poster Session (Board #63), Sat, 8:00 AM-11:00 AM
A functional measurement of MAPK pathway activation to predict response to MEK inhibitors in RAS-mutated patients. First Author: Shumei Kato, University of California San Diego, La Jolla, CA

Background: MEK inhibitors can be used to treat patients with mutations that affect the MAPK pathway. Several MEK inhibitors are currently FDA-approved and effectively treat BRAF-mutated tumors, but RAS-mutated cancers are considered more resistant. However, it is unclear how the many distinct RAS variants impact the MAPK pathway and are affected by MEK inhibitors. We hypothesized that the level of MAPK pathway activation induced by different RAS mutations may predict response to MEK inhibition. Methods: Thirteen RAS mutations from 34 patients treated with MEK inhibitors at UCSD were synthesized, expressed in a HeLa-derived cell line and analyzed in vitro using a functional mutational analysis assay based on assessing downstream reporters in order to measure the activity of these mutations on the MAPK pathway. Each mutation received an activity score based on known oncogenic RAS mutation. Results: The most common type of cancer was colorectal cancer (N = 13). All patients received the MEK inhibitor, trametinib, based therapy. Patients were stratified into two groups: above an activity score of 1 (14 pts) or below it (20 pts). Median progression-free survival (PFS) after MEK inhibitor treatment correlated with higher MAPK activity score (9 vs 3 months; P = 0.041). Conclusions: Using a novel functional assay methodology for characterization of MAPK activation, we show that various RAS mutations activate the MAPK pathway to different levels. Higher activity is associated with longer PFS after MEK inhibitor treatment, suggesting that the relationship between signal transduction strength and clinical relevance merits additional exploration.

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Clinical impact of tissue of origin testing and mutation profiling in the Solving Unknown Primary Cancer (SUPER) national prospective study: Experience of the first two years. First Author: Pradeep Poonnen, Princess Alexandra Hospital, Brisbane, QLD, Australia

Background: Cancer of unknown primary (CUP) has a poor prognosis with a median survival of less than 12 months. SUPER is a prospective cohort study designed to create a national biobank of patients (pts) with no confirmed primary site following diagnostic work-up. Tumor and blood samples underwent mutational profiling for actionable mutations using the 386 gene PeterMac Comprehensive Cancer Panel (ICP) plus CUPGuide, a microarray gene-expression site-of-origin assay. We aimed to determine the clinical impact of CUPGuide and CCP profiling. Methods: 172 pts were enrolled between 2013-2015. Baseline demographics, treatments, investigations and clinico-pathological characteristics were collected over 12 months. Clinicians completed clinical management questionnaires before and after receiving results. Results: Molecular analysis was performed for 124/172 (72.1%) pts with sufficient DNA and/or RNA. CUPGuide was completed for 97/124 (78.2%); primary site predictions were made in 84/97 patients (86.6%). The most common primary site predictions were lung, gastric, ovary and breast. CUP- Guide predictions resulted in a change in the management of 112 (12%) of cases and confirmed current management already commenced by the clinician in 53/84 (63%). Mutation profiling was completed in 103/124 (83.1%) pts with actionable mutations found in 11 pts, 4 of whom received subsequent targeted therapy. Testing was considered to have a clinical impact in 70/120 cases (58%) either resulting in a change in treatment (n = 14), diagnosis of a pathogenic germline finding (n = 8) or a moderate/high confidence tissue of origin prediction (n = 58). There were two deaths prior to the availability of the CUPGuide results and eleven deaths prior to availability of the CCP results. Conclusions: Molecular analysis for CUP pts has clinical impact in the majority of cases. Timeliness of results, drug access and insufficient tissue for testing are barriers to greater impact that need to be addressed to improve the care of pts affected by CUP.

Genomic analysis of metastatic solid tumors in veterans: Findings from the VHA National Precision Oncology Program. First Author: Pradeep Poonnen, Duke University Health System/Durham VA Medical Center, Durham, NC

Background: Scalable next generation sequencing (NGS) technologies have enabled incorporation of precision oncology into clinical practice, informing treatment decisions based on tumor genomics. The Veterans Health Administration (VHA) is the largest integrated healthcare system in the U.S., serving a higher percentage of rural patients (36%) than the national average (14%). To implement and standardize the practice of precision oncology across a diverse healthcare system, the VHA established the National Precision Oncology Program (NPOP). Methods: Tumor or peripheral blood specimens were collected from Veterans with advanced solid tumors who were eligible for treatment with targeted or immunotherapeutic drugs. Specimens were sequenced using cancer gene panels at two commercial laboratories. Annotated results were generated by the vendors and independently using IBM Watson for Genomics. Levels of evidence treatment recommendations were based upon OncoKB criteria. Results: Between July 2016 and June 2018, 3713 samples were collected from 72 facilities; the sequencing success rate was 86%. The majority of samples came from males with lung, prostate and colorectal cancers. Thirty-four percent of samples submitted were from rural patients. The most commonly mutated genes included TP53, ATM and KRAS. Over 70% of samples sequenced had at least one actionable mutation, and clinical trials were the recommended option in over 50%. The most frequent therapies prescribed in response to NGS testing were immune checkpoint inhibitors, EGFR kinase inhibitors and PARP inhibitors. Interestingly, prostate cancers among Veterans had a higher frequency of mutations in genes associated with a neuroendocrine phenotype compared with the general population. Conclusions: Implementation of precision oncology into clinical practice is feasible across the diverse VHA system, including rural community sites. Veterans have unique occupational exposures that might impart underlying causes of distinct mutation signatures identified here. Our results highlight the importance of increasing the availability of clinical trials for Veterans.
Ovarian Cancer

Hepatocellular

Non-Small Cell

between 2013 and 2018 were included. Patients having focused molecular tests for testing performed as part of routine oncology care. All patients opportunistically tested results in a direct impact on patient therapy in a minority of patients only. We reviewed In Ireland the cost of these tests is not covered by insurance companies and must be commercially available panel tests has entered routine clinical practice in many countries.

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Tumor Types

Background:

3076 Poster Session (Board #68), Sat, 8:00 AM-11:00 AM
Utility of somatic mutation panel testing in patients with advanced cancer receiving treatment in an Irish teaching hospital. First Author: Hadia Khan, Bon Secours Hospital, Cork, Ireland

Methods:

We performed a retrospective study of patients who had commercial panel testing performed as part of routine oncology care. All patients opportunistically tested between 2013 and 2018 were included. Patients having focused molecular tests for approved therapies (e.g., RAS mutations in colon cancer, EGRF and ALK mutations in non-small cell lung cancer) were excluded. We reviewed medical records to assess the frequency and utility of mutations detected, the impact of testing on next and subsequent lines of therapy, and the effectiveness of therapy. Results: 74 panel tests were performed in 71 patients. 39 tests (53%) detected mutations, of which 21 (28%) were potentially actionable. 36 patients (51%) had further treatment after testing was performed. 9 tests (12%) led to test-based treatment. The mean duration of test-based treatment was 34 days (range 1-90 days). No patients had benefit from test based treatment, defined as tumour response or disease stabilisation on restaging scans. 23 patients died within 90 days of panel tests being requested. Among patients starting and completing a subsequent line of therapy after testing, the mean duration of therapy with test-based treatment was 39 days (range 6-90) and for standard of care treatment was 56 days (range 1-262 days). Conclusions: While testing for tumor-specific somatic mutations with proven predictive benefit is very useful, somatic mutation panel testing for non-standard of care alterations is not routinely used in this real world setting. Its role in Ireland should be limited to identification of suitable early phase clinical trials. Discussions of panel testing should include frank discussion of expected benefits, and should also address factors such as patient ability to travel for clinical trials.

3078 Poster Session (Board #70), Sat, 8:00 AM-11:00 AM
MET kinase domain rearrangements across 10 cancer types. First Author: Jun Zhao, Beijing Cancer Hospital, Beijing, China

Background: MET is a transmembrane receptor tyrosine kinase and deregulated in many kinds of tumors by mutation, rearrangement and amplification. Since the first constitutively active MET rearrangement (TPR-MET) was discovered, many other MET rearrangements have been identified in various tumor types. However, the frequency and characteristic of MET rearrangement in Chinese cancer patients is still unclear. Methods: Targeted sequencing using 1021-gene panel covering MET gene and 320 hotspot mutations in 843 9052 based ctDNA samples from 9052 unique patients across 10 cancer types. All MET exons were sequenced, but MET intronic breakpoints were not specifically baited. Results: 24 (0.27%) MET kinase domain rearrangements (KDRE) were identified in 9052 patients. Specifically, 0.25% (16/66284) in non-small cell lung cancer (NSCLC), 0.69% (22/2960) in gastric adenocarcinoma, 0.32% (2/897) in colorectal cancer, 0.33% (2610) in breast cancer, 0.3% (1/330) in hepatocellular carcinoma and 0.69% (1/145) in ovarian cancer, none in 139 pancreatic cancer, 113 thyroid cancer, 110 renal cell carcinoma and 110 esophageal squamous cell carcinoma. Among all of the MET KDRE, 17 were fusions with 3 identified partner, 3 were kinase domain duplication (KDD) and 4 were probable fusions with unidentified partner. The most common 5 ‘partner’ gene was CAPZA2, followed by CD47 and TES. In the MET KDRE cases in NSCLC, 56.25% (9/16) did not find any clinical actionable variants referring to the NCCN guideline. In addition, MET amplification, EGFR L858R or exon 19 deletion and KRAS mutation co-occurred in 25% (4/16), 18.75% (3/16) and 12.5% (2/16) of NSCLC MET KDRE cases respectively. Conclusions: Our results, for the first time, illustrate the MET KDRE across 10 cancer types among Chinese population and might provide some novel targets to develop new therapies for patients with METKDRE. MET KDRE across different tumor types.

3077 Poster Session (Board #69), Sat, 8:00 AM-11:00 AM
Proteomic profile of high-risk luminal A early breast cancers. First Author: Nawale Hajaji, Centre Oscar Lambret, Lille, France

Background: Breast cancer is a heterogeneous disease with a wide range of outcomes. Among the intrinsic breast cancer subtypes, luminal A tumors are considered to have a favorable prognosis. However, molecular studies characterizing the genomic landscape of luminal A tumors revealed a molecular heterogeneity within this subtype, which also translated to variability in survival. A better understanding of the biology of this tumor subgroup is therefore needed to determine the appropriate therapeutic strategy. The aims of the study were to determine the frequency of high-risk luminal A tumors in a real life cohort of early breast cancers and provide a proteomic characterization of this subgroup using a mass spectrometry approach. Methods: 222 early breast cancer patients with hormone receptor positive and HER2 negative tumors treated at our institution had a PAM50-based genomic assay Prosigina to estimate their risk of recurrence. This assay assigned each tumor sample to an intrinsic molecular subtype of breast cancer. Luminal A and B tumors were analyzed with MALDI mass spectrometry imaging combined with proteomics, a spatially-resolved on-tissue shotgun proteomic technology, to determine the proteomic profiles of both cancer cells and stroma. Results: Among the 129 luminal A breast cancers identified in our cohort, 67 (51%) had a risk of distant recurrence of 10% or more (32% had a 10% to 15% risk, and 19% a risk greater than 15%). High-risk luminal A tumors had a distinctive proteomic profile compared to low-risk luminal A or to luminal B tumors. Overexpression of the methionine biosynthesis pathway was the main differential protein expression observed in cancer cells and stroma of high-risk luminal A. Inflammation mediated by chemokine and cytokine signaling pathway and integrin signaling were also overexpressed in high risk luminal A compared to luminal B. In the stroma of luminal B tumors, EGR signaling, Ras and FGF pathways and angiogenesis were overexpressed compared to high-risk luminal A tumors. Conclusions: Proteomics data showed a significant proteomic signature in high-risk luminal A breast cancers. MALDI mass spectrometry proteomics revealed distinctive tumor and microenvironment profiles in this breast cancer subgroup.

3079 Poster Session (Board #71), Sat, 8:00 AM-11:00 AM
An artificial intelligence approach to variant calling of ALK resistance mutations. First Author: Jochen K Lennerz, Massachusetts General Hospital, Boston, MA

Background: ALK tyrosine kinase inhibitors (TKIs) are effective in treating advanced anaplastic lymphoma kinase (ALK) fusion-positive non-small-cell lung cancers (NSCLC), and specific ALK variants are associated with the development of resistance to specific TKIs. Humans struggle to harness the full potential of the highly complex next-generation sequencing bioinformatics pipeline output. As a consequence, the decision to report a variant remains difficult, and we considered the discrete nature of the data and the binary decision (report vs. not-report) as an ideal setting to apply an artificial intelligence (AI) approach for variant reporting. Methods: We assessed diagnostic performance of an AI model in calling ALK-resistance mutations in n = 50 consecutive ALK fusion positive patients who relapsed on TKI-therapy and underwent repeat biopsy at MGH. The random forest model was derived from independent datasets (training and validation) capturing the reporting decision on > 36,000 variants with ~500 features per variant resulting in a matrix of > 18 million data points. The model output is a contiguous prediction score from 0 (not report) to 1 (report) and a visual drill-down functionality allows exploration of the underlying features that contributed to the decision. Results: Examination of n = 76 tests from n = 50 patients with a total of n = 130 reported variants (and n = 115 not reported variants) included a total of n = 31 ALK point mutations: p.1156N (n = 2), p.1171N (n = 8), p.1174N (n = 2), p.1180N (n = 2), p.1196N (1), p.1202N (1) = 1203N (1), p.1204N (1), p.1206N (1), p.1269N (1), p.1296N (1), p.1269N (4). Setting a screening threshold of the model at > 10% for reporting showed only one false-negative (p.Ile1171Asn) variant and 96.7% sensitivity. The average model score for ALK variants was 0.664 (range: 0.08–0.98; median 0.8) and did not show significant differences from other reported variants. Setting a threshold of 0.60–1.0; 0.7; 0.66. The model would have called n = 18 of the non-reported control variants (average 0.07; range < 0.001-0.64; P < 0.0001) and was 84% specific. Review of the drill-down function identified prior call frequency, allelic ratio, and predicted transcript consequences as common model features. Important to note the model is currently agnostic to the medical literature and will not take clinical parameters (e.g. TKI type) into account, which may further improve performance. Conclusions: Applying artificial intelligence to large discrete datasets is one approach to help identify clinically relevant variants in the setting of ALK resistance in ALK-fusion positive NSCLC.

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Background: The genomic profiling of breast cancers has led to a greater understanding of the mutational landscape of metastatic breast cancer (MBC) with potential therapeutic implications. Despite these advances, there is a paucity of data regarding the additive value and relevance of gene expression across histological and molecular subtypes, which represents the majority of informative and actionable findings identified in the BC personalized oncogenomics programme (POG). Informative findings with potential clinical application from whole genome sequencing (WGS) and whole transcriptome sequencing (WTS) in MBC patients between 2012-2018 were reviewed. Variants observed in pathway genes of potential clinical relevance, as defined by a curated list of genes, were examined across histological subtypes. High and low expression outliers relative to TCGA breast cancers, defined as expression greater than 98th percentile and FC > 2 compared to Illumina breast dataset and lower than 25th percentile and FC < -2 compared to Illumina breast dataset, respectively, were then analyzed to establish how many outliers were observed in pathways of potential clinical relevance. Results: A total of 113 cases were included. WGS revealed that TP53 was the most frequent single nucleotide variant (SNV) in triple negative breast cancer (23/30, 77%), whereas PIK3CA (37/78, 47%), PTEN (11/78, 14%) and ESR1 (19/78, 24%) were most frequent in ER positive cases and CDKN2A (2/18, 11%) in HER2 positive cases. Across all subtypes, the mTOR and cell cycle pathways were found to have the highest frequency of SNVs, with the identification of 86 and 71 variants, respectively. Expression data for 113 RNA-sequenced patients revealed a high frequency of expression outliers in the mTOR pathway (26 high expression and 424 low expression outlier genes) and cell cycle pathways (35 high expression and 331 low expression outlier genes), but also in the WNT pathway (96 high expression and 490 low expression outlier genes) and NOTCH pathway (84 high expression and 564 low expression outlier genes). Conclusions: Frequently identified SNVs across histological subtypes were correlated with expression outliers in pathways of clinical relevance in breast cancer. Additional informative findings, in pathways of potential clinical relevance not historically targeted in breast cancer, were identified with WTS. The clinical utility of these findings warrants further study.

Transcriptome-based cancer type prediction for tumors of unknown origin. First Author: Jack Michuda, Tempus, Chicago, IL

Background: Tumors of unknown origin occur in approximately 5% of newly diagnosed cancers and are difficult to treat without establishing the tissue type from which they derive. Establishing tumor origin guides standard of care treatment for several NCCN targeted therapy guidelines. Leveraging tissue specificity in gene expression profiles, classification models based on RNA expression offer a promising approach to identify the likely primary cancer site in tumors of unknown origin. Methods: In this study, we developed a transcriptome-based cancer type classifier trained on over 10,000 tissue samples annotated by pathologists and sequenced for RNA expression to identify conserved patterns of expression characteristic of 30 tumor types across primary and metastatic tissue sites. The classifier probabilistically ranks cancer of origin. Results: Overall, the accuracy of the most probable cancer prediction was 85%, 88% within primary tumors and 77% within metastatic tumors. The top three cancers types with the highest accuracy were colorectal (accuracy in metastatic: 93%, accuracy in primary tumors: 99%), breast (95%, 96%) and lung (87%, 94%). Classifier performance was lower in low-purity metastatic tumors where the surrounding normal tissue obscures the tumor transcriptional profile, though the classifier still achieves 71% accuracy on metastatic tumors with less than 50% purity. Conclusions: We present a novel method to probabilistically predict tumor type for cancers of unknown origin using RNA-Seq. Our method achieves robust classification that is applicable to primary and metastatic tumors and demonstrates the value of utilizing RNA-Seq to aid cancer diagnosis and treatment decisions.
3084 Poster Session (Board #76), Sat, 8:00 AM-11:00 AM

Determining clinical relevance of genomic heterogeneity in an ethnically diverse cohort of newly diagnosed patients with breast cancer. First Author: Panchara Sheila Rajagopal, The University of Chicago, IL

Background: The trajectory from early breast cancer to distant metastasis has not been precisely characterized. We are building an ethnically diverse, longitudinal cohort of prospectively ascertained breast cancer patients with integrated genomic, transcriptomic, epidemiological and clinical data, with the goal of identifying biomarkers that can improve on clinical predictors.

Methods: Our goal is 500 histologically confirmed invasive cases with a minimum follow-up of 5 years. To date, Tempus Labs, Inc. has completed 17 assays (595-gene panel DNA-seq and full-transcriptome RNA-seq) on 127 cases with matched tumor-normal samples. Clinical information was obtained from electronic health records and our cancer registry. Results: Median age of diagnosis was 51, with 47% African-Americans. 73% had stage 2 or 3 disease (2 patients were stage 4), 24.4% had TNBC, 30% had HR+ and 62.2% had HR- status. Somatic alterations were identified in 560 genes with most common mutations in TP53 (56%), MCL1 (35%), PIK3CA (30%) and ERBB2 (17%). Somatic mutations in BRCA1 (10%) and BRCA2 (5%) were associated with increased tumor mutation burden (TMB). 2 patients were MSI high; 6 were equivocal. After a median follow-up of 6.5 years, 46 patients died and 38 had recurrent disease. With adjustment for clinical factors, TMB showed a slight nonsignificant negative association with recurrence-free survival (HR: 0.97, 95% CI: 0.91-1.00, p = 0.31). TP53 was associated with recurrence-free survival (HR: 1.76, 95% CI: 0.94-3.29; p = 0.08) as was MSI (HR: 0.24, 95% CI: 0.06-1.06, p = 0.06). Results: As of 1 Nov 2018, 28 pts (78.6% female, median age 66.5 y) were treated in 7 cohorts: 2 mg QD (3 pts), 5 mg QD (3 pts), 10 mg QD (3 pts), 10 mg BID (5 pts), 15 mg BID (4 pts), 20 mg BID (7 pts), and 30 mg QD (3 pts). Treatment was ongoing in 8 pts at data cut-off. Proportional increase in Cmax and AUC were observed across the dose range tested. Tmax ranged from 0.5 to 3 h and t1/2 was 6 h. Dose-dependent changes in exposure to CDK4/6 or PI3K pathway inhibitors. PD studies include analyses of PIK3CA mutational status in patients with advanced solid cancers—Safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) analysis of the dual combination. First Author: Juanaizia Suzanne Lopez, Drug Development Unit-The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

3086 Poster Session (Board #78), Sat, 8:00 AM-11:00 AM

c-AMPK/PI3K dysregulation and its impact on survival and response to immunotherapy in advanced melanomas. First Author: Rami Al-Rohil, Duke University Medical Center, Durham, NC

Background: Immunotherapies blocking the interaction of CTLA-4 or Programmed Death 1 (PD-1) with their ligands are the standard of care for advanced MEL although many pts fail to benefit from immunotherapy. Herein, we seek to identify somatic and genetic signatures associated with lack of response in patients treated with immunotherapy. Methods: We performed whole exome sequencing of 580 cancer-related genes and whole-genome DNA methylation array targets (850K CpG sites) covering promoters, enhancers, and transcription factor sites in 28 MEL samples from patients treated with c-AMPK/PI3K inhibitors. Findings were correlated with collected clinical history. Results: Findings are summarized in the table. Unsupervised clustering and multi-parametric analysis showed a distinct methylation signature independent of age, sex, stage, site of metastasis, or type of treatment (adj. p<0.01). Pathway analysis identified c-AMPK/PI3K dysregulation signaling pathways (adj. p<2.10E-05 and 8.19E-06, respectively) enrichment in non-responders. Conclusion: c-AMPK/PI3K signaling inhibition and c-AMPK/PI3K dysregulation were associated with a worse OS and PFS but not worse response rate (p<0.04, p<0.01), and (p<0.20). PDE4DIP/deletional events were associated with decreased response rate, worse OS and PFS (p=0.002, p=0.002, p=0.0003). Conclusions: Convergent epigenetic dysregulation of c-AMPK/PI3K signaling and inactivation of PDE4DIP is associated with worse outcome and lack of response to immunotherapy, respectively.

3087 Poster Session (Board #79), Sat, 8:00 AM-11:00 AM

PIPA: A phase Ib study of selective B-isomorph sparing phosphatidylinositol 3-kinase (PI3K) inhibitors (T) plus pembrolizumab (P) in patients (pts) with advanced solid cancers—Safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) analysis of the dual combination. First Author: Author: Judy Sing-Zan Wang, Florida Cancer Specialists and Sarah Cannon Research Institute, Sarasota, FL

Background: BRD4 is a bromodomain and extraterminal (BET) protein that regulates oncogenic programs by modifying gene transcription and additional mechanisms. AZD5153 is a novel, reversible BRD4 inhibitor with bivalent mechanism of action and enhanced antitumor activity in preclinical models. This report is from a phase 1, multicenter, dose escalation study (NCT03205176) assesses AZD5153’s safety, pharmacokinetics (PK), and pharmacodynamics (PD). We report here preliminary, unvalidated data from AZD5153 monotherapy in pts with RR solid tumor, including lymphoma. Methods: Adult pts received oral AZD5153 QD/BID to determine the MTD. During dose escalation, a continual reassessment model was used to estimate toxicity and all final decisions were made by the Safety Review Committee. PK and PD were characterized using standard methods. Results: As of 1 Nov 2018, 28 pts (78.6% female, median age 66.5 y) were treated in 7 cohorts: 2 mg QD (3 pts), 5 mg QD (3 pts), 10 mg QD (3 pts), 10 mg BID (5 pts), 15 mg BID (4 pts), 20 mg BID (7 pts), and 30 mg QD (3 pts). Treatment was ongoing in 8 pts at data cut-off. Findings showed 50% of pts experienced treatment-related AEs. 25% of pts experienced treatment-related Grade ≥3 AEs, which were thrombocytopenia and fatigue (7.1% each), and anemia, diarrhea, and platelet count decreased (3.6% each). SAEs were observed in 25% of pts; none of the SAESs was attributed to AZD5153. Overall, limiting toxicity was grade 1 (1 pt) and diarrhea with herpetic rash leading to discontinuation (1 pt occurred at 20 mg BID. 53.6% of pts discontinued due to disease progression. Total median treatment duration was 1.3 mo (range up to 8.9 mos). Dose proportional increase in Cmax and AUC were observed across the dose range tested. Tmax ranged from 0.5 to 3 h and t1/2 was 6 h. Dose-dependent changes in expression of target genes (eg, HEXIM1, HIST2H28B, CD274, and CCR2) and platelet counts were observed in the peripheral blood. Conclusions: AZD5153 monotherapy is safe and tolerated at doses up to 30 mg QD and 15 mg BID. Linear increase in PK was observed. Additional safety and efficacy updates will be reported at the annual meeting. Clinical trial information: NCT03205176.

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Developmental Therapeutics and Tumor Biology (Nonimmuno)
Distinct radiological patterns of drug-induced pneumonitis (R-DIP) in early-phase clinical trials and predictive factors affecting outcome: A 10-year systematic review from the Royal Marsden Hospital Phase I Drug Development Unit experience. First Author: Angelika Terbush, Royal Marsden Hospital and The Institute of Cancer Research, Sutton, United Kingdom

Background: We studied clinical and radiological parameters influencing DIP in patients (pts) participating in phase I clinical trials, aiming to investigate predictive factors affecting DIP, in particular those affecting outcome. Methods: 2439 consecutive stage IV cancer pts on phase I clinical trials from 2007 to 2017 were identified. Pts with respiratory symptoms or abnormal lung imaging were reviewed in detail, with longitudinal analysis of imaging by an experienced radiologist. R-DIP was categorized according to internationally recognized criteria. Results: 60 pts developed R-DIP (overall incidence 2.5%); most frequent in pts receiving drug conjugates (31.1%) followed by targeted therapies (8.3%). Hypersensitivity pneumonitis was most common (33.3%) followed by non-specific interstitial pneumonitis (30%) and cryptogenic organising pneumonitis (26.7%). 45% pts who developed R-DIP were clinically asymptomatic. The number of affected lobes (OR 1.47, 95% CI: 1.19-1.81, p < 0.001) and the pattern of R-DIP (OR 5.83 for ARDS, 95% CI: 0.38-90.24, p = 0.002) were significantly associated with the CTCAE pneumonitis grading. 23% pts (14/60) had investigational medicinal product (IMP) temporarily discontinued or had a dose reduction while 42% pts (25/60) had IMP permanently discontinued. 48% pts were treated with steroids. The number of affected lobes, pattern of R-DIP and steroid therapy did not influence an improvement in R-DIP (p = 0.65, 0.27 and 0.23 respectively). Continuation of treatment resulted in worsening of DIP in 42% of cases. The only predictive factor for an improvement in DIP was an interruption of treatment (OR 0.05, 95% CI: 0.01-0.35, p = 0.01). 14 pts were retreated with a reoccurrence of R-DIP in 4 pts (28.6%). Conclusions: R-DIP from novel agents is a challenging problem. Pts with clinical abnormalities typically present with one lobe and R-DIP typically occurs in the lower lobes. Continuous treatment is associated with deterioration of R-DIP. Improvement of DIP was observed in pts withdrawing treatment. Close clinical and radiological surveillance is recommended should IMP be restarted.

Design, engineering, and characterization of a novel long-acting (Pegylated) single domain isomer arginase for arginine deprivation as a treatment. First Author: Kuo-Ming Yu, Athensex, Inc., Hong Kong, China

Background: Arginine deprivation therapy is an attractive strategy to treat arginase-autotrophic cancers with deficient expression of argininosuccinate synthetase, argininosuccinate lyase or ornithine transcarbamylase. We have designed and engineered a novel human arginase with single site pegylation exerting excellent preclinical pharmacological profile to serve as a new class of therapy. Methods: Human arginase has three cysteines (at position 45, 168, 303) and none of them is in or close to the active site. Two cysteines were mutated to serines, leaving the only cysteine at 45 for the simple and cost-effective synthesis of a single isoform of pegylated human arginase. Different forms of PEG moieties were evaluated for the selection of a drug candidate (PT01), followed by extensive characterization. Results: Converting Cys at 168 and 303 to serine impacted least on enzymatic activity (with cobaltation). Pegylation with different sizes and shapes showed that 20 and 40 kDa (linear and branched) had similar PK/PD profile with decreasing enzymatic activity. Therefore, arginase modified with a linear 20 kDa PEG was chosen as the candidate. A single 0.4 mg/kg IV dose of PT01 in rats induced 4 days of complete plasma arginase depletion, while 6–7 days of depletion between 1.2 and 2 mg/kg. Plasma arginase levels were reversible. First-order clearance of both plasma PT01 concentration and activity suggested a terminal half-life of about 20 hours. In vitro assay showed very potent cytotoxicity at sub-nM level against various cell lines of breast, prostate, and pancreas in origins. In two mouse cancer models (hard-to-cure pancreas and castration-resistant prostate), weekly infusion at 10 mg/kg induced significant tumor growth inhibition of 44-67%. All mice experienced dose-dependent but rapidly reversible weight loss following each weekly dose. Conclusions: A novel single isoform of pegylated human arginase was created, showing excellent enzymatic activity, PK/PD profiles, and cytotoxicity in vitro. Mouse xenograft models showed good tumor growth inhibition activity with tolerable toxicity as manifested on transient weight loss during therapy.

Phase 1 study of prexasertib, a checkpoint kinase (CHK1) inhibitor, and LY3023414, a dual inhibition of phosphatidylinositol 3-kinase (PI3K) and the mammalian target of rapamycin (mTOR) in patients with advanced solid tumors. First Author: David S. Hong, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Prexasertib inhibits CHK1, a kinase involved in DNA repair and replication. LY3023414 inhibits PI3K/mTOR signaling, implicated in the development of malignant disease. Prexasertib + LY3023414 has resulted in single-agent activity in triple-negative breast cancer (TNBC) and endometrial cancer (EC). In vitro models. Methods: This Phase 1b study in patients (pts) with solid tumors assessed escalating doses of prexasertib (60-105 mg/m2 IV every 14 days [q14d]) and LY3023414 (100-200 mg orally twice daily [BID]). Dose escalation ceased once the maximum tolerated dose of each monotherapy was reached. An initial expansion cohort (Arm E) explored prexasertib 1300 mg tid and if at least 2 pts were treated without toxicity, further expansion was planned. Conclusions: The combination of ABTL0812+PC was safe and tolerated, efficacious, with tumor responses observed, and biomarker modulation confirmed drug activity. The triple combination is currently being evaluated in both indications in a Phase 2 study. Clinical trial information: NCT03366480.

A phase Ib study of prexasertib, a checkpoint kinase (CHK1) inhibitor, and LY3023414, a dual inhibition of phosphatidylinositol 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) in patients with advanced solid tumors. First Author: Lorena Farinas-Madrid, Vall d’Hebron University Hospital Institute of Oncology (VHIO), Barcelona, Spain

Background: ABTL0812 is a novel anti-cancer agent that induces a strong autophagy-mediated cell death by a dual mechanism. It inhibits the Akt/mTOR axis by upregulating TRIB3, an endogenous Akt inhibitor, and induces reticulal (ER)-stress. Preclinical data in squamous non-small cell lung carcinoma (Sq-NSCLC) and endometrial cancer (EC) has indicated drug effect as single agent and potentiation of chemotherapy. Methods: A phase 1 clinical study was designed where ABTL0812 was administered orally in combination with 175 mg/m2 paclitaxel/carboplatin AUC5 D1 every 3 weeks (P/C), and posterior ABTL0812 as a maintenance therapy until disease progression or unacceptable toxicity. The study included first-line patients (pts) with advanced Sq-NSCLC or advanced/recurrent EC. The design included a 3+3-dose escalation followed by an expansion cohort, where the starting dose of ABTL0812 was 1300 mg tid and if at least 2 pts experienced a DLT, the dose level would be de-escalated to 1000 mg tid. Safety and tolerability were the primary endpoints and preliminary efficacy according to RECIST 1.1 and phosphatidylinositol 3-kinase (PI3K) and CHOP an ER-stress biomarker, by qPCR in whole blood were the secondary endpoints. Results: 16 EC and 5 Sq-NSCLC pts were enrolled. One DLT, a grade 4 neutropenia, appeared in the first cohort of 6 pts and no de-escalation was applied. Fourteen pts were included in an expansion cohort with the same dose of ABTL0812 and 2, 10% each for grade 4 neutropenia and grade 4 thrombocytopenia. All 14 pts completed at least two treatment cycles were evaluable for efficacy; 1 CR (EC), 8 PR (7 EC and 1Sq-NSCLC), 7 SD (5 EC and 2 Sq-NSCLC) and 1 PD (Sq-NSCLC) who completed at least two treatment cycles were evaluable for efficacy. 1 CR, 8 PR and 7 SQ-NSCLC were observed. Pharmacodynamic biomarkers showed increased TRIB3 and CHOP levels. Conclusions: The combination of ABTL0812+P/C was safe and tolerated, effective, with tumor responses observed, and biomarker modulation confirmed drug activity. The triple combination is currently being evaluated in both indications in a Phase 2 study. Clinical trial information: NCT02124148.

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Preclinical testing of ultra-rapid FLASH total abdominal irradiation demonstrates survival benefit and decreased gastrointestinal toxicity compared to conventional external beam radiation. First Author: Karen Levy, Stanford University, Stanford, CA

Background: Total abdominal irradiation (TAI) is not widely used in the treatment of ovarian cancer due to high abdominopelvic toxicity. Ultra-rapid FLASH irradiation has been shown to spare the lung, skin and brain from radiation toxicity in preclinical models. Conventional radiotherapy delivers a dose-rate of 3-4 Gy/minute, while our small animal FLASH system uses a linear accelerator to generate a dose-rate of 200 Gy/second. This demonstrates that use of FLASH-TAI in a preclinical model protects against death from irradiation and confers gastrointestinal (GI) protection when compared to conventional external beam irradiation. Ongoing studies are evaluating the potential for tumor control in an ID8 mouse model of ovarian cancer. Methods: Female C57BL/6 mice received TAI using FLASH and conventional (CONV) radiation at increasing doses: 8.5 Gy, 10.5 Gy and 12 Gy. Unirradiated controls and irradiated cohorts were analyzed at 5-days and 12 months post-irradiation. Normal tissue toxicity was determined by measuring total body weights, stool counts, laboratory analysis, histological analysis, immunohistochemistry, and survival. Results: Solid stool production was preserved in FLASH mice, whereas a 50-63% decrease was observed in the CONV cohorts. Histology demonstrated that FLASH preserves small intestinal architecture. TUNEL analysis demonstrated an increase in apoptosis throughout the small intestine of only the CONV cohort. Exploratory necropsy of mice exposed to 12 months post-irradiation was notable for secondary transmural proximal duodenal adenocarcinomas within the radiation field in 25% of only the aged CONV cohorts. There was no laboratory evidence of long-term hematopoietic, liver or kidney toxicity at 12 months. Survival analysis was notable for death of all 12 Gy CONV mice by 21 days post-irradiation whereas 75% of the 12 Gy FLASH mice were alive at 11 months. Conclusions: FLASH protects against death from TAI, improves small intestine epithelial integrity following TAI, protects against radiation-induced apoptosis and may protect from secondary gastrointestinal tumors in the radiation field. Our discovery that FLASH is a safe strategy to deliver effective doses of total abdominal irradiation potentially identifies a new opportunity to utilize FLASH-TAI for treatment of ovarian peritoneal metastases.

Poster Session (Board #85), Sat, 8:00 AM-11:00 AM
First-in-human imaging of nanoparticle entrapped docetaxel (CPC634) in patients with advanced solid tumors using 89Zr-Df-CPC634 PET/CT. First Author: H.C. Medema, UMC Utrecht, Utrecht, Netherlands; 1st Author: Trudy van der Meulen, Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam, Netherlands

Background: CPC634 is a nanoparticle entrapping docetaxel designed to improve tumor accumulation and tolerability compared to conventionally administered docetaxel by taking advantage of the presumed enhanced permeability and retention (EPR) effect. In vivo imaging with zirconium-89 (89Zr)-desferal (Df)-CPC634 will provide valuable information on the biodistribution and will quantify tumor retention. Methods: Patients with solid tumors not amenable to standard therapy received 37 MBq, 0.1-2mg of 89Zr-Df-CPC634 tracer and whole body PET/CT scans were obtained at 24 and 96h post-injection (p.i.). Patients were administered CPC634 (60mg/m2) two weeks later followed by a second tracer injection and scans at 24 and 96h p.i. Biodistribution was quantified by delineating organs of interest and calculating mean %ID/kg. Visual tumor retention was defined as focal uptake in tumor lesions exceeding local background and quantified as standardized uptake peak values (SUVpeak) in volumes of interest. Results: Five patients were enrolled. Blood-dose of 89Zr-Df-CPC634 showed significant retention in healthy liver, and spleen compared to lung (respectively 2.54, 1.61 and 0.56 mean %ID/kg at 96h p.i.), supporting apparent opsonization of nanoparticles in cells of the reticuloendothelial system. Visual retention was observed in 16/37 evaluable tumor lesions with the highest intensity at 96h p.i. Pre-administered unlabeled CPC634 did not change the mean tumor retention of 89Zr-Df-CPC634 (at 96h p.i. mean 3.50 %ID/kg [1.64-9.97]). However, four additional lesions were visible in comparison to tracer only. Conclusions: 89Zr-Df-CPC634 was safely administered with low-dose gemcitabine as a prolonged exposure of nanoparticle containing docetaxel. 89Zr-Df-CPC634 showed high retention in tumors confirming the EPR effect of the nanoparticles in human, and supporting their further development for tumor targeting of therapeutic agents. A Phase II efficacy study in platinum resistant ovarian cancer (NCT03742713) is currently ongoing. Clinical trial information: NCT03712423

Poster Session (Board #86), Sat, 8:00 AM-11:00 AM
A first-in-human phase II trial of SRA737 (a Chk1 inhibitor) in subjects with advanced cancer. First Author: Elizabeth McCarthy, Northern Centre for Cancer Care, Newcastle-upon-Tyne, United Kingdom

Background: SRA737 is a potent, highly selective and orally-bioavailable inhibitor of checkpoint kinase 1 (Chk1). SRA737-01 was designed to investigate the safety and tolerability of continuous, daily dosing with SRA737 and to evaluate preliminary efficacy in expansion cohorts of preselectively-selected genetically-defined subjects with advanced tumors. Methods: The escalation phase was phase I study with subject-specific dose-escalating design. A planned enrollment of five patients with preselected subjects (phase I) followed by a rolling-6 design once SRA737-related Grade 2 toxicity was observed during Cycle 1. The expansion phase enrolled subjects prospectively selected by next-generation sequencing with high grade serous ovarian, colorectal, metastatic castration-resistant prostate, non-small cell lung, and head and neck cancers. Results: In escalation, 18 subjects received SRA737 in 9 dose level cohorts, from 20 to 1300 mg QD; median treatment duration 62.5 days (range 1 to 226). Of these subjects, 3 experienced dose limiting toxicity (DLT; inability to receive 75% of the planned dose), 2 at 1300 mg QD due to gastrointestinal intolerance and 1 at 500 mg QD due to thrombocytopenia. The maximum tolerated dose (MTD) was established at 1000 mg QD or 500 mg BID. The Cmin and AUCC0-24 at 1000 mg QD were 2391 ng/mL and 26795 ng/mL respectively and the Cmin (411 ng/mL) exceeded that determined in preclinical models to be effective. Of 462 subjects prospectively screened for genetic alterations associated with Chk1 sensitivity, 93 were enrolled in expansion across all tumor types. Overall, the most commonly reported treatment-emergent adverse events were diarrhea (70%), nausea (64%), vomiting (51%), and fatigue (47%); the majority were of mild to moderate severity. Conclusions: In this first-in-human trial of SRA737 monotherapy, the MTD was 1000 mg at 1300 mg QD. The successful enrollment of prospectively-selected genetically-defined subjects will allow response data to be correlated with genomic profiles hypothesized to confer sensitivity to Chk1 inhibition. Clinical trial information: NCT02797964

Poster Session (Board #87), Sat, 8:00 AM-11:00 AM
A phase I/II first-in-human trial of oral SRA737 (a Chk1 inhibitor) given in combination with low-dose gemcitabine in subjects with advanced cancer. First Author: Uday Banerji, Drug Development Unit-The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

Background: SRA737 is a potent, highly selective and orally-bioavailable inhibitor of checkpoint kinase 1 (Chk1). SRA737-02 was designed to investigate the safety, tolerability and preliminary activity of SRA737 in a novel combination with sub-therapeutic doses of gemcitabine (low dose gemcitabine; LDG) utilized to potentiate SRA737’s activity by induction of replication stress in subjects with advanced solid tumors. Methods: Phase 1 dose escalation investigated cohorts of 3 to 6 subjects receiving escalating doses of SRA737 for 2 days after LDG administration on days 1, 8, 15 of 28-day cycles. Results: Phase 2 expansion cohorts explored the hypothesis that LDG strongly synergizes with SRA737 in subjects with genetically-defined tumors hypothesized to be sensitive to Chk1 inhibition: urothelial, high grade serous ovarian, small cell lung, soft tissue sarcoma, and cervical or anogenital cancers. Results: A total of 55 subjects received SRA737 in 13 dose escalation cohorts at doses of 40 to 600 mg SRA737 combined with LDG doses of 50 to 300 mg/m2. No protocol-defined dose limiting toxicities (DLTs) have been observed. The pharmacokinetic profile of SRA737 revealed an AUCC0-24 and Cmax of 3550 ng/mL and 548 mg/mL at 150 mg SRA737. At this dose, the Cmin (52 ng/mL) exceeded that determined in preclinical models to be effective. Enrollment into expansion cohorts was initiated at 500 mg SRA737 plus 100 mg/m2 LDG with intra-patient dose escalation permitted to 250 mg/m2 LDG. Approximately 80 subjects were planned and 82 have been treated. Median treatment duration was 51 days (range 1 to 358). The most common treatment-emergent adverse events were nausea (53%), vomiting (45%), fatigue (40%), diarrhea (38%), and anemia (28%); the majority were of mild to moderate severity. Proof-of-concept clinical activity has been seen in tumor types such as anal, cervical, and rectal. Conclusions: The combination of LDG and SRA737 has been well tolerated. This first-in-human clinical study provides proof-of-concept that sub-therapeutic LDG effectively potentiates SRA737 in subjects with genetically-defined tumors. Clinical trial information: NCT02797977.

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A phase 1 study of the APE1 protein inhibitor APX3330 in patients with advanced solid tumors. First Author: Safi Shahda, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN

Background: APX3330 is an orally administered anti-cancer, anti-CIPN agent targeting the APE1 protein. APE1 maintains NFkB, STAT3, AP-1 and HIF-1a in a reduced form, acting as a regulator of transcription factors. A dual function protein, APE1 also plays a role in protecting against oxidative DNA damage in neurons. APX3330 is a highly selective inhibitor of APE1 redox function in tumors that enhances the neuronal protection function of APE1. Methods: We report a phase I study NCT03335909 evaluating APX3330 in patients with incurable malignancies. Eligibility required adequate organ function, PS 0-2 and tumors not amenable to curative therapy. 1 and 2 objectives included determining the recommended phase 2 dose (RP2D), the safety and PK/PD profiles of APX3330 and reporting any RECIST anti-tumor activity. Patients received APX3330 b.i.d. in 21-day cycles. AE evaluation included 1 p/cycle until the occurrence of ≥ G2 toxicity at which time the study proceeded in a 3+3 design. Additional patient were also recruited in cohorts in order to attain PK/PD and biopsy samples. Results: Between 2/18 and 8/18, 19 subjects (13M, 6F) with median age of 69 yrs started therapy. Dose (mg/d) escalation and number of patients treated (n) per each cohort proceeded as follows: 240 mg (1), 360 (4), 480 (2), 600 (6) and 720 (6). APX3330 was well tolerated at dose levels from 240-600 mg/d. The most frequent treatment-related adverse event (all grades) was G1 fatigue. A G3 rash occurred in two subjects at the 720 mg level defining 600 mg/d as the RP2D for further development. Six subjects had disease stabilization and of these, four in which APE1 driver mutation (RAS, PIK3CA) was detected. RECIST response and days on study included: (CRC, PR, SD; 365), (Endometrial, SD, 316), (Melanoma, SD, 245), (Prostate, SD, 246). Final PK and PD data, including proteomic, transcriptome, APE1 serum levels and CTc analyses are pending and will be reported at the conference. Conclusions: APX3330 is an orally administered inhibitor of APE1. The phase I study identified 600 mg PO daily as the RP2D for further development. RECIST evaluation identified signs of clinical activity in this un-selected population of patients with advanced cancer. PD analyses indicate APX3330 mediated targeting of the APE1 protein. Clinical trial information: NCT03375086.

FGRF2: A pan-genomic target. First Author: Russell Madison, Foundation Medicine, Inc., Cambridge, MA

Background: FGFR2 genomic alterations (GA) have been described in a variety of solid tumors and emerged as biomarkers for investigational agents undergoing clinical trials. Methods: 201,766 primarily resected/refractory malignancies were evaluated with a hybrid-capture based sequencing assay Tumor mutational burden (TMB) was determined on 0.8-1.1 Mbp of sequenced DNA and reported as mut/kb. Microsatellite instability (MSI) was determined on 114 loci. PD-L1 expression was determined by IHC (Dako 22C3 antibody). Results: FGRF2 GA were detected in 2,993 (1.5%) cases featuring short variant (SV) mut (42%), copy number changes (27%), rearrangements/fusions (28%) and multiple GA (3%). The most frequent SV GA were S252W, N549K, C382R, P253R, Y375C, K659E and R646W. A small cohort (2%) of tumors featured the V564L and V564L GA that are associated with resistance to TK1 drugs. The FGRF2-altered cases were female 167/31% male with median age of 61 yrs. Most frequent GA in FGRF2 altered cancers: TP53 (47%), PIK3CA (22%), Pten (20%), ARID1A (18%), CDKN2A (18%) and MYC (12%). FGRF2 SVs most common in endometrial, breast carcinomas (ca) and CUP. FGRF2 amplification most common in breast, gastroesophageal and lung ca. FGRF2 rearrangement/fusions most common in cholangioca (37%), CUP (15%), pancreaticobiliary (12%) and breast ca (6%). The FGRF2-BICC1 was the most frequent fusion followed by fusions with TACC2, AHCYL1, CCDC6, VCL, and KIAA1217. Conclusions: FGRF2 GA occur at low frequency in a variety of tumors and may be of potential clinical relevance.
3100 Poster Session (Board #93), Sat, 8:00 AM-11:00 AM
Patient-derived organoid (PDO), a new personalized therapy selection tool for prompt clinical decision making in metastatic gastrointestinal (mGI) cancer patients.
First Author: Hayoung Kim, Mayo Clinic, Rochester, MN
Background: PDO is a promising translational tool that recapitulates the biology and drug response of donor cancer patient. However, an unmet need is to have PDO drug-screening data available for treatment decision making in clinic. We conducted a pilot study to determine whether PDO testing results will be available at critical treatment decision points in metastatic GI cancer patients. Methods: Metastatic GI cancer patients undergoing core-needle biopsy were eligible. Tumor tissues isolated from <4 fresh biopsy tissues were grown in a Matrigel-based culture. PDO drug response to anti-cancer drugs were evaluated; and when available, correlated with donors’ clinical response to the same agent(s). PDO response was defined as IC50 < 0.1 x published Cmax of the drug clinically; stable as IC50 between 0.1 to 10 x Cmax. Radiographic response was per RECIST criteria. Results: We enrolled 27 refractory metastatic GI cancer patients (9 colorectal (CRC), 9 pancreas, and 9 biliary tract). Median lines of therapy were 4, 2, and 2; the success rate of organoid establishment was 89%, 44%, and 55%, respectively. The median time from biopsy to availability of drug-testing data was 64 days (range: 24 to 93 days). The median time from biopsy to next CT re-staging in donors was 64 days. The established PDOs shared histological and genomic features with donor clinical tissue. PDO and clinical responses to the same agent(s) were correlated in 2 CRC donors including (1) BRAF/MEK inhibitor (M+Bi) showed 100% response, and (2) KRAS/FGF inhibitor (D+T) showed > 60% response. Conclusions: We showed the feasibility of completing PDO drug sensitivity testing in metastatic GI cancer patients within a short time that could impact clinical decision making, particularly in CRC. PDO drug response showed correlation with clinical response. Further refinement, PDO can be a powerful tool for personalization of cancer therapy in metastatic GI cancer patients.

3102 Poster Session (Board #94), Sat, 8:00 AM-11:00 AM
Molecular biology and treatment strategies for non-V600 BRAF-mutant NSCLC.
First Author: Marcello Valletti Negro, Department of Thoracic / Head and Neck Medical Oncology - The University of Texas MD Anderson Cancer Center, Houston, TX
Background: BRAF alterations (alts) account for ~4% of non-small cell lung cancers (NSCLC) with 50% being non-V600 alts. Because these alts are functionally heterogeneous and have a poorly characterized genomic landscape, determining appropriate treatment strategies is a challenge. Methods: A Cancer Genome Atlas (CGA) clinical database was used. Collected clinical and tumor tissues were grown in a Matrigel-based culture. PDO drug response to anti-cancer (AAs) was assessed. In vitro: (1) addition of drug on day (d) 0 to d8 of Aa. We studied the activity of adding ME344 or placebo to Bev (K67 deletion) in E-NHERCNEB Pt. A secondary objective we measured the activity of the combination in patients (Pts) showing VN activity to FET-PET. Methods: Untreated E-NHERCNEB Pts with T > 1cm, any N0 underwent a baseline FET-PET (d1) and received a single dose of Bev (150mg/kg) prior to randomization (1:1) to a Arm (A) FET-PET on d8 followed by ME344 10 mg/kg IV on d8, d15 and d21) or Arm B (B) FET-PET on d8 followed by placebo on d8, d15 and d21). Tumors were biopsied on d0 and 28. A 40 Pts sample size was powered to detect a 30% relative difference between arms in digitally acquired KI67 decrease from d0 to 28 (alpha 0.05, beta 0.2). Results: Arm A: 20 Pts; Arm B: 21 Pts. Baseline characteristics were in Arm A vs B: age 58.4(41.5-75.3) vs 53.6(39-82.8); T1(30.2)/T2(60.7)/T3(19.8) vs T1(52.2)/T2(48.2)/T3(19.8); PET SUV 13.3 - 16.4. PET SUV was > 10% from d0 to d8 in 6/20 (Arm A) and 6/21 (Arm B) Pts. Tumor Ki67 increased between Day 1 (D1) and Day 28 (D28) in patients without VN by FDG-PET (-23.9% - 186%). In patients with VN, tumors escape upregulating mitochondrial metabolism. Mitochondrial inhibition with ME344 induced synergy with various Aas. We also found that relative Ki67 change D1 to D28 in patients without VN by FDG-PET was (-18.8% - 6.7%), while relative Ki67 change D1 to D28 in patients with VN by FDG-PET was (13.3 - 10%); (2) KRAS/FGF inhibitor (D+T) showed > 60% response. Conclusions: BRAF/MEK inhibitor (M+Bi) showed 100% response, and (2) KRAS/FGF inhibitor (D+T) showed > 60% response. Further refinement, BRAF/MEK inhibitor (M+Bi) could be used in the clinic, particularly in CRC. PDO drug response showed correlation with clinical response. Further refinement, PDO can be a powerful tool for personalization of cancer therapy in metastatic GI cancer patients.

3103 Poster Session (Board #95), Sat, 8:00 AM-11:00 AM
The Circulating Cell-free Genome Atlas (CCGA) Study: Size selection of cell-free DNA (cfDNA) fragments.
First Author: Darya Filippova, GRAIL, Inc., Menlo Park, CA
Background: Detection of somatic copy number aberrations in individuals with cancer via cfDNA whole-genome sequencing (WGS) is challenging at low tumor fractions. Given that tumor-derived cfDNA fragments are shorter than those from healthy tissues, this exploratory analysis evaluated the potential effect of size selection on the ability to detect cancer. Methods: CCGA WGS libraries include clinical and in vitro size-selected to estimate the change in tumor fraction by tumor types (breast, lung, and colorectal) (CRC) and stage (I-III vs IV). In silico analyses used clinically evaluable training set samples with WGS assay results (n = 1422: 560 non-cancer (NC), 862 cancer (C) stages I-IV; classification (cancer/non-cancer) performance was estimated using fragments within the 90-150 bp range. In vitro analyses used a subset of samples (n = 93: 28 NC, 65 C stages I-IV), including C cases sampled within a range of tumor fractions; tumor fraction was also measured at each progressive removal of maximum-length fragments (intervals of 10 bp: 150 bp down to 50 bp). Results: In silico and in vitro analyses, respectively, resulted in median 2.00-0.58-fold (at 6.91:2.64X depth) and 2.00-0.52-fold (at 23.4:4.45X depth) increases, in overall tumor fraction (compared to non-size-selected 36X depth). This was consistent across tumor types (in silico: 1.78-0.73 breast, 2.00-0.58 CRC, 2.00-0.41 lung; in vitro: 2.00-0.82 breast, 2.51-0.52 CRC, 2.53-0.94 lung) and stages (in silico: 2.00-0.74 I-III, 1.78-0.52 IV; in vitro: 2.00-0.55 I-III, 1.68-0.29 IV). Tumor fraction increased with initial fragment length titrations, but not following size selection to shorter lengths (< 140 bp). Classifier trained on in silico size-selected data had increased sensitivity at 98% specificity compared to those trained on non-size-selected data (p = 1e-5). Conclusions: In silico and in vitro size selection consistently increased tumor fraction across cancer types and stages, and this increase was maximized by tuning the length range of size selection. Relative to full-depth data, classification performance improved significantly. These data suggest that size selection targeting cfDNA under 140 bp may enhance cfDNA-based cancer detection. Clinical trial information: NCT02889978.
Conclusions: YYB101 has a favorable safety profile in patients with refractory solid tumors. YYB101 demonstrated dose proportionality up to 100 mg/kg and exhibited a PK profile consistent with a once daily dosing regimen. The clinical trial in CRC patients as salvage treatment is ongoing. The predictive power of mesenchymal solid tumors and a dose-proportional PK. Efficacy data are encouraging and future clinical investigation of this novel oral small molecule agent is warranted.

Methods: N = 17; 7 (of 13) CRC, 3 (of 4) melanoma, 1 (of 2) sebaceous carcinoma, 1 (of 1) lung cancer. Of note, 1 sebaceous carcinoma patient who had failed 1+4 months of lines of chemotherapy, had been responding to YYB for 14 months. We analyzed 59,347 samples from 56,970 adult patients with cancer: 24.2%, 7.7% of identified missense mutations were found in 2.0% of tumor samples; 136 (11.7%) truncating mutations (9.6%), and 21 in-frame mutations (20%) were observed. Pre-planned biomarker analysis was performed in parallel. Results: 39 heavily pre-treated refractory cancer patients were enrolled and received YYB101. No DLT was observed. YYB101 demonstrated dose-proportional PK up to the dose of 30 mg/kg. No patients discontinued treatment because of adverse events. Based on PK analysis and toxicity data, the recommended dose was determined to be 20 mg/kg. Of 39 evaluation patients, there was 1 confirmed partial response for > 14 months (2.5%, N = 1; 1 of 2 sebacocarcinoma) and 17 stable disease as best response (43.5%, N = 17; 7 of 13) CRC, 3 of 4 melanoma, 1 of 2 sebacocarcinoma, 1 of 3 basal cell carcinoma, 2 of 1 ILC, 1 (of 1) lung cancer). Of note, 1 sebacocarcinoma patient who failed to receive YYB101 demonstrated PK response to YYB. Two long-term responders had mesenchymal signature in YB responders will be defined prospectively. Clinical trial information: 02499224.

Conclusions: YYB101 has a favorable safety profile in patients with refractory solid tumors and a dose-proportional PK. Efficacy data are encouraging and future clinical investigation with YYB101 is planned to be open in metastatic CRC patients as salvage treatment. The predictive power of mesenchymal signature in YB responders will be defined prospectively. Clinical trial information: 02499224.

Methods: The landscape of RET alterations from 56,970 adult patients with cancer: Clinical implications. First Author: Alexander Andreew-Drakhlin, MDA, Houston, TX

Background: Activating receptor-tyrosine kinase rearranged during transfection (RET) mutations and fusions have been recognized as potent drivers of oncogenesis. Recent identification of highly potent and selective RET inhibitors holds great promise in the management of RET-dependent tumors. Here we present a comprehensive analysis of RET alterations in cancer and novel clinical implications. We analyzed RET mutations and fusions in patients available from AACR Project GENIE (Genie Discov. 2017) database for the prevalence of RET fusions, mutations, and copy number alterations in diverse cancer types. Results: A total of 1414 RET alterations were detected, including 91 fusions (6.4%), 1166 missense mutations (82.5%), 136 truncating mutations (9.6%), and 21 in-frame mutations (1.5%). RET fusions were observed in 0.15% of tumor samples and were most commonly identified in non-small cell lung cancer, thyroid cancer, colorectal cancer, prostate cancer, and gastric cancer (62.6%, 18.6%, 5.5%, 4.4%, 3.3% of identified RET fusions, respectively). RET fusions were significantly co-ocurred with MAPK3/ERK1 (p = 0.045), SETD2 (p = 1.36E-07), and EIF4E (p = 0.045), while there was a negative association between RET fusions and EGRF (p = 0.009634), TP53 (p = 0.02267), and KRAS (p = 2.5E-05) alterations. Most common RET gene upstream partners were KIF5B, CCDC6, and NCOA4 (42.9%, 24.2%, 7.7% of identified RET fusions, respectively). RET missense mutations were found in 2.0% of tumor samples; 136 (11.7%) of identified missense mutations, including 8 RET gatekeeper YB04AML mutations, were characterized as likely oncogenic, 12 (1.0%) as likely benign, and 1018 (87.3%) as variants of unknown significance using OncoKB database. RET amplifications occurred in 1.5% of tested samples. Conclusions: While RET fusions represent extremely rare events in multiple cancers, RET missense mutations occur in 2% of malignancies. Most RET missense variants are described as variants of unknown significance, limiting the impact of precision oncology for the majority of patients with RET alterations. Further functional characterization of RET variants is warranted. MAPK pathway co-alterations in patients with RET fusion may present a strategy for future therapeutic combination.
3108 Poster Session (Board #100), Sat, 8:00 AM-11:00 AM
Prediction of olaparib sensitivity for variants of unknown significance in homologous repair genes. First Author: Sandy Chevrier, Research Platform in Biological Oncology, Center for Lecithin, St Louis, MO

Background: the recent use of PARP inhibitors in clinical practice gives very interesting outcome for ovary tumors with BRCA1 or BRCA2 mutation but also in other tumors with homologous repair deficiency. Nevertheless, no hotspot mutations are present, consequently, more than 85% of observed variants have unknown significance, blocking the use of PARP inhibitor. Methods: Exome analysis was performed on a cohort of 27 patients treated with olaparib. After bioinformatics analysis of somatic mutations in BRCA1/2, VUS as potentially benign or potentially deleterious. VUS were classified as potentially benign or deleterious. Among the 27 patients analyzed, 16 harbored already classified variants (3 benign and 13 pathogen variants) and 11 had VUS. The first Progression Free Survival (PFS) analysis showed that benign variants did not respond to olaparib with a median survival of 62 days, whereas pathogenic variants had a median of 109 days. Surprisingly, VUS had a median of 136 days, suggesting that some of them could be classified as potentially deleterious. On the subset of 11 patients with VUS, we applied PROVEAN prediction classifying 5 variants as benign and 6 variants as deleterious, with a median PFS of 54 days and 140 days (p=0.3235), respectively. With the second prediction, based on variant allelic frequency, we obtained different predictions for benign variants and 10 days for deleterious ones (p=0.29). By combining both predictions, we classified benign, VUS predicted benign with both predictions, and as deleterious, VUS predicted as deleterious with at least one prediction. Consequently, we perfectly discriminated benign from deleterious variants with a median PFS of 36 days for predicted benign and 177 days for predicted deleterious (p=0.0084). From all patients, PFS were significantly different (p=0.0003) between benign (n=6, 56 days) and deleterious variants (n=21, 140 months). Conclusions: Our work tends to show that VUS of homologous repair genes could be predicted as benign or deleterious, and could help to determine the number of patients eligible for a treatment by PARP inhibitors. The number of patients needs to be increased in order to validate our prediction algorithm.

3110 Poster Session (Board #102), Sat, 8:00 AM-11:00 AM
Clinical, pathological and genetic predictors of patient-derived xenograft (PDX) engraftment in lung adenocarcinoma (LUAD). First Author: Sebastiao N. Martins-Filho, University Health Network, University of Toronto, Toronto, ON, Canada

Background: PDX are useful preclinical models to study drug response and resistance. Different specimen types have been used to generate PDX models including histological (surgery and CT-guided biopsy) and cytological preparations (EBUS and pleural effusions). We hypothesize that engraftment is tumor specific and is affected by many factors including sample type and tumor pathological and molecular properties. To improve sample selection and cost-effectiveness of PDX experiments, we investigated clinical, histological and genetic correlates of engraftment in EGFR-mutated LUAD. Methods: We assessed PDX engraftment from 96 surgical resections, 13 CT-guided biopsies, 21 EBUS and 14 pleural effusions of EGFR-mutated LUAD. Sixty-five samples, including 6 engrafted (XG) and 54 non-engrafted (noXG) were evaluated by exome sequencing. Results: Engraftment was successful in 9/96 (9%) surgical resections, 6/13 (46%) CT-guided biopsies, and 0/35 cytological samples. Biopsies taken at time of treatment failure (compared to treatment naive biopsies) correlated with greater engraftment (p=0.007, AUC = 0.68). Multivariable regression analysis of clinical variables at the time of sampling identified advanced (vs early) stage (p = 0.003) and histological (vs cytological) preparations (p < 0.001) as the strongest predictors of engraftment (AUC = 0.79). Among tumor histologic features, solid (vs lepidic, acinar and papillary) pattern was associated with greater engraftment (p < 0.001). Presence of EGFR-T790M (p = 0.004) and TP53 (p = 0.009) mutations were associated with greater engraftment; all XG samples carried TP53 mutations. EGFR-Ex19del (p = 0.076) showed a trend towards engraftment whereas EGFR-L858R (p = 0.086) trended toward non-engraftment. Conclusions: Advanced stage, post-therapy tumors, T790M+ and TP53+ EGFR-mutated LUAD samples obtained for histological processing are more likely to engraft as PDXs. Despite low engraftment rates, these models are useful to study novel therapeutic strategy and elucidation of resistance mechanisms.

3109 Poster Session (Board #101), Sat, 8:00 AM-11:00 AM
Cell-specific upregulation of lung “cancer signature genes” in the small airway epithelium of asymptomatic smokers. First Author: Mahboubeh Rostam, Weill Cornell Medical College, New York, NY

Background: Most lung cancers are derived from the small airway (6th–23rd generations) epithelium (SAE). While a pathogenic mutation in a driver gene is critical to transform a SAE cell to a malignant cell, single cell analysis of lung cancers has demonstrated that individual cancer cells have transcriptional alterations in many “cancer signature genes” (Lambrecht D et al, Nature Med 2018; 24:1277) that are not driver genes, but likely support the malignant state. Based on the concept that dysregulation of many of these genes facilitate the malignant state, we hypothesized that, with the stress of smoking, some of these cancer-supporting transcriptional modifications occur long before the random hit with a driver mutation, providing a soil for the driver mutation. Methods: To assess this hypothesis, we applied drop-seq single cell transcriptome analysis to assess SAE recovered by fiberoptic bronchoscopy and brushing of n = 3 healthy non-smokers and n = 3 healthy smokers. Using unsupervised clustering, 11 cell types were identified including major SAE cell types (basal, intermediate, club, mucous and ciliated), rare epithelial cells (ionocyte, neuroendocrine and undefined NCLhi) and rare immune/inflammatory cell types (Tcell, mast, antigen presenting). Results: Comparison of smokers and non-smokers showed that smoking significantly altered the transcriptome (n = 426 genes upregulated, n = 572 genes downregulated) in different SAE cell types; 21% -56% of smoking-upregulated genes in the major SAE cell population are identified as “cancer signature genes”, where a non-smoker have regulated expression. Conclusions: For SAE cells, within individual cell types including HSPB1 in mucous cells, ADH7 in ciliated, LAMB3 in basal and intermediate cells, MIF intermediate and club cells, ALDH3A1 in all major SAE cell types. Conclusions: These data support the concept that cigarette smoking, long before the development of cancer, reprograms specific SAE cells to provide the biological soil to support driver genes to function.

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Genomic somatic alterations of human epidermal growth factor-2 (HER2) gene: A pan-cancer analysis. First Author: Xinhua Zhu, Nanjing Drum Tower Hospital; The Affiliated Hospital of Nanjing University Medical School, Nanjing, China

Background: Human epidermal growth receptor 2 (HER2) is a well-known oncopgenic drive gene with multiple targeted therapeutic options. In this study, we aim to assess the landscape of HER2 alterations in solid tumors and evaluate the feasibility of circulating tumor DNA (ctDNA) tested by next-generation sequencing (NGS) as a tool to detect HER2 alterations. Methods: Alterations of HER2 were assessed by NGS (Illumina NextSeq 5000) on DNA extracted from 6,970 plasma samples. The mean depth of sequence was 100X. The mean depth of circulating tumor DNA (ctDNA) test was 500X and 5000X, respectively. 11,013 patients were used for gene expression using ctDNA were included in this analysis. Results: Of 11,013 patients tested using tumor tissue, any HER2 and known or likely deleterious HER2 mutations were identified in 739 (6.7%) and 531 (4.8%) patients, respectively. Of 531 patients who carried known or likely deleterious HER2 mutations, 28% (143/531) had HER2 amplification and 259 (48.8%) had single nucleotide variations (SNVs). Across all tumor types, breast cancer was found to have the highest frequency of HER2 amplification (14.9%, 45/307), followed by gastric cancer (6.6%, 313/470), and breast cancer (5.8%, 33/617). Moreover, 11% (8/73) of duodenal cancer, 4.5% (7/154) of urothelial cancer, 2.0% (94/4586) lung cancer, 2.8% (14/4562) of colorectal cancer and 2.7% (9/323) of breast cancer carried known or likely deleterious HER2 SNVs. Of 6970 patients tested using ctDNA, any HER2 and known or likely deleterious HER2 mutations were identified in 592 (8.5%) and 277 (4.0%) patients, respectively. In the ctDNA cohort, 15.7% (36/230) of breast cancer and 3.1% (5/161) of urothelial cancer harbored known or likely deleterious HER2 SNVs in ctDNA cohort. Conclusions: HER2 alterations existed across tumor types and the landscape of genomic alterations in HER2 gene varied according to different type of tumors. In addition, ctDNA can be used as a potential tool to detect HER2 alterations.

Development and clinical validation of Lantern Pharmacia’s AI engine: Response algorithms positioning in a Rescue (RADR). First Author: Unmesh Kathad, Lantern Pharmacia, Dallas, TX

Background: The Response Algorithm for Drug positioning and Rescue (RADR) technology is Lantern Pharmacia’s proprietary Artificial Intelligence (AI)-based machine learning approach for biomarker identification and patient stratification. RADR is a combination of three automated modules working sequentially to generate drug- and tumor type-specific gene signatures predictive of response. Methods: RADR integrates genomics, drug sensitivity and systems biology inputs with supervised machine learning strategies and generates gene expression-based responder/ non-responder profiles for specific tumor indications with high accuracy, in addition to identification of new correlations of genetic biomarkers with drug activity. Pre-treatment patient gene expression profiles along with corresponding treatment outcomes were used as algorithm inputs. Model training was typically performed using an initial set of genes derived from cancer cell line data when available, and further applied to patient data for model tuning, cross-validation and final gene signature development. Model testing and performance computation were carried out on patient records held out as blinded datasets. Response prediction accuracy and sensitivity were among the model performance metrics calculated. Results: On average, RADR achieved a response prediction accuracy of 80% during clinical validation. We present retrospective analyses performed as part of RADR validation using more than 10 independent datasets of patients from selected cancer types treated with approved drugs including chemotherapy, targeted therapy and immunotherapy agents. For an instance, the application of the RADR program to a Paclitaxel trial in breast cancer patients could have potentially reduced the number of patients in the treatment arm from 92 unselected patients to 24 biomarker-selected patients to produce the same number of responders. Also, we cite published evidence correlating genes from RADR derived biomarkers with increased Paclitaxel sensitivity in breast cancer. Conclusions: The value of RADR platform architecture is derived from its validation through the analysis of about ~17 million oncology-specific clinical samples across 900 patients to 24 biomarker-selected patients to produce the same number of responders. Development and validation of robust biomarker panels for pre-selecting true responders for recruitment into clinical trials which may improve the success rate of oncology drug approvals.

A modeling and simulation study of less frequent dosing of nivolumab 480 mg. First Author: Cody J. Peer, National Cancer Institute, Bethesda, MD

Background: Nivolumab was originally approved at 3 mg/kg q2w. However, there is abundant evidence that doses as low as 0.1 mg/kg q2w are effective, and a randomized trial in RCC demonstrated equivalence across a dose range of 0.3–1 mg/kg q3w. Modeling and simulation have been used to amend the labeled dosage to 240 mg q2w or 480 mg q4w, with the latter yielding an estimated steady-state trough concentration (Ctrough) of ~50 uM. Given the high cost of nivolumab and the lack of a dose-response relationship, we hypothesized that less frequent dosing of 480 mg would maintain therapeutically efficacious Ctrough concentrations. The objective of this study was to use modeling and simulation to develop alternative dosing strategies. Methods: A simulation model was built from a published population pharmacokinetic model, incorporating time-dependent clearance. Various alternative dosing schedules were simulated, beginning with the third dose (doses 1 and 2 were 480 mg at wk 1 and 5). We conservatively chose 4.5 mg/mL as the target concentration (TC), slightly above the mean simulated Ctrough of 0.3 mg/kg q3w (4.1 uM/mL), although even lower levels are likely efficacious. The simulated dose schedules were q8w, q10w, q12w and q14w, beginning with the third dose. Simulations were performed on 50 simulated patients, with each simulation replicated 5 times. Results: The simulated Ctrough following doses 2-4 are presented in the table below. Dosing q12w should maintain TC in >70% of patients, and q14w dosing should achieve TC in >50% of patients. Conclusions: Modeling and simulation provide evidence that nivolumab can be effectively dosed q8-14w (after the first 2 doses), resulting in a potential 70% cost savings. As responding patients generally have a 35-45% decrease in clearance over the first 6 months of treatment, even less frequent dosing may be required for subsequent doses. Randomized trials of this interventional pharmacoeconomic strategy are indicated. Similar opportunities may exist for other checkpoint inhibitors.

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A phase I dose-escalation study of two cycles carboplatin-olaparib followed by olaparib monotherapy in patients with advanced cancer. First Author: Jill J.J. Geenen, Netherlands Cancer Institute, Amsterdam, Netherlands

Background: The PARP inhibitor olaparib has single-agent activity in BRCA mutated ovarian and breast cancer. Preclinical studies show synergistic effects when combining PARP-inhibitors and platinum drugs in BRCA1/2 mutated cancer cell models. A formulation change from olaparib capsules to tablets initiated a new dose finding study of olaparib tablets BID continuing with carboplatin. Methods: Patients were included in a 3+3 dose escalation schedule in the following dose levels: carboplatin 25mg BID and carboplatin AUC 3 d1/d22, olaparib 25mg BID and carboplatin AUC 4 d1/d22, olaparib 50mg BID and carboplatin AUC 4 d1/d22, olaparib 75mg and carboplatin AUC 4 d1/d22 and olaparib 100mg BID and carboplatin AUC 4 d1/d22. After two cycles patients continued olaparib 300mg BID in monotherapy. Primary objective was to assess the Maximum Tolerable Dose (MTD). Secondary objectives were to investigate the preliminary response rate, pharmacodynamics and systemic exposure. Results: In total 24 patients were included with breast cancer (n = 18), ovarian cancer (n = 3), melanoma (n = 1), colorectal cancer (n = 1) and enopharyngeal cancer (n = 1). Nineteen out of 24 patients had a germline BRCA mutation (79%). Most common AEs were nausea (46%), fatigue (33%) and platelet count decrease (33%). The majority of AEs (83%) were grade 1/2 in severity. Because two dose-limiting toxicities (consisting of ≥ 7 days dose delay of cycle 2 or missing ≥ 5 doses of olaparib due to hematologic toxicity) occurred in dose-level 4, dose-level 3 (olaparib 75mg and carboplatin AUC 4; n = 6 patients) was determined to be the MTD. Fourteen out of 24 patients (56%) had a partial response as best response, according to RECIST 1.1. Systemic exposure of the olaparib tablet formulation appeared comparable to the previous capsule formulation with an olaparib tablet AUC of 16.3 mg.h/µL at MTD. PARP activity in PBMCs was decreased by 98.7% ± 0.14% at day eight compared to day one for dose-level 3. Conclusions: Olaparib tablets 75mg BID and carboplatin AUC 4 for two cycles preceding olaparib monotherapy is feasible and tolerable treatment schedule with encouraging clinical antitumor activity. Clinical trial information: NCT02864030.

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**3120 Poster Session (Board #112), Sat, 8:00 AM-11:00 AM**

Long-term follow-up of pharmacokinetics (PK) and immunogenicity of the anti–PD-1 antibodies nivolumab (Nivo) and pembrolizumab (Pembro) in real-world practice. First Author: Masahide Fukudo, Department of Hospital Pharmacy and Pharmacology, Asahikawa Medical University, Asahikawa, Japan

**Background:** The PD-1 blockers Nivo and Pembro are widely used to treat patients (pts) with various types of cancer, but their PK and immunogenicity have not been adequately characterized in clinical practice. Here we report the first long-term follow-up of PK and anti-drug antibodies (ADAs) of Nivo and Pembro, correlated with efficacy and safety. **Methods:** We included 147 pts receiving Nivo (n = 98) or Pembro (n = 49) between May 2016 and Jan 2019. Plasma samples were longitudinally collected before each infusion and after discontinuation for as long as samples were obtainable. Drug concentrations were measured by ELISA (LLOQ: 0.0125 μg/mL), and ADAs were evaluated by bridging ELISA. **Results:** Median (range) follow-up was 6.0 (0.1-38.7) mo, and 1718 samples were analyzed. ADAs were confirmed at baseline or at last sample for both Nivo (2 [2.2%] and 4 [4.5%] pts, respectively) and Pembro (2 [4.2%] and 3 [6.7%] pts). Of the 4 baseline ADA-positive pts, 3 experienced drug-induced fever after initial infusion. Pts developing ADAs at last sample had earlier progression than ADA-negative pts (median PFS: 46 vs 119 days, log-rank P = 0.0827). Persistent drug exposure until ~1 y beyond discontinuation was observed for both drugs. In 1 Nivo-treated pt with delayed adrenal insufficiency 8.6 mo after discontinuation, Nivo was still detectable.

**Conclusion:** Long-term follow-up of PK and ADAs for Nivo and Pembro was observed for both drugs. In 1 Nivo-treated pt with delayed adrenal insufficiency 8.6 mo after discontinuation, Nivo was still detectable.

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A phase I study of a novel MM2-P53 antagonist APG-115 in Chinese patients with advanced soft tissue sarcomas. First Author: Xing Zhang, Medical Oncology Unit, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: APG-115 is a novel and orally active small-molecule MM2 inhibitor. APG-115 alone or in combination with chemotherapy targeted or IO agents have shown potent antitumor activities in multiple human xenograft tumor models and human cancer patient derived xenograft (PDx) models. Methods: The patients with advanced solid tumors were enrolled in this study in China (CTR2017079757). The study objectives included the safety, pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activity of APG-115. The patients received APG-115 (ranging 100–200 mg) orally QOD for first 21 days of a 28-day-cycle, until disease progression. Antitumor response assessment was performed every 8 weeks per RECIST v1.1. Archived tumor tissues were collected for analyses of MDM2 and TP53 before treatment. Results: As cut-off on Jan 4 2019, total 13 patients (9 soft tissue sarcomas (STSs), 2 adenoid cystic carcinomas (ACCs) and 2 osteosarcomas) were treated in 3 cohorts of APG-115 (100mg, 150mg, 200mg). The median number of prior systemic anticancer therapies was 2 (range 0-4). Two DLTs were observed in one patient at 200mg. Thrombocytopenia, vomiting, hypercholesterolaemia, and leukopenia. SAEs included lipase increase and Bell’s palsy, MTD was determined at 150mg. Nine of 27 pts (33.3%) experienced at least 1 TEAE. The most common TEAEs (≥50% of pts) included: anemia, thrombocytopenia, vomiting, hypercholesterolaemia, and leukopenia. SAES occurred in 7 patients (54%), four of which were treatment related. The most common Grade 3 or 4 TRAEs were anemia (38.5%), thrombocytopenia (38.5%), leukopenia (38.5%), and neutrophilia (38.5%). A dose limiting toxicity was observed in a liposarcoma patient with MDM2-amplification and TP53-wild type at the 150mg cohort, 5 patients (3 STSs, 2 ACCs) had SD as the best response. 20% of pts had SD as the best response. Conclusion: Preliminary data suggested that APG-115 had promising anti-tumor activity in treatment of patients with MDM2-amplification and TP53 WT liposarcoma. Safety profile and PD effect were consistent with other MM2 inhibitors. Dosing regimen optimization are ongoing. Clinical trial information: CTR2017079757.
Cytoplasmic cyclin E independently predicts recurrence in older patients with primary breast cancer. First Author: Simon Johnston, University of Nottingham, Nottingham, United Kingdom

Background: Primary breast cancer in the older (> 70 years) population has distinct biological characteristics associated with favourable outcome, such as higher rate of estrogen receptor (ER) positivity. Due to comorbidities, older patients with primary breast cancer are more likely to die of non-breast cancer-related causes compared to their younger counterparts. Biomarkers that may influence treatment strategy therefore require interpretation in the specific biological and clinical context of older women. Cyclin E, by regulating cell cycle transition from G1 to S phase, and its deregulation is implicated in breast cancer pathogenesis. Tumour-specific isoforms of cyclin E localise to the cytoplasm. Expression of cytoplasmic cyclin E (c-cyclin E) is linked with poor clinical outcome. We now present multivariate analysis of breast cancer-specific survival (BCSS) by c-cyclin E and clinical markers of disease biology from a cohort of older women. The primary outcome, BCSS, excludes deaths from competing causes and is used as a surrogate for tumour biology.

Methods: Between 1973 and 2010, 813 older women underwent initial surgery for early breast cancer and were followed up in a dedicated clinic in Nottingham. Excised tumours from 517 of these patients were successfully incorporated into a tissue microarray (TMA). Expression of c-cyclin E was assessed by IHC using an assay developed at MDACC, along with a panel of 24 biomarkers. Of these, ER, progesterone receptor (PR), human epidermal growth factor receptor 1 (HER2) and Ki67 are in current clinical use and are analysed alongside c-cyclin E. Expression was assessed as: 0: < 0.01; 1: 0.01–0.05; 2: > 0.05. In multivariate analysis, primary tumour tissue.

3128 Poster Session (Board #120), Sat, 8:00 AM-11:00 AM

Clinicopathologic characteristics of NRG1 fusion-positive cancers: A single-institution study. First Author: Alison M. Schram, Memorial Sloan Kettering Cancer Center, New York, NY

Background: NRG1 rearrangements are oncogenic drivers across several tumor types. Chimeric proteins encoded by NRG1 fusions activate HER3, resulting in heterodimerization with HER2 and activation of downstream signaling. Preclinical and preliminary clinical data suggest that targeting HER3 may be an effective treatment strategy for patients with NRG1 fusion-positive tumors. We aimed to describe the clinical and genomic characteristics of patients identified at our institution with NRG1 fusions.

Methods: We analyzed results from prospective targeted exome and RNA sequencing performed at Memorial Sloan Kettering between 2014-2018 involving > 30,000 samples. NRG1 fusion-positive tumors were identified and these cases were manually reviewed. Results: NRG1 fusions were detected in 24 patients. Cancer types included lung (N = 9), pancreas (N = 7), breast (N = 5), prostate (N = 1), gallbladder (N = 1), diffuse B-cell lymphoma (N = 1), and cancer of unknown primary (N = 1). 6/9 lung cancers had mucinous differentiation. The majority of patients were Caucasian (N = 17), half were female (N = 12) and ages ranged from 24-82 years old. Targeted exome sequencing identified the fusion in 20/23 cases tested, including 2 not confirmed by RNA. The remaining 14 were detected using RNA. Fusion partners included CD74 (N = 6), SLC3A2 (N = 2), SDCC (N = 2), ATBP1 (N = 2), FOXA1 (N = 1), SLC4A4 (N = 1), ROCK1 (N = 1), TNKS2 (N = 1), CCND1 (N = 1), PAK1 (N = 1), STAU3 (N = 1), RAD21 (N = 1), CD41 (N = 1), NCOA1 (N = 1), RBM3 (N = 1), and WHSC1 (N = 1). Pancreas cancers were considered KRAS wildtype and lung cancers had no co-occurring alterations in ALK, ROS1, EGF, RET, MET, RAS, or RAF. All tumors were microsatellite stable. A durable response was achieved with anti-HER3 antibody therapy (GSK2849330) in a patient with a CD74-NRG1-rearranged invasive mucinous adenocarcinoma (previously reported). In patients treated with the dual HER2 inhibitor (afatinib) did not respond to treatment, suggesting direct targeting of HER3 may be superior to HER2 inhibition in patients with NRG1 fusion-positive tumors. Conclusions: NRG1 fusions occur in several tumor types and may be amenable to targeting with HER3-directed therapy.

3130 Poster Session (Board #122), Sat, 8:00 AM-11:00 AM

Measuring phospho-MET by multiplex immunofluorescence to aid in selection of patients with MET-positive tumors. First Author: Tony Navas, Clinical Pharmacodynamics Biomarker Program, Applied/Developmental Directorate, Frederick National Laboratory for Cancer Research, Frederick, MD

Background: Currently, patient selection criteria for clinical testing of MET inhibitors are limited. Robust studies selecting patients based on MET protein expression, MET gene amplification, or mutations have not met their efficacy goals. Development of microscopy-based assays to quantify levels of phospho-MET is needed. Tumor samples from primary colorectal (CRC) cancers were analyzed using NGS (MiSeq on 47 genes, NextSeq on 592 genes), immunohistochemistry. Tumor mutational burden (TMB) was calculated based on somatic nonsynonymous missense mutations, and microsatellite instability (MSI) was evaluated by NGS of known MSI loci. Results: In total, 11871 tumors samples were examined, comprising primaries (N = 5862), distant (N = 5605) and LNs mets (N = 404). The most frequently mutated genes in LNs were TP53 (72%), APC (61%), KRAS (39%), ARID1A (20%), and PIK3CA (12%). LNs showed a higher mean TMB (13 mut/MB) vs distant tumors (9, P < .0001). TMB-high (17 mut/MB) was more frequent in primaries and LNs vs distant mets (9.5% and 8.8% vs 4.2%, P < .001 and P = .001 respectively), as well as MSI-H (8.8% and 6.9% vs 3.7%, P < .001 and P = .017 respectively). TMB-high is significantly higher in LNs vs distant mets and primaries (P < .0001), independent of MSI-H status. Analyzing distant mets by location, LNs showed higher TMB compared to lung, liver and peritoneum mets (P < .0001). Overall, LNs showed significantly different rates of mutations in APC, KRAS, PIK3CA, KDM6A, and BRIP1 (P < .01 for all comparisons) vs primaries; while presenting a distinct molecular profile compared to distant mets (TP53 72% vs 67%; KRAS 39% vs 50%; RNF43 47 vs 4%; ATM 5 vs 3%; KDM6A 4% vs 1%; BRCA2 4% vs 2%; MSH3 3% vs 2%; PTCH1 4% vs 1%; BRCA1 28% vs 1%; GNAS 2% vs 5%; P < .05 for all comparisons). Our cohort of 30 paired samples confirmed the molecular heterogeneity between primaries, LNs, and distant mets. Conclusions: This is the largest study to investigate the molecular differences between LNs mets, distant mets and primary tumors in CRC patients. Our data support the hypothesis that lymphatic and distant mets harbor different mutation profiles with suggested they may arise from distinct clonal events.
3132 Poster Session (Board #124), Sat, 8:00 AM-11:00 AM
Actionable alterations in breast tumors with pathogenic mutations in the homologous recombination DNA damage repair pathway. First Author: Anjel Lutterman Heeke, Levine Cancer Institute, Atrium Health, Charlotte, NC
Background: Homologous recombination (HR) deficient breast tumors may have genomic alterations that suggest responsiveness to targeted therapies other than PARP inhibitors. Methods: Comprehensive molecular profiles of 4,647 breast tumors performed at Caris Life Sciences using 592-gene NGS (average read depth 500X) were reviewed to identify somatic pathogenic mutations in HR genes ARID1A, ATM, ATRX, BAP1, BLM, BRCA1/2, BRIP1, CHEK1/2, FANCD2/FANCG, FKM2D, MRE11, NBN, RAD50, RAD51, PALB2, and BRCA1/2 and PALB2 markers associated with treatment response. Results: Overall, 19.7% of breast tumors have HR mutations (HR-MT, 831/4647). HR-MT is seen most in HER2– disease (hormone receptor+ (hr)+HER2– (18.3%, n=2183), TNBC (18.2%, n=1568), hr+/HER2+ (12.9%, n=2171). Mean TMB is higher for HR-MT tumors across subtypes (9.2 mut/Mb vs 7.6 Mb, p<0.0001) and independent of MS status. HR-MT hr+/HER2+ tumors are more likely to have PD-L1 overexpression (25% vs 13.1% hr+/HER2+ W, p=0.10), whereas MSI is more prevalent in HR-MT HER2– (hr+/HER2– 2.3%, TNBC 1.4%, HER2– 0%). Mutations in chromatin remodeling genes (*) are more common in HR-MT. Additional co-alterations are outlined in the Table. Conclusions: In breast cancer, HR-MT is associated with HER2– disease & markers of response to immunotherapy. Clinical trials combining HRD targeted agents & immunotherapy are underway & could be enriched through comprehensive molecular profiling. Mutations were identified in both HR-MT & HR WT tumors that suggest other targets for treatment.

<table>
<thead>
<tr>
<th>HR-MT (%)</th>
<th>HR WT (%)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>ARID1A</td>
<td>17 (21/123)</td>
<td>30 (115/392)</td>
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<tr>
<td>ATR</td>
<td>13 (104/798)</td>
<td>11 (40/3677)</td>
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<tr>
<td>PALB2</td>
<td>8.2 (67/820)</td>
<td>7.9 (298/3790)</td>
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<td>4.9 (377/554)</td>
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<td>BRCA1/2</td>
<td>2.1 (17/817)</td>
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<td>2.6 (104/3812)</td>
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<td>CHEK1/2</td>
<td>1.3 (10/796)</td>
<td>0.5 (20/3677)</td>
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Pathogenic mutation frequency < 1%: AR, BRF4, CDK1, CDK4, CDK6, EGFR, EGRB3, IDH1, IDH2, JAK2, KIT, MET, MTO8, DET, SMARCB1*, SMARCE1*, SMARCA4*, SS18L1*.

No mutations: ATR, AURKB, BCL7A*, BCL11A*, Cdk4, EGFR, NTRK1/2/3, PBRM1*, PTEN

By IHC (HR-MT vs WT): AR 52.3 (415/794) vs 54.9 (2014/3669) [p=0.18], EGFR 28.6 (4/14) vs 55.2 (230/422) [p=0.008], MET 7.6 (10/133) vs 16.7 (63/380) [p=0.001].

Conclusions: In breast cancer, HR-MT is associated with HER2– disease & markers of response to immunotherapy. Clinical trials combining HRD targeted agents & immunotherapy are underway & could be enriched through comprehensive molecular profiling. Mutations were identified in both HR-MT & HR WT tumors that suggest other targets for treatment.

3133 Poster Session (Board #125), Sat, 8:00 AM-11:00 AM
HER family protein expression and activation predicts response to combination T-DM1/pertuzumab in HER2+ patients in the I-SPY 2 TRIAL. First Author: Julianne Womanot, Division of Cancer Treatment & Diagnosis, National Cancer Institute, MD
Background: T-DM1 (T), a conjugate of the anti-HER2 therapeutic antibody trastuzumab and the microtubule assembly inhibitor emtansine, was administered in combination with pertuzumab (P), an anti-HER2 therapeutic antibody, to HER2+ breast cancer patients in the I-SPY 2 TRIAL, and graduated in all HER2+ subtypes. Pre-specified biomarker analysis was performed to identify candidate biomarkers associated with pCR using logistic regression (likelihood ratio test; p < 0.05). We hypothesized that quantitative measurement and activation of HER2 and activation of its major dimerization partner, EGFR, would predict response to T+P. Methods: In the T+P treatment arm, 49 had RPPA and pcr data. 40 RPPA endpoints including 14 total/phospho-proteins in the HER family were assessed for association with pCR using logistic regression (likelihood ratio test; p < 0.05). Analysis was also performed adjusting for HR status and within HR subsets. Markers were analyzed individually; multiple comparison correction (Benjamini-Hochberg) was applied to all p-values. Our statistics are descriptive and do not adjust for multiplicities of other biomarkers or features. Results: The results showed that HER2, phospho-HER2, phospho-EGFR, phospho-MAPK, and to support clinical development of FGFR inhibitors. Funded by NCI Contract HHSN261200800001E.

3135 Poster Session (Board #127), Sat, 8:00 AM-11:00 AM
Machine learning methods with salivary metabolomics for breast cancer detection. First Author: Toshihisa Mutata, Department of breast surgery, National Cancer Center Hospital, Tokyo, Japan
Background: Saliva is non-invasively accessible and informative biological fluid which has high potential for the early diagnosis of various diseases. The aim of this study is to develop machine learning methods and to explore new salivary biomarkers to discriminate breast cancer patients from healthy controls. Methods: We conducted a comprehensive metabolite analysis of saliva samples obtained from 101 patients with invasive carcinoma (IC), 23 patients with ductal carcinoma in situ (DCIS) and 42 healthy controls, using capillary electrophoresis and liquid chromatography with mass spectrometry to quantify hundreds of hydrophilic metabolites. Saliva samples were collected under 9h fasting and were split into training and validation data. Conventional statistical analyses and artificial intelligence-based methods were used to access the discrimination abilities of the quantified metabolite. Multiple logistic regression (MLR) model and an alternative decision tree (ADTree)-based machine learning methods were used. The generalization abilities of these mathematical models were validated in various computational tests, such as cross-validation and resampling methods. Results: Among quantified 260 metabolites, amino acids and polyamines showed significantly elevated in saliva from breast cancer patients, e.g. spermine showed the highest area under the receiver operating characteristic curves (AUC) to discriminate IC from C; 0.766 (95% confidence interval [CI]; 0.671 – 0.845, P < 0.0001). These metabolites showed no significant difference between C and DCIS, i.e., these metabolites were elevated only in the samples of IC. The MLR yielded higher AUC to discriminate IC from C; 0.790 (95% CI; 0.699 – 0.859, P < 0.0001). The ADTree with ensemble approach showed the best AUC; 0.912 (95% CI; 0.838 – 0.961, P < 0.0001). In the comparison of these metabolites in the analysis of each subtype, seven metabolites were significantly different between Luminal A-like and Luminal B-like while, but few metabolites were significantly different among the other subtypes. Conclusions: These data indicated the combination of salivary metabolomic profiles including polyamines showed potential ability to screening breast cancer in a non-invasive way.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
The Cancer Molecular Screening and Therapeutics Program (MoST): Actionable mutation frequencies in a population with rare and less common cancers. First Author: Mimi Giam (Garvan Institute of Medical Research, University of New South Wales (Faculty of Medicine), Darlinghurst, NSW, Australia

Background: Personalizing therapy will arguably have no greater impact than on patients (pts) with rare (< 6 per 100,000 population) or less common cancers (6-12/100,000). MoST combines a molecular screening platform and biomarker-driven treatments for pts with advanced cancer, with a particular focus on rare and less common cancers (RLCs). Molecular screening was performed using in-house and commercial panels on archival tumor tissue. A Molecular Tumor Board by consensus reported on pathogenic variants with potential therapeutic actionability. Tiers of actionability were defined as: Tier 1—eligible for a MoST substudy; Tier 2—clinical evidence of efficacy in any cancer type; Tier 3—preclinical evidence. The clinical and molecular character of the first 1,000 pts are presented here. Results: Pts were recruited from Sept 2016 to Dec 2018. A report was issued in 94% of cases in a median of 7.7 weeks from consent. In 6%, there was insufficient tissue. The median age at cancer diagnosis was 35 years (range 4-85 years), and 49% were male. Pts had a median of 2 lines of prior systemics (77%). Method(s): Actionable muts in RLC, providing a rational basis for assessing the potential of actionable mutations (muts).

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Conclusions: Among 3136 pts, 182s Developmental Therapeutics and Tumor Biology (Nonimmuno)
3140 Poster Session (Board #132), Sat, 8:00 AM-11:00 AM

Prediction of biomarker status, diagnosis and outcome from histology slides using deep learning-based hypothesis free feature extraction. First Author: EIda Kleinman, Roche Pharma Research and Early Development, Roche Innovation Center Munich, Penzberg, Germany

Background: Recently, histological pattern signatures obtained from diagnostic H&E images have been found to predict mutation, biomarker status or outcome. We report here on a novel deep learning based framework designed to identify and extract predictive histological signatures. We have applied this framework in 3 experiments, predicting specifically the microsatellite status (MSS) of colorectal cancer (CRC), breast cancer (BC) micrometastasis in lymph nodes (LN) and Pathologic Complete Response (pCR) in BC diagnostic biopsies.

Methods: Our deep learning based algorithm was trained on histology images at 20X magnification. Algorithms were trained for binary classification for each of the three cohorts. We used 75% of the images for training and test our algorithm on the remaining 25% of the images. Cohort details are as follows: MSS for CRC; 94 patients’ H&E stained tissue images from the Roche internal CRC80 dataset (MSS n=24; MSI n = 70) were used. BC LN: 270 patients’ H&E stained tissue images from the CAMELYON16 dataset (LNN = 110; LNC = 160) were used. pCR for BC: 225 patients’ H&E stained tissue images from the Tryptaena Study (BC2229c) were used, Trastuzumab/Pertuzumab chemotherapy treatment.

Conclusions: We present a novel approach to generate predictive signatures based on conventional diagnostic H&E images and a novel machine learning framework. The CRC80 and CAMELYON16 cohorts served as a confidence building experiments with predictive features well matched by Area Under the Curve (AUC). Study BO22280, neoadjuvant, Trastuzumab/Pertuzumab chemotherapy compared toStandard Algorithm performance on each of the cohorts by Area Under the Curve (AUC).

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.

3142 Poster Session (Board #134), Sat, 8:00 AM-11:00 AM

Effects of immune architecture on response to adjuvant capecitabine in triple-negative breast cancer (FinXX trial). First Author: Saranya Chumsri, Mayo Clinic, Jacksonville, FL

Background: Recent studies have demonstrated a benefit of adjuvant capecitabine, particularly in triple negative breast cancer (TNBC) patients with residual disease after neoadjuvant chemotherapy. However, biomarkers to predict which patients are more likely to benefit from capecitabine are needed. We present a new approach to generate predictive signatures based on conventional diagnostic H&E images and a novel machine learning framework.

Results: Prediction of MSS in the CRC80 status yielded AUC 0.9. Prediction of LN invasion on CAMELYON16 dataset yielded AUC 0.85. Prediction of pCR on the Tryptaena cohort yielded an AUC 0.8. Conclusions: Similar to patients with ex14sk mt, substitutions and small indels at Y1021 exhibit Clinicopathological features such as previous smoking history and older age, mutual exclusivity with oncogene drivers and MET protein overexpression. The rarity of these analogous ex14sk mt suggests deletions of exon 14 provide cellular advantages beyond Cbl-mediated ubiquitination of MET. Although rare, the impact of these mutations on efficacy of Met-directed therapy deserves further exploration.

3143 Poster Session (Board #135), Sat, 8:00 AM-11:00 AM

Vascular endothelial growth factor A (VEGF-A) amplification and long-term response to ramucirumab in metastatic gastric cancer (mGC): The VERA study. First Author: Alessandra Raimondi, Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: The anti-VEGFR-2 monoclonal antibody ram, alone or with paclitaxel, is a cornerstone of second-line treatment of mGC. Even if about half patients do not benefit from ram, no predictive biomarkers have been identified so far. In TCGA, VEGF-A amplification was found in 7% of cases, almost exclusively in chromosomal instability subtype. We hypothesize that VEGF-A amplification in tumor cells could lead to autocrine/paracrine stimulation of tumor growth beside angiogenesis, potentially identifying a patients’ subgroup with exceptional responses to ram.

Methods: VERA was a multicentric, prespective study based on a translational hypothesis. mGC patients were included according to the following criteria: 1) complete (CR) or partial response (PR) to single-agent ram; 2) >6 months PFS to single-agent ram; 3) >10 months PFS to paclitaxel+ram. According to a Fleming single-stage design, hypothesizing a prevalence of VEGF-A amplification of 1% and 15% among all-comers and exceptional responders, 20 exceptional responders were required to reject the null hypothesis of low prevalence of VEGF-A amplification, with alpha- and beta- errors of 0.05 and 0.10, respectively. VEGF-A amplification (defined as ≥10 tumor cells with ≥10 VEGF-A copies, variably sized signal clusters or a ratio of VEGF-A gene to centromere of ≥2) was centrally assessed through fluorescent in situ hybridization on pretreatment FFPE tumor tissue.

Results: Of 17 Italian Centers, we included 20 patients satisfying the 1st (n=11), 2nd (n=2), or 3rd (n=7) criterion. Clinical-pathological features were: M/F, 11/9; median age 63 years; gastric/GEJ, 17/3; intestinal/diffuse, 14/6, HER2+/HER2-, 4/16. Median PFS and overall survival to ram-based treatment were 15.6 and 25.7 months, with best responses: CR/P/PR, 0/10/10. VERA met its primary endpoint, revealing 3/20 (15%) patients with VEGF-A amplification (1 case presenting big clusters, 1 small clusters and 1 with >10 tumor cells with ≥10 VEGF-A copies). Conclusions: Validation analyses of first- and second-line randomized trials could confirm VEGF-A amplification as a biomarker of long-term response to ram-based treatment in mGC patients, advancing treatment personalization.
Reassignment of HER2 status for subgroups of breast cancer according to the 2018 updated American Society of Clinical Oncology and College of American Pathologists guidelines: The impact of combined immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) reflex testing in a large national reference laboratory. First Author: Katherine Geiersbach, Mayo Clinic, Rochester, MN

Background: Updated ASCO/CAP Guidelines for HER2 testing in breast cancer have been most impactful on the resolution of certain challenging groups of FISH results. We review the change in assignment of HER2 status in this large series of breast cancers referred for FISH testing following the introduction of the 2018 updated guidelines. Methods: Patient samples submitted to the Mayo Clinic Cyto genetics Laboratory (N = 2208) were analyzed by FISH. Samples with Group 2, Group 3, or Group 4 FISH results were reflexed to immunohistochemistry (IHC) in our central laboratory; FISH slides for those cases with equivocal 2+ IHC results were re-scored in the records of invasive cancer showing more intense membranous staining. A subset of 202 samples with Group 4 FISH results were also reflexed to the previously employed reflex FISH assay (HER2/D17S122), and these were also re-analyzed according to the new reflex IHC/FISH process. Results: 382 of 2208 breast cancer samples tested (17.3%) had FISH results categorized as Group 2 (N = 17, 0.8%), Group 3 (N = 34, 1.5%), or Group 4 (N = 331, 15%) and required reflex IHC testing, and of those, 75% were 2+ equivocal and required targeted re-analysis of the FISH slide according to the 2018 updated guidelines. Re-analysis of the FISH slide resulted in switching between Groups 1-5 in 19.4% of cases, but HER2 status was changed by FISH re-scoring in only 7.7% of cases re-scored (1.0% of all samples), generally due to only minor shifts in HER2 copy number and HER2/control ratios between the initial and IHC-guided reflex FISH scores. In the subset of 202 cases tested by both reflex methods, the previously employed HER2/D17S122 reflex probe set was positive in 123 cases (60.9%), whereas reflex IHC/FISH was positive in only 10 cases (7.9%). Including positive reflex IHC (0.4%) and positive reflex FISH results (2.1%), the overall assignment of positive HER2 status on our series of 2208 cases was 11.5%. Conclusions: Overall rates of HER2 positive FISH results have declined under the most recent ASCO/CAP guideline update as a consequence of new recommendations for reflex testing for Groups 2-4. This change is largely due to reassessment of Group 2 and Group 4 results as negative in the absence of positive IHC.

TPS3146 Poster Session (Board #13a), Sat, 8:00-11:00 AM
First-time in-human study of VMD-928, an allosteric and irreversible TrkA selective inhibitor in patients with solid tumors or lymphoma. First Author: Vincent Chung, City of Hope, Duarte, CA

Background: Tropomysin receptor kinase A (TrkA) is a protein encoded by the NTRK1 gene. NTRK fusions involving the kinase domain are oncogenic for multiple tumor types and larotrectinib was recently approved for advanced solid tumors harboring NTRK gene fusions. Larotrectinib, an ATP-competitive, reversible pan-TrkA/B/C inhibitor, has shown impressive response rates in patients harboring these fusions; however, resistance can develop due to acquired ATP-site mutations. This has been previously identified in other oncogenic driver kinases such as ALK and EGFR treated with ATP-competitive kinase inhibitors. A newly approved allosteric ALK/EGFR inhibitor brigatinib was able to clinically overcome acquired resistance of many ATP-competitive ALK/EGFR inhibitors (1). Also, irreversible EGFR inhibitors such as afatinib (ATP- competitive) were active against tumors resistant to first-generation inhibitors (2), although their efficacy can be compromised by acquired ATP-site mutations (3). VMD-928 is the first oral small-molecule TrkA (NTRK1) selective inhibitor with dual allosteric and irreversible mechanisms of action. It inhibits TrkA non-competitively at an allosteric (non-ATP) site and has no resistance in vitro to acquired ATP-site mutations such as G667C. VMD-928 in vitro has little or no activity against 348 other kinases including TrkB (NTRK2) and TrkC (NTRK3). We are conducting the first time in human phase 1 trial of oral VMD-928, a novel allosteric and irreversible TrkA selective inhibitor. Methods: This is an open label, Phase 1 study investigating the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of oral VMD-928 in adults with advanced solid tumors or lymphoma (NCT03556228). In part 1 of the study, an accelerated titration scheme will be utilized to determine the recommended phase 2 dose and evaluate PK/ PD of VMD-928. In part 2, expansion cohorts including patients with thymic, pancreatic, triple-negative breast carcinoma, or solid tumors with TrkA alterations will be accrued to further evaluate safety and efficacy. Part 3 of the study will characterize the biologically active dose. The study is open and accruing patients at City of Hope. Clinical trial information: NCT03556228.

TPS3147 Poster Session (Board #13b), Sat, 8:00-11:00 AM
A first-in-human study of, NUC-7738, a 3′dA phosphorodiamidate, in patients with advanced solid tumors or lymphoma. First Author: Hagen P Schneider, University of Oxford, Oxford, United Kingdom

Background: Nucleoside analogs form the backbone therapy for both hematological and solid malignancies. However, their clinical effectiveness is severely limited by key cellular resistance mechanisms linked to increased break down, impaired activation and transport. NUC-7738 is a phosphor -amidate transformation of cordycepin (3′-deoxyadenosine; 3′-dA), a de- rivative of adenosine that was first isolated from Cordyceps sinensis. The cytotoxic effect of 3′-dA is largely attributed to intracellular generation of the triphosphate metabolite, 3′dATP, terminating DNA and RNA synthesis. Although 3′-dA has shown potent anti-tumor activity in non-clinical studies, it has not been successful in clinical studies mainly because of rapid enzymatic degradation by adenosine deaminase. NUC-7738 is not a substrate for adenosine deaminase and has been designed to bypass the key resistance pathways which have limited the clinical effectiveness of cordycepin. Methods: NuTide:701 is a two-part, first-in-human Phase I study in patients with advanced solid tumors and lymphoma who have exhausted all standard treatment options. The primary objective is to determine the RP2D and schedule of NUC-7738. Secondary objectives include safety, PK/PD and anti-tumor activity. Part 1, in patients with advanced solid tumors, will establish the RP2D and dose administration schedule of NUC-7738 for Part 2. Part 2 will further evaluate the selected RP2D and designated dosing schedule in an expansion cohort of patients with advanced solid tumors or lymphoma. The study initiated in Q1 2019. Clinical trial information: NCT03829254.
Background: The nucleoside analog 5-aza-1'-thio-2'-deoxycytidine (Aza-TdC) inhibits DNA methyltransferase 1 (DNMT1), a methyltransferase involved in methylation-mediated silencing of tumor suppressor genes. Attenuation of DNA methylation via DNMT1 inhibitors results in reactivation of silenced tumor suppressor genes and can lead to tumor growth arrest and apoptosis. The DNMT1 inhibitors decitabine and 5-aza-cytidine are currently FDA-approved for use in myelodysplastic syndromes and are also used in patients with acute myeloid leukemia. Relative to these compounds, Aza-TdC exhibits enhanced stability and incorporation into DNA and has shown improved preclinical anticancer activity in both leukemia and solid tumor xenograft models. This study seeks to evaluate the safety and maximum tolerated dose (MTD) of oral Aza-TdC in patients with advanced solid tumors.

Methods: Patients are treated with Aza-TdC on days 1-5 and 8-12 of each 21-day cycle. The study follows Simon's 3+3 dose escalation design, with 100% dose increments and 1 patient per dose level. Accelerated titration will continue until 1 patient experiences a dose-limiting toxicity (DLT) or 2 patients experience drug-related grade 2 toxicity at any dose level, after which a 3+3 dose escalation design will be used. Blood samples are collected for PK and CTC analyses. An MTD expansion cohort: 8 patients in stage I and 16 more in stage II if no DLTs are observed in the first stage. Primary endpoints include objective response rate, stable disease at 16 weeks, and grade $3$ adverse events. Since the start of recruitment in September 2016, 870 patients have been enrolled for review and 365 patients (42%) have started treatment in one of 101 opened cohorts. Eight cohorts have graduated to the second stage, two cohorts completed accrual in either their first or second stage, and one cohort was closed due to a registered indication. Twenty-two different study treatments (i.e., immunotherapy, monoclonal antibodies, and PARP/small molecule inhibitors), provided by 11 different pharmaceutical companies, are currently available in DRUP. Data sharing with similar trials such as TAPUR and CAPTUR enables to achieve completion of slow accruing cohorts and affirm conclusions.

Clinical trial information: NCT03767075.
A phase I study of [225Ac]-FPI-1434 radioimmunotherapy in patients with small cell lung, prostate, and breast cancers. [225Ac]-FPI-1434 is a radioimmunoconjugate consisting of a humanized monoclonal antibody that binds to the external domain of IGF-1R, a proprietary bifunctional chelate, and an alpha-emitting radionuclide actinium-225 (Ac-225), which binds to the external domain of IGF-1R. Internalization of the conjugate and decay of Ac-225 causes tumor cell death primarily through double stranded DNA breaks. The indium111 analog, [111In]-FPI-1547, with the identical antibody and bifunctional chelate is used for patient selection, in-vivo imaging, and quantification of IGF-1R targets prior to therapy. Based on anti-tumor activity of [225Ac]-FPI-1434 in preclinical models, favorable toxicology studies in cynomolgus monkeys, and prior human experience with the unconjugated antibody, the first in human clinical evaluation was initiated. **Methods:** This open-label multi-center phase I study (NCT03746431) follows a modified 3+3 dose-escalation design to characterize the safety profile, determine a maximum tolerated dose (MTD), evaluate dose-limiting toxicities (DLT), pharmacokinetics, and tissue correlates will also be assessed. Enrollment (Cohort 2: 40 pts) includes platinum-ineligible pts who progress after prior CPI. First Author: Emerson A. Lim, Columbia University.

A phase II study for prostate cancer monitoring using 18F-DCFPyL and blood-based biomarkers. **First Author:** Ericson A. Lim, Columbia University-Herb Irving Comprehensive Cancer Center, New York, NY. **Background:** Assessing treatment response in castrate resistant prostate cancer (CRPC), remains a challenge due to the limited sensitivity and specificity of existing imaging modalities. Understanding prostate cancer biology with tumor biopsies does not address the issue of tumor heterogeneity or cellular degradation during the decalcification process of bone biopsies. Next generation positron emission tomography (PET) imaging and circulating biomarkers might provide additional insights on treatment responses and inform clinical decision-making earlier in therapy. 18F-DCFPyL (PyL) is a second-generation fluorinated PSMA PET tracer that has superior sensitivity and specificity to detect prostate cancer compared to standard imaging. Its role in assessing tumor response to therapy has not been evaluated. Circulating tumor DNA (ctDNA) in blood can provide tumor genomic information, while exosomes in serum and urine may provide data on the proteomic landscape of tumors. **Methods:** We are conducting a prospective study of 15 men with metastatic CRPC who are scheduled to start a new systemic therapy for their disease. Upon enrollment, subjects will have baseline assessments with standard cross-sectional imaging, 90mTc bone scan, and blood work. Standard scans will be performed every 8-12 weeks until progression of disease. PyL PET/Ct scans and liquid biopsies (ctDNA and exosomes) will occur at baseline, 6 weeks after starting their new therapy, and at disease progression. Lessons seen on PET/CT images will be identified by a certified reader. The maximum standardized uptake value (SUVmax) will be measured and recorded in up to the five hottest lesions and normalized to a background SUVmean, measured in the liver, spleen, kidney, mediastinum, and parotid glands. Changes in the normalized SUV from baseline to the 6-week PyL PET scan will be correlated to PSMA-R1 expression by the Pearson’s correlation coefficient. The Kaplan-Meier method will be used to evaluate progression-free survival and overall survival dichotomized by the median value of SUV change. Blood for ctDNA and exosomes will be stored for future analysis. The study is open with two patients enrolled at the time of submission. One patient has completed his initial PyL PET/CT scan. Clinical trial information: NCT03585114.

**TPS3153** Poster Session (Board #141b), Sat, 8:00 AM-11:00 AM

TROPHY-U-01: A phase II open-label study of sacituzumab govitecan (IMMU-132) in patients with advanced urothelial cancer after progression on platinum-based chemotherapy and/or anti-PD-L1/PD-1 checkpoint inhibitor therapy. **First Author:** Scott T. Tagawa, Sandra and Edward Meyer Cancer Center, New York, NY. **Background:** Patients (pts) with advanced urothelial cancer (UC) who progress after checkpoint inhibitor (CPI) therapy (following failure of or ineligibility for platinum-based chemotherapy) have limited options. Tro-2 is an epithelial cell surface antigen overexpressed in UC (Avelini. Oncotarget 2017). Sacituzumab govitecan (SG) is an antibody-drug conjugate that targets Trop-2 and delivers the active metabolite SN38 to the topoisomerase I inhibitor irinotecan to tumor cells (Starodub. Clin Cancer Res 2015). In a phase 1/2 trial, pts with advanced cancers received SG on days 1 and 8 of a 21-day cycle. In the UC cohort, 45 evaluable pts received SG 10 mg/kg with a median of 2 (range 1–6) prior therapies. Objective response rate (ORR) was 31%; median duration of response was 12.9 mo. Grade ≥3 adverse events in ≥5% of pts were neutropenia/neutrophil count decreased (38%), anaemia (13%), hypophosphatemia (11%), diarrhoea (9%), fatigue (9%), and febrile neutropenia (7%). Median progression-free survival (PFS) was 7.3 mo and overall survival (OS) 16.3 mo (Tagawa 2019 ASCO Genitourinary Cancers Symposium). These results warrant further investigation in a dedicated phase 2 trial. **Methods:** TROPHY-U-01 (NCT03547973) is a single-arm, global phase 2 trial evaluating the antitumor activity of SG (10 mg/kg on days 1 and 8 of a 21-day cycle) in 140 pts with advanced UC and measurable disease. Patients are also required to have an Eastern Cooperative Oncology Group Performance Status score of 0 or 1 and creatinine clearance ≥30 mL/min. The pivotal cohort (Cohort 1: progression after both platinum chemotherapy and CPI) will enroll 100 evaluable pts in a Simon 2-stage design with > 90% power accounting for dropouts to exclude the null hypothesis or ORR < 12%; an exploratory cohort (Cohort 2: 40 pts) includes platinum-ineligible pts who progress after prior CPI. The primary objective is ORR per RECIST 1.1, assessed by central review. Secondary objectives include response duration, PFS, and OS. Adverse events, pharmacokinetics, and tissue correlates will also be assessed. Enrollment began August 2018. Clinical trial information: NCT03547973.

**TPS3154** Poster Session (Board #142a), Sat, 8:00 AM-11:00 AM

Clinical Trial in Progress: The FLEX Big Data Platform explores new gene expression profiles and investigates biomarker-guided protocols in early-stage breast cancer. **First Author:** Sarah Unitch, Agenda, Irvine, CA. **Background:** Genomic signatures are revolutionizing the definition, identification, and treatment of breast cancer. To precisely stratify breast cancers into actionable subgroups, full genome expression data and matching clinical data must be aggregated into a large data set. Such a data set will accelerate research and discovery, especially for smaller patient subsets who are not as widely represented within the current body of literature. **Methods:** FLEX is a multicenter, prospective, population-based, observational trial for patients with Stage I, II, and III breast cancer. All patients with stage I to III breast cancer who receive MammaPrint, with or without BluePrint on a primary breast tumor are eligible for enrollment. The study’s primary aim is to create a large-scale, population-based registry of full genome expression data matched with clinical data to investigate new gene associations with prognostic and/or predictive value. Secondary objectives include utilizing the shared study infrastructure to examine and generate hypotheses for targeted subset analyses and/or trials based on full genome expression data. The design of FLEX allows targeted sub-studies and sub-analyses to be added as appendices after the initial baseline study is opened. Patients enrolled in the initial study are also eligible for inclusion in sub-studies where they meet all criteria and additional consent is not required. Additional clinical data will be collected as specified in the appendix protocols. The FLEX collaborative platform allows participating investigators the opportunity to author their own sub-study protocols, as approved by the FLEX Steering Committee of their peers. 13 sub-studies have been created that are being developed and are under development. Eligibility: The study will enroll a minimum of 10,000 patients aged ≥18 years with histologically proven invasive stage I-II breast cancer who signed informed consent. Enrollment began April 2017 and 1506 patients have been enrolled. Clinical trial information: NCT03053191.
TPS3156
Poster Session (Board #143a), Sat, 8:00 AM-11:00 AM
TIFFANY study: A multicenter phase II basket-type clinical trial to evaluate efficacy and safety of pan-FGFR inhibitor TAS-120 for advanced solid malignancies with FGFR alterations identified by circulating tumor DNA.
First Author: Tomoko Jogo, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Approximately 7% of advanced solid malignancies have FGFR gene alterations. However, standard treatment for FGFR-altered malignancies has not been established. Moreover, circulating tumor DNA (ctDNA) analysis has a potential to accurately identify FGFR alterations by assessing spatial and temporal intratumoral heterogeneity, which have shown to be associated with a poor prognosis and resistance to anti-cancer therapy.

Methods: We are conducting an investigator-initiated multicenter phase II basket-type trial to investigate efficacy and safety of TAS-120, a high selectivity and highest potency pan-FGFR inhibitor, for the patients with advanced solid malignancies with FGFR alterations identified by ctDNA analysis as a part of the Nationwide Cancer Genome Screening Project (GOZILa study, UMIN0000293153). Eligibility criteria include histologically confirmed unresectable advanced or recurrent solid tumors regardless of histology, VEGC PS of 0 or 1; refractory or intolerant to the standard therapies; and clonal FGFR alterations (FGFR1-3 gain-of-function mutations, FGFR1-2 amplifications and FGFR2-3 fusions) identified by a 73-gene sequencing ctDNA panel (Guardant360). Enrolled patients will receive TAS-120 20 mg once daily, orally, in a 21 day-cycle. The primary endpoint is to clarify objective response rate (ORR) assessed by investigators per RECIST v1.1. The secondary endpoints are to evaluate progression-free survival, duration of response, time to treatment failure, overall survival, ORR by central determination, and incidence of adverse events.

Target sample size is determined as 26 to test the null hypothesis of ORR as 5% with one-sided alpha level of 2.5% and power of 80% to detect an expected value of ORR as 25%. Furthermore, tumor tissue and ctDNA will be serially collected and analyzed to assess target resistant mechanism and provide clinically meaningful biomarker which may be used for identifying and implementing treatment changes. Clinical trial information: NCT0194624.

TPS3158
Poster Session (Board #144a), Sat, 8:00 AM-11:00 AM
A phase I open label study evaluating VT1021 in patients with advanced solid tumors.
First Author: Michael Cieslewicz, Vigeo Therapeutics, Cambridge, MA

Background: VT1021 is a cyclic pentapeptide that functions as a potent inducer of thrombospondin-1 (Tsp-1) expression in the tumor microenvironment (TME). By triggering the production of Tsp-1, VT1021 reprograms the TME from one that is immune-suppressive and tumor-promoting, to one that activates the adaptive immune system and is tumor-inhibiting. Tsp-1 reprograms the TME to: (i) induce apoptosis in tumor cells that express CD36 on their cell surface, (ii) convert macrophages from M2 to M1 polarization, which promotes phagocytosis and blunt immunosuppression and (iii) inhibit angiogenesis. Preclinical studies have shown robust anti-tumor activities of VT1021 in animal models of ovarian, pancreatic and breast cancer, including complete tumor regression and reprogramming of the immune TME. These observations led to the initiation of the first-in-human study of VT1021.

Methods: This study is a first-in-human, Phase 1, open-label, multicenter, dose escalation (Part 1) study with dose expansion (Part 2) in advanced solid tumors. The primary objectives are to assess the safety and tolerability of VT1021, to assess dose-limiting toxicities (DLT), and to determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D). Secondary objectives include the evaluation of pharmacokinetics (PK) and pharmacodynamic (PD) effects of VT1021 in tumor and tumor microenvironment, and assessment of preliminary antitumor activity. VT1021 is administered intravenously twice weekly. DLTs will be assessed in the first cycle (Days 1-28) of the dose escalation cohort and are defined as grade 3 adverse events related to VT1021. In Part 1 of the study, 24-30 patients will be enrolled to determine the MTD and RP2D for expansion. In Part 2 of the study, 80-100 patients will be enrolled, grouped into cohorts based on disease subtypes (ovarian, pancreatic, Triple-negative breast cancers, and glioblastoma). Blood samples and biopsy samples from patients will be collected to assess PK properties and PD responses systemically as well as in the TME. No formal statistical hypothesis testing will be conducted in this study. This study is currently open for enrollment in the US. Clinical trial information: NCT03364400.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Tisotumab vedotin (TV) is being developed for patients with cervical cancer and other solid tumors known to express Tissue Factor (TF). Expression of TF on tumor cells has been associated with poor prognosis in several tumor types. Four tumor types were chosen for this study based on unmet medical need and TF expression. TV is an antibody-drug conjugate composed of a TF-targeted fully human monoclonal immunoglobulin G1 conjugated via a protease-cleavable valine citrulline linker to the drug monomethyl auristatin E (MMAE). TV-mediated delivery of MMAE drives antitumor activity through cytotoxic cell killing and has been shown to induce immunogenic cell death (ICD). In preclinical studies, TV treatment resulted in potent and long-lasting tumor regression in TF-expressing xenograft models derived from a variety of solid cancers, including patient-derived xenograft models with heterogeneous TF expression. TV has shown preliminary evidence of activity through cytotoxic cell killing and has been shown to induce immunogenic cell death (ICD).

A phase I/II multiple expansion cohort trial of MRTX849 in patients with advanced solid tumors with KRAS G12C mutation. First Author: Kyrilakis P. Phaedrakis, South Texas Accelerated Research Therapeutics, San Antonio, TX

Background: KRAS mutations occur in approximately 30% of all human cancers and result in constitutive KRAS activity, which has been associated with poor prognosis in various cancer types. The development of agents that selectively target the KRAS G12C mutation has been a significant advancement in the treatment of cancers with KRAS G12C alteration. MRTX849 is a novel KRAS inhibitor with nanomolar potency against wild-type KRAS and approximately 300-fold selectivity against VEGFR2. This phase 1 study is assessing the safety and tolerability of MRTX849 in patients with advanced solid tumors with RET gene alterations.

Methods: NCT03878249 is a phase 1 study in patients with advanced solid tumors with RET gene alterations including non-small cell lung cancer, colon cancer, breast cancer, non-small cell lung cancer, and NSCLC/MTC with prior specific RET gene-fusion NSCLC; 2) RET gene-mutant MTC; and 3) other RET gene-altered advanced tumors or NSCLC/MTC with prior specific RET gene alterations. RET gene alteration status will be assessed locally but confirmed at a central testing lab. The first patient entered in 01/2019. Clinical trial information: NCT03780517.

Methods: NCT03780517 is a phase 1, open label, multicenter dose escalation trial to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of BOS172738, an orally dosed novel RET inhibitor with nanomolar potency against RET and approximately 300-fold selectivity against VEGFR2. This phase 1 study is assessing the safety and tolerability of BOS172738 in patients with advanced solid tumors with RET alterations. Methods: NCT03780517 is a phase 1, open label, multicenter, dose escalation trial to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of BOS172738, an orally dosed RET kinase inhibitor, in patients with advanced solid tumors with RET gene alterations. RET gene alteration status will be assessed locally but confirmed centrally. The study is comprised of 2 parts: in Part A (dose escalation), patients with advanced solid tumors with RET gene alterations will receive BOS172738 orally once daily in each 28-day cycle. Select patients in Part A are eligible for intrapatient dose escalation. On establishing the recommended phase 2 dose (RP2D), Part B (expansion) will enroll up to an additional 60 patients to 1 of 3 tumor type-specific cohorts. The 3 expansion cohorts will each consist of up to 20 advanced cancer patients with: 1) RET gene-altered NSCLC; 2) RET gene-mutant MTC; and 3) other RET gene-altered advanced tumors or NSCLC/MTC with prior specific RET gene-targeted therapy. Patients in expansion cohorts will receive BOS172738 daily at the RP2D until disease progression or other discontinuation criteria have been met. The study is currently open to enrollment globally with the first patient entered in 01/2019. Clinical trial information: NCT03780517.
Phase 1 study of procaspase activating compound -1 (PAC-1) in combination with temozolomide (TMZ) for the treatment of recurrent malignant glioma. First Author: Martin Kelly-Nicholas, University of Illinois at Chicago, IL

Background: The caspase family of cysteine proteases play key roles in the initiation and execution of apoptosis. The activation of procaspase-3 to caspase-3 is critical in both the intrinsic and extrinsic apoptotic cascades. Procaspase-3 levels are elevated in many cancers, including glioblastoma (GBM). As a result, caspase-3 levels are abnormally low in these tumors; thus they avoid apoptosis. PAC-1 is a small molecule that directly activates procaspase-3 and induces apoptosis of cancer cells. PAC-1 has activity against a wide range of cancer cell lines, and in animal models of cancer. PAC-1 crosses the blood brain barrier and has been shown to synergize with TMZ in both canine malignant glioma and meningioma that arise spontaneously.

Methods: This Phase I dose escalation study uses a modified Fibonacci 3+3 design to determine the MTD of PAC-1 when combined with TMZ in patients with recurrent malignant gliomas: anaplastic astrocytoma (AA) and GBM (open to enrollment). Here, we focus on component 2 of the study. Primary objectives: to establish MTD of PAC-1 when combined with a fixed dose of TMZ, tolerability, and toxicity using CTCAE v.4. Secondary and correlative objectives: pharmacokinetics, pharmacodynamics, anti-tumor activity, correlation with procaspase-3 expression in tumor tissue, radiographic responses: pharmacokinetics, pharmacodynamics, preliminary anti-tumor activity.

Patient eligibility: pharmacokinetics, pharmacodynamics, anti-tumor activity correlation with procaspase-3 expression in tumor tissue, radiographic responses: pharmacokinetics, pharmacodynamics, preliminary anti-tumor activity.

Results: A total of 27 patients were enrolled in Component 2 of this study: 11 patients in Arm A and 16 patients in Arm B. The dose escalation was stopped at dose level 4 (375-650 mg daily (up to 3 dose levels) on days 1-21 of each 28-day cycle). A fixed dose of TMZ, (150 mg/m2), is administered orally, days 8 -12 of each cycle. The study is currently enrolling patients for Component 2. Clinical trial information: NCT02355535.

TPS3165 Poster Session (Board #147b), Sat, 8:00 AM-11:00 AM

A window of opportunity trial of atorvastatin in p53-mutant and p53 wild type malignancies. First Author: Mohammad Telfah, University of Kansas Cancer Center, Lawrence, KS

Background: Mutations in p53 contribute to tumor progression. A rational approach is to destabilize mutant (m) p53. The Group at the University of Kansas Cancer Center screened compounds that suppress m p53 in a preclinical model. Luciferase-based reporter assay identified statins as suppressors of m p53 expression. In vitro validation assay demonstrated atorvastatin (A) suppressed m p53 level and cell growth selectively; and depletion of mevalonate altered degradation of m p53. These effects were limited to squamous non-small cell lung cancer (SQNSCLC) and in wild-type p53 tumors. The primary objective of this trial is to determine if A decreases the level of conformational m p53. The secondary objective is to assess the effects of A on Ki-67 and caspase-3 in conformational m p53 tumors.

Methods: This is an open-label, window of opportunity pilot trial to see if A is given for 1 to 4 weeks at a dose of 80 mg/day is sufficient to reduce the levels of conformational m p53 in the tumor tissues. Subjects with new diagnosis of malignancy with a prior clinical therapy, and subjects with previously treated AML, in between treatment regimens, are eligible. Tissues from solid tumors, and bone marrow or peripheral blood samples from AML will be used to screen for m p53 by immunohistochemistry (IHC). Subjects will receive A at 80 mg/day po for 1 to 4 weeks. Pharmacokinetics at pre-dose and 1-hour post-dose on Day 1-21 of each cycle. The day of surgery will be done. Multinomial analysis using exome sequencing technique will be done on m p53. Using IHC, the amount of p53 in pre-treatment and post-treatment samples will be measured and compared simultaneously. The levels of Ki67 and caspase-3 will be tested and compared between pre-treatment and post-treatment samples. Subjects with squamous cell lung cancer (SQNSCLC). Patients will be randomized to receive: A) AML (NCT03096054).

A CRUK first-in-human phase I trial of a CDC7 Inhibitor, LY3143921 hydrate, in patients with advanced/metastatic solid tumors. First Author: Peter F. Gallagher, Queen’s University Belfast, Belfast, United Kingdom

Background: CDC7 is a protein with key roles in DNA replication initiation, the intra-S-phase checkpoint and M-phase completion. CDC7 is overexpressed in malignant compared to non-malignant cells, particularly those with TP53 mutations, making it an attractive therapeutic target. LY3143921 hydrate is an orally administered ATP-competitive CDC7 inhibitor. Preclinical studies in colorectal cancer (CRC) and squamous non-small cell lung cancer (sqNSCLC) demonstrate favourable anti-cancer activity, particularly in squamous NSCLC and in CRC with TP53 null and missense mutations. We hypothesise that solid tumours mutated in TP53 will be sensitive to LY3143921 therapy. Methods: This is a first-in-human, phase I trial of LY3143921 hydrate (LY3143921) monotherapy given twice daily, continuously on a 21 day schedule until disease progression, patient (pt) withdrawal or unacceptable toxicity (NCT03096054). Eligible pts have histologically proven advanced/metastatic solid tumours for which no further standard therapy exists and WHO PS 0-1. Pts have regular clinical assessment and tumour imaging every 2 cycles. Phase Ia (dose escalation) is recruiting in a 3+3 design following 3 initial single patient cohorts (starting dose 30 mg OD), enriching for patients with malignancies associated with p53 mutations (CRC, sqNSCLC, high grade serous ovarian, squamous cell esophageal, squamous cell head & neck, urothelial, pancreatic and triple negative breast cancer). Recruitment to cohort 6 (180 mg BD) is ongoing. On determination of the maximum tolerated dose (MTD) and recommended phase II dose and schedule (RP2D), 2 expansion cohorts (< 25 pts each) of patients with CRC and sqNSCLC will be evaluated. Primary objectives: assess safety and tolerability of LY3143921, determine MTD and RP2D. Secondary objectives: evaluate preliminary efficacy and PK profile of LY3143921. All pts will have archival tumour tissue retrospectively analysed, while patients in phase IIb will also have pre- and on-treatment tumour biopsies. Evaluation of potential predictive and pharmacodynamic biomarkers including p53 mutations, phosphorylated MCM2, cyclin B1 and molecular subgroups of target tumours will be included. Clinical trial information: NCT03096054.
Background: Leomico: A comprehensive proteomic analysis towards discovery of predictive patterns of protein expression to ribociclib sensitivity and resistance—A compLeEMent-1 Canadian correlative sub-study. First Author: Stephen K. L. Chia, BC Cancer Agency, Vancouver, BC, Canada

Background: Despite developments in the treatment of advanced hormone receptor positive (HR+) breast cancer, human epidermal growth factor receptor 2 negative (HER2-) breast cancer, primary or acquired resistance eventually occurs in all cases and is still very limited understanding of the mechanisms of resistance to therapy. Leomico is a sub-study of the main compLeEMent-1 (N = 3255 patients enrolled, CLEE011A2404 v03) trial, an open-label, phase 3b study evaluating ribociclib + letrozole as first-line therapy in an advanced breast cancer patient population which recruited over 250 Canadian patients. The purpose of this Canadian correlative sample collection study is to explore the mechanisms of response and resistance to ribociclib in combination with letrozole through proteomic and cDNA analysis. Methods: The British Columbia Cancer Research Centre team developed a novel and optimized MS/MS platform called SP3-Clinical Tissue Proteomics (SP3-CTP) to perform in-depth proteome profiling (> 8,000 proteins) from formalin fixed paraffin embedded (FFPE) material (10-micron section). SP3-CTP analysis of the proteome of the study patients who did not achieve clinical benefit (primary resistance: progression within 3 months of treatment) will be compared to the proteome of the sub-group of prolonged responders (time to progression of 22 months or more) in order to identify biomarkers that can predict response or de-novo resistance to therapy. Archival tumor biopsies (primary or metastatic) collected from the study will be submitted for proteomic analysis to identify proteomic expression levels that may serve as predictor of response. It is anticipated that over 150 samples will be collected. If available, blood samples taken at time of progression or end of treatment will also be analyzed for cDNA for genetic profiling and to study if there is any correlation between genetic mutations and response or resistance to therapy. Currently, both tissue and blood samples are being collected and no analysis has been conducted thus far. Clinical trial information: NCT03654547.
Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: NAC is well established in many solid tumours but has not undergone large-scale evaluation in colon cancer. Methods: Pts had operable, non-obstructed colon cancer; CT-predicted stage T3-4, N0-2, M0, and were fit for FOLFOX and surgery. They were randomized 1:2 to the novel sequence (6 wk FOLFOX NAC, then surgery, then 18 wk FOLFOX) or control (surgery then 24 wk FOLFOX). RAS-wt pts allocated to the novel arm could optionally be randomized 1:1 to panitumumab (pan) during the NAC phase. Two ‘dealer’s choices’ allowed total chemo duration 12 wk instead of 24 (in older/low-risk pts) and OxCap in place of FOLFOX (except in pts randomized 2:1; pan). Primary endpoint is freedom from recurrent or persistent disease after 2 yrs, by ITT. Secondary endpoints include safety, histological stage, completeness of resection, OS. Results: 1052 pts were randomized, Jun 2008-Dec 2016, at 85 centres in UK, Denmark and Sweden. Conclusions: NAC was well tolerated and safe, with no increase in perioperative morbidity and a trend toward fewer serious postoperative complications. Evidence of histological regression was seen in 59% pts after NAC, including some pCRs. This resulted in a histological downstaging and a halving of the rate of incomplete resections. We observed an improvement in 2-yr failure rate (HR=0.77), but this fell short of statistical significance (p=0.11). NAC for colon cancer improves surgical outcomes and can now be considered as a treatment option; longer follow-up and further trials are required to confirm the long-term benefits, refine its use and optimise case selection. Clinical trial information: RCT2921256.

**Table 1. Novel vs Control**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Novel</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts</td>
<td>698</td>
<td>354</td>
<td></td>
</tr>
<tr>
<td>Received ≥ 1 cycle NAC</td>
<td>674 (97%)</td>
<td>349 (99%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Complete resection (R1, R2 or nil)</td>
<td>68% (98%)</td>
<td>33% (35%)</td>
<td>0.001</td>
</tr>
<tr>
<td><em>pCR</em></td>
<td>25 (4%)</td>
<td>0 (p=0.0001)</td>
<td></td>
</tr>
<tr>
<td><em>pT stage: ≤2;3;4</em></td>
<td>16:64:20 (6%)</td>
<td>16:64:20 (6%)</td>
<td>0.96</td>
</tr>
<tr>
<td><em>pN stage: 0;1;2;3;4</em></td>
<td>60:25:15:14 (7%)</td>
<td>33:53:16:14 (7%)</td>
<td>0.96</td>
</tr>
<tr>
<td><em>Complication prolonging postop stay</em></td>
<td>72% (12%)</td>
<td>72% (14%)</td>
<td>0.96</td>
</tr>
<tr>
<td><em>Anastomotic leak</em></td>
<td>22 (3%)</td>
<td>20 (6%)</td>
<td>0.56</td>
</tr>
<tr>
<td><em>2-yr failure (relapse/persistent dis.)</em></td>
<td>98 (14%)</td>
<td>62 (18%)</td>
<td>HR=0.77 (p=0.11)</td>
</tr>
</tbody>
</table>

(Items marked * provisional pending final data checks)

**Table 2. Comparison of FOxTROT and FOLFOXIRI+BEV**

<table>
<thead>
<tr>
<th>Variable</th>
<th>FOxTROT</th>
<th>FOLFOXIRI+BEV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (median in m)</td>
<td>9.3</td>
<td>12.4</td>
<td>0.0004</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>52.0</td>
<td>59.0</td>
<td>0.1685</td>
</tr>
<tr>
<td>OS (median in m)</td>
<td>17.6</td>
<td>21.7</td>
<td>0.862</td>
</tr>
</tbody>
</table>

**Table 3. Summary of PFS2 (months)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>FOxTROT</th>
<th>FOLFOXIRI+BEV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
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<td>0.1685</td>
</tr>
<tr>
<td>OS (median in m)</td>
<td>17.6</td>
<td>21.7</td>
<td>0.862</td>
</tr>
</tbody>
</table>

**Table 4. Comparison of FOxTROT and FOLFOXIRI+BEV**

<table>
<thead>
<tr>
<th>Variable</th>
<th>FOxTROT</th>
<th>FOLFOXIRI+BEV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
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<td>0.1685</td>
</tr>
<tr>
<td>OS (median in m)</td>
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<td>0.862</td>
</tr>
</tbody>
</table>

**Table 5. Comparison of FOxTROT and FOLFOXIRI+BEV**

<table>
<thead>
<tr>
<th>Variable</th>
<th>FOxTROT</th>
<th>FOLFOXIRI+BEV</th>
<th>p-value</th>
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<tr>
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</tr>
<tr>
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<td>21.7</td>
<td>0.862</td>
</tr>
</tbody>
</table>

**Table 6. Comparison of FOxTROT and FOLFOXIRI+BEV**

<table>
<thead>
<tr>
<th>Variable</th>
<th>FOxTROT</th>
<th>FOLFOXIRI+BEV</th>
<th>p-value</th>
</tr>
</thead>
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<td>OS (median in m)</td>
<td>17.6</td>
<td>21.7</td>
<td>0.862</td>
</tr>
</tbody>
</table>
A randomized phase II trial of second-line CAPTEM versus FOLFOXIRI in MGMT methylated, RAS mutated metastatic colorectal cancer (mCRC) patients. First Author: Filippo Pietrantoni, Fondazione IRCCS Istituto dei Tumori, Milan, Italy

Background: Overall response rate (ORR) to temozolomide (TMZ) is –10% in re-fracture mCRC pts with MGMT methylated detected by qualitative assays, e.g. methyl-specific PCR (MSP). ORR to irinotecan in second-line trials was 4-16%. The efficacy of TMZ may be improved by its combinatorial use in earlier lines and molecular selection beyond MSP. Lack of MGMT expression by immunohistochemistry (ICH) and high MGMT % methylation by MethylBEAMING (MB) are prognostic factors (ORR). NTRK1/2 treated mCRC pts in a multicentric, randomized phase 2 trial investigated PFS superiority of second-line CAPTEM (Arm A: capcitabine 750 mg/m² bid days 1-14/TMZ 75 mg/m² bid days10-14q28 days) over FOLFOXIRI (Arm B) in RAS mutated mCRC pts with MGMT methylation confirmed by MB. Eligible pts: ECOG PS 0-1, measurable disease, failure of 1st-line oxaplatin-based tx (or relapse within 6 mos from oxaplatin-based adjuvant tx). Randomization was stratified by time from the start of oxaplatin-based therapy to PD (< 6-9 months); prior bevacizumab (yes/no). A one-sided log-rank test with a sample size of 82 pts (41 per arm) achieved 90% power at a 5% significance level to detect mPFS increase from 2 to 4 mos. Secondary endpoints: safety, QoL, OS. ORR. Exploratory endpoints: predictive value of MGMT IHC/MB.

Conclusions: The use of TMZ should be explored by phase 3 trials enrolling MGMT IHC-negative +/- high MGMT % methylated mCRC. Clinical trial information: NCT02414009.

CGT CO.26: Updated analysis and update of plasma-detected microsatellite instability (MSI) and tumor mutation burden (TMB) in a phase II trial of durvalumab (D) plus tremelimunab (T) and best supportive care (BSC) versus BSC alone in patients (pts) with refractory metastatic colorectal carcinoma (mCRC). First Author: Feng Chen, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Targeting both PD-L1 and CTLA-4 may be synergistic in immuno-therapy approaches. CO.26 evaluated if dual inhibition leads to improved pt survival vs BSC alone in mCRC. Methods: rrCRC pts were randomized 2:1 to D+T vs BSC. Treatment consisted of D (1500 mg) D1 q 28 days and T (75 mg) q1w in first 4 cycles, and supportive measures. Primary endpoint was overall survival (OS). Two-sided p<0.10 was considered statistically significant. Cell-free (cf)DNA sequencing for MSI and TMB used GuardantOMNI panel and baseline plasma. Results: From 08/2016-06/2017, 180 pts were enrolled. Pt characteristics were balanced between arms. At median follow-up of 15.2 months (mos), median OS for D+T and 4.1 mos for BSC (p = 0.07; Hazard ratio (HR): 0.72, 90% confidence interval (CI): 0.54 – 0.97). Progression free survival (PFS) was 1.8 mos for D+T and 1.9 mos for BSC (p = 0.34). Disease control rate (DCR) was 22.6% for D+T and 6.6% for BSC (p = 0.006). cfDNA analysis was successful in 168/169 pts (99.4%). Two pts were MSI-high. In 166 MSS pts, HR was 0.66 (p = 0.004; 90% CI 0.49-0.90). Excluding the MSI-H cases (TMB of 7.4) and for 1.27 Mts/Mb, mean TMB was 20.4 ± 16.3 mts/Mb (range: 9.64 – 114.0). In MSS pts, a pre-specified cutoff of 20 mts/Mb stratified pts into high and low TMB groups but was not predictive for OS, PFS, or DCR (interaction p-value > 0.7). Using a minimum p-value approach, pts with TMB > 28 mts/Mb (21% of MSS pts) achieved the greatest breadth of clinical benefit (HR 0.34, 90% CI 0.18-0.65 and D+T interaction p = 0.07). High TMB was associated with a trend in worse prognosis for OS in the BSC arm using both 20 mts/Mb (HR 1.26, 90% CI 0.76-2.12) and 28 mts/Mb (HR 2.59 90% CI 1.46-4.62) cutpoints. Conclusions: D+T significantly prolonged OS in pts with mCRC. High TMB may be a biomarker of benefit in mCRC patients. High TMB is an independent prognostic in the BSC arm. This is the first study showing combined PD-L1 and CTLA-4 inhibition prolongs survival in pts with MSS mCRC. Updated results based on deaths in more than 90% of pts will be presented. Clinical trial information: NCT02870520.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Validation of the Immunoscore prognostic value in stage III colon cancer patients treated with oxaliplatin in the prospective IDEA France cohort study (PRODIGE-GERCOR). First Author: Franck Pages, INSERM, Laboratory of Integrative Cancer Immunology, Equipe Labellisee Ligue Contre le Cancer, Paris, France

Background: The Immunoscore (IS), which has been shown to prognostically classify stage I-III colon cancer (CC) patients, was assessed in the IDEA France cohort study evaluating 3 versus 6 months of oxaliplatin-based adjuvant chemotherapy in stage III CC patients. Methods: Densities of CD3+ and cytotoxic CD8+ T cells in the tumor and invasive margin of each patient were quantified by digital pathology and converted to IS using pre-defined published cut-off. The performance of IS to predict disease-free survival (DFS) was assessed in the modified intention-to-treat population, in each study arm, and was adjusted with relevant clinical features in multivariable Cox models. Harrell’s C-statistics was used to investigate the IS performance.

Results: 1322 patients were included; 82 were excluded due to pre-analytical non-conformity. IS was successfully analyzed in 1062 (85.6%) eligible patients. In a 2-category IS analysis, Low and (Int+High) IS were observed in n=599 (43.6%) and n=463 (56.4%) patients, respectively. IS was significantly correlated with T stage, T/N stage (T1-3 and N1 versus T4 and N2), and microsatellite instability status. The study met its primary objective of validating that Low IS identifies patients with higher-risk of relapse or death (HR=1.84; 95%CI 1.24-2.73, p=0.001). The 3-year DFS rates were 66.80% (95%CI 62.23-70.95) and 77.14% (95%CI 73.50-80.35) for Low IS and (Int+High) IS, respectively. In multivariable analysis, IS remained independently associated with DFS (p<0.0012) when combined with T/N stage. The addition of IS to the T/N stage significantly improved the model discrimination after re-calibration using bootstrap C index mean difference, 0.022; 95%CI 0.005-0.04. In addition, IS is in 3 categories (Low, Int, High) and as a continuous variable were also both significantly associated with DFS (all p<0.001). In univariable analysis, IS was also associated with DFS in 6 months arm (p<0.0001); a similar trend was observed in 3 months arm (p=0.09).

Conclusions: IS was confirmed as a prognostic factor of DFS in Stage III CC patients in the prospective IDEA France cohort study. Clinical trial information: NCT03422601.

LBA3516 Poster Discussion Session; Displayed in Poster Session (Board #8), Mon, 8:00 AM-11:00 AM,Discussed in Poster Discussion Session, Mon, 11:30 AM-1:00 PM

Long-term survival after laparoscopic versus open resection for colorectal liver metastases. First Author: Åsmund Avdem Fretland, Oslo University Hospital, Oslo, Norway

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Monday, June 3. Onsite at the Meeting, this abstract will be printed in the Monday edition of ASCO Daily News.
Tumor deposits (TDs) are isolated tumor foci in the pericolic, perirectal or mesocolic fat without residual lymph node (LN) tissue. TDs seem to impact the prognosis of stage III colon cancer (CC) patients (pts) but are only included in IDEA France trial were retrospectively analyzed. DFS according to the presence or absence of TDs was evaluated using Kaplan-Meier estimator. Multivariable Cox model analysis was performed to evaluate the association of TDs with DFS; p = .0046). The 3-year DFS rates were 65.59% [95% confidence interval (30%). All characteristics were similar according to the presence of TDs, 68), pts without treatment (n = 12). TDs were found in 184 pts (9.47%), of 1942 (96%) were analyzed. 80 pts were excluded: no pathological report (n = 25), clinical follow-up period (median, 47.2 months). Plasma samples were collected 4 to 10 weeks after surgery. Mutations in ctdna were assayed using Safe-SeqS. Results: ctdna was detected after surgery in 59 (12%) pts overall (11.0%, 12.5% and 13.8% respectively for samples taken at 4-6, 6-8 and 8-10 weeks; P = 0.740). ctdna detection was associated with nodal status; 8.7%, 16.7% and 32.4% in NO, N1 and N2 disease (P < 0.0001), but remained an independent adverse prognostic factor in multivariable analysis. ctdna detection was associated with poor overall survival for pts treated (mortality ratio, 3.0, P = 0.007) or not treated (adjuvant chemotherapy (mortality ratio, 5.17, P = 0.0001). The median MAF (mutant allele frequency) in pts with detectable ctdna was 0.046%. For pts not treated with adjuvant chemotherapy, 3 year recurrence free survival (RFS) was 9% in pts with a MAF > 0.046% vs 33% with a MAF ≤ 0.046% (HR, 2.7; P = 0.032). For chemotherapy treated pts, DFS was 25% vs > 40% vs 70% with a MAF ≤ 0.046% (HR, 3.1; P = 0.025). In 90 pts with recurrence, ctdna had been detected post surgery in 3 of 20 (15%) with locoregional recurrence, 27 of 60 (45%) with distant recurrence and 5 of 10 (50%) with both (P = 0.044). Conclusion: Where samples for ctdna analysis were collected > 4 weeks post surgery, sampling timing may not significantly impact detection rates. The prognostic significance of ctdna detection can be further stratified by MAF level, but MAF level may not impact adjuvant treatment benefit. ctdna analysis is most sensitive for detecting minimal residual disease at distant sites.

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3521  Poster Session (Board #13), Mon, 8:00 AM-11:00 AM
Nivolumab (NIVO) + low-dose ipilimumab (IPI) as first-line (1L) therapy in microsatellite instability-high (MSI-H)/mismatch repair deficient (MSI-H/MMRd) metastatic colorectal cancer (mCRC): Clinical update. First Author: Hainz-Josef Lenz, USC Norris Comprehensive Cancer Center, Los Angeles, CA
Background: In the phase 2 CheckMate 142 trial, NIVO + low-dose IPI provided robust and durable clinical benefit and was well tolerated as 1L therapy for MSI-H/dMMR mCRC (Lenz et al. Ann Oncol 2018;29:LBA18). Longer follow-up data will be presented. Methods: Patients with MSI-H/dMMR mCRC and no prior treatment for metastatic disease received NIVO 3 mg/kg every 2 weeks + low-dose IPI 1 mg/kg every 6 weeks until disease progression or discontinuation. The primary endpoint was investigator-assessed objective response rate (ORR). Results: For all 45 patients (median follow-up = 13.8 months), ORR was 60% (95% CI 44.3–74.3). Responses were consistent with the overall population across subgroups including age, Eastern Cooperative Oncology Group (ECOG) performance status, prior adjuvant/neoadjuvant therapy, and mutation status (Table). Seven patients (16%) had grade 3–4 treatment-related adverse events (TRAEs); 3 (7%) had any grade TRAEs leading to discontinuation. Updated response, survival, and safety data after a longer follow-up (median 19.9 months) will be presented. Conclusions: NIVO + low-dose IPI demonstrated robust and durable clinical benefit and was well tolerated. Evaluated subgroups had responses consistent with the overall population. NIVO + low-dose IPI may represent a new 1L treatment option for patients with MSI-H/dMMR mCRC. Clinical trial information: NCT02060188.

ORR ** in overall patients and subgroups.

<table>
<thead>
<tr>
<th>NIVO + low-dose IPI</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall patients</strong></td>
<td>60.0 (60)</td>
</tr>
<tr>
<td><strong>Subgroups</strong></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>27/45 (60)</td>
</tr>
<tr>
<td>≥65</td>
<td>18/24 (75)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12/19 (63)</td>
</tr>
<tr>
<td>1</td>
<td>17/26 (65)</td>
</tr>
<tr>
<td>Prior adjuvant/neoadjuvant therapy Yes/No</td>
<td>12/19 (63)</td>
</tr>
<tr>
<td>Mutation status</td>
<td></td>
</tr>
<tr>
<td>BRAF/KRAS wild type</td>
<td>8/13 (62)</td>
</tr>
<tr>
<td>BRAF mutation*</td>
<td>12/17 (71)</td>
</tr>
<tr>
<td>KRAS mutation</td>
<td>5/10 (50)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2/5 (40)</td>
</tr>
</tbody>
</table>

*Investigator assessed. **Median follow-up defined as time on study from first dose to data cutoff, which was 13.8 months (range 9–19). **Previously reported.

3523  Poster Session (Board #15), Mon, 8:00 AM-11:00 AM
A regulatory program that promotes metastasis in colorectal cancer (CRC) through modulation of mRNA stability. First Author: Hani Goodarzi, UCSF, San Francisco, CA
Background: CRC progression accompanies dysregulations in pathways of gene expression control. Regulatory pathways that govern RNA decay have emerged as key mechanisms coopted by cancer cells. Here, we have described a novel regulatory program that acts as a suppressor of metastasis in CRC. Methods: We have developed a computational approach called PRADA that identifies master regulators of aberrant mRNA stability. By applying this tool to a compendium of gene expression data collected from patient samples and colon cancer cell lines, we have identified a novel regulatory program involved in CRC metastasis. We have used xenograft models and genomic technologies to functionally dissect this pathway. We have also performed multivariate analysis in public datasets, as well as qPCR-based measurements in tumor samples to establish its clinical relevance. Results: PRADA identified the RNA-binding protein RBMS1 as a key factor in CRC metastasis. RBMS1, which is silenced in highly metastatic cells, binds and stabilizes a large regulon of mRNAs. Silencing RBMS1 in established lines resulted in increased liver colonization and xenograft models and its overexpression reduced metastasis. We also identified the set of genes that are directly bound and regulated by RBMS1 and function downstream. Loss of RBMS1 and its regulon provide a signature predictive of RFS in localized CRC (n = 574, HR = 0.48, p = 0.038) even when controlled for known prognostic factors in a multivariate analysis (Table). We also observed a 4-fold reduction (P<1e-5) in the expression of RBMS1 in stage IV tumors relative to earlier stage disease. Conclusions: In sum, we have discovered a previously unknown regulatory pathway of RNA stability that acts as a suppressor of metastasis in CRC which may inform new therapeutic targets among the RBMS1 regulon for adjuvant therapy.

Multivariate analysis of gene expression indicates that RBMS1 silencing is associated with poor relapse-free survival in CRC patients.

<table>
<thead>
<tr>
<th>Gene</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBMS1 low vs high</td>
<td>0.015</td>
</tr>
<tr>
<td>Stage 1 vs 3+</td>
<td>0.0155</td>
</tr>
<tr>
<td>Stage 3v1</td>
<td>0.016</td>
</tr>
<tr>
<td>Stage 4v1</td>
<td>0.00</td>
</tr>
<tr>
<td>MSS vs MSI</td>
<td>0.001</td>
</tr>
<tr>
<td>BRAF mut vs WT</td>
<td>0.377</td>
</tr>
<tr>
<td>KRAS wt vs WT</td>
<td>0.98</td>
</tr>
<tr>
<td>CMSS v CMSS</td>
<td>0.477</td>
</tr>
<tr>
<td>CMSS v CMSS</td>
<td>0.242</td>
</tr>
<tr>
<td>CMSS v CMSS</td>
<td>0.470</td>
</tr>
</tbody>
</table>

3522  Poster Session (Board #14), Mon, 8:00 AM-11:00 AM
Recent changes in overall survival of real-life stage IV colorectal cancer patients. First Author: Patricia Harmers, University Medical Center Utrecht, Utrecht, Netherlands
Background: In the past decade, the reported median overall survival (mOS) in phase 3 trials of metastatic colorectal cancer (mCRC) patients increased from approximately 16 to over 36 months. However, only 2.5–20% of cancer patients participate in clinical studies and these are often patients with favourable prognostic factors. Therefore, we explored for which proportion of real-life stage IV CRC patients OS improved in recent years. Methods: Nationwide population-based data of all stage IV (synchronous metastatic) CRC patients diagnosed between 2008-2016 in the Netherlands who received local and/or systemic antitumor therapy were obtained from the Netherlands Cancer Registry (NCR). Initial treatment was registered in the NCR. Vital status was recorded until January 31st 2018. OS per incidence year was determined for various percentiles, which represent the number of months after which 10-30-50-70-90-90% of the patients had died. For some percentiles survival time exceeded follow-up duration. Results: The total study population comprised 21,047 patients. mOS remained unchanged in the period 2008-2016 at around 15 months. OS of p10 and p30 increased by 1.5 months to 3.6 and 10, respectively. For the ‘best’ (longest-living) patients (p70-p80) OS improved in the period 2008-2016 by 4 and 6 months to 30 and 43 months, respectively. Follow-up duration is insufficient to analyse change over time for the 10% ‘best’ patients. mOS did not change for any of the treatment subgroups except for the patients who received exclusively non-systemic therapy (e.g. metastasectomy, radiotherapy) in which OS improved by 11 months to almost 50 months. Conclusions: mOS of real-life stage IV CRC patients has not improved since 2008. We observed a clinically relevant survival improvement in only 30% of all treated patients and in all patients who received exclusively non-systemic therapy. These data illustrate the different outcomes between trial patients and total patient populations which emphasizes the need for a more refined and accurate selection of patients with favourable prognosis. Our results highlight the value of real-life data to determine efficacy of innovations in daily clinical practice.

3524  Poster Session (Board #16), Mon, 8:00 AM-11:00 AM
The role of maintenance strategy in metastatic colorectal cancer (mCRC): A systematic review and meta-analysis. First Author: Mohamad Bassam Sonbol, Mayo Clinic, Phoenix, AZ
Background: In mCRC, induction combination chemotherapy with targeted agents is considered the mainstay of treatment. This is typically followed by maintenance therapy vs. observation which had been examined in various trials. However, it remains unclear how best optimize maintenance strategy. We aim to evaluate comparative effectiveness to support best maintenance strategy. Methods: We searched PubMed, Embase, and Cochrane CENTRAL for randomized controlled trials (RCT) evaluating different maintenance strategies in previously untreated mCRC patients (pts): observation (obs), bevacizumab (bev), fluoropyrimidine (FP), FP+bev, or continuing induction regimen (CTX). Outcomes of interest included OS and PFS. The overall effect was pooled using the DerSimonian random effects model. We conducted network meta-analysis based on White’s multivariate meta-regression to pool evidence from direct and indirect comparisons. Agents were ranked using surface under the cumulative ranking (SUCRA) probabilities. Higher SUCRA scores correspond to greater efficacy. Results: Twelve trials at low risk of bias (55/40 pts) were included. Network meta-analysis shows no benefit of CTX over obs in terms of PFS (HR 0.7; 95% CI 0.46-1.09) and OS (HR 0.95; 95% CI 0.85-1.07). Compared to obs, maintenance therapy shows PFS benefit (HR 0.58; 95% CI 0.43-0.77) with only a trend in OS (HR 0.91; 95% CI 0.83-1.09). All maintenance strategies (FP, FP+bev, and bev) show significant improvement in PFS vs obs. On SUCRA analysis, maintenance treatment (FP or FP+bev) has the highest likelihood of achieving better PFS (67.1% for FP and 99.8% for FP+bev) and OS (81.3% for FP and 73.2% for FP+bev). Conclusions: A maintenance strategy with at least a FP with or without the addition of bevacizumab is preferred. However, given the lack of a clear OS benefit, obs is an acceptable alternative. Optimized maintenance strategies should be based on assessing patient preferences, cost and toxicities.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Prognosis of microsatellite instability and/or mismatch repair deficiency (MSI/dMMR) in stage III colon cancer patients after disease recurrence: Results of an accent meta-analysis of seven studies.

First Author: Georges-Pompidou, Sorbonne Paris Cite/Paris Descartes University, Paris, France

Background: Microsatellite instable/deficient mismatch repair (MSI) metastatic colorectal cancers have been reported to be of poor prognosis. The interaction between MSI and BRAFV600E mutation complicates the picture.

Methods: Patients with resected stage III CC from 7 studies with disease recurrence and data available for MSI and BRAFV600E status were analyzed. The primary endpoint was survival after recurrence (SAR) to assess the prognostic roles of MSI and BRAFV600E, respectively. Associations of markers with SAR were analyzed using Cox proportional hazards models adjusted for clinicopathologic features (data collected 12/1998 to 11/2009).

Results: Among 2630 patients with cancer recurrence (1491 men [56.7%], mean age, 58.5 [19-85] years), multivariable analysis revealed that patients with MSI tumors (n = 220) had significantly better SAR [adjusted hazard ratio (aHR), 0.82; 95% CI, 0.69-0.98; P = .029] than patients with microsatellite stable/proficient MMR (MSI) tumors (n = 1756). This was also observed when looking at patients treated by the standard FOLFOX regimen (aHR, 0.76; 0.58-1.00; P = .048). Same trends were observed when looking at MSI/dMMR patients outcome in BRAFV600E wild-type (aHR, 0.84; P = .10) and mutant (aHR, 0.88; P = .43) subgroups separately, without reaching statistical significance. As previously described poor SAR was observed in BRAFV600E mutants vs wild-type patients (n = 244; aHR, 2.00; 95% CI, 1.73-2.32; P < .0001) and this was also true in BRAFV600E mutants MSI/dMMR patients (n = 77, aHR, 2.65; 95% CI, 1.67-4.21; p < .0001). Other factors associated with a poor SAR were: older age, male gender, T4/N2, proximal primary tumor location, poorly differentiated adenocarcinoma, and early recurrence (by 1y increase).

Conclusions: In stage III colon cancer patients recurring after adjuvant chemotherapy and before the era of immuno-oncologic agents, MSI/dMMR was associated with a better survival compared to MSS. BRAFV600E mutation seems to be a poor prognostic factor for both MSI/dMMR and MSS/pMMR patients.

Apatinib monotherapy for chemotherapy-refractory metastatic colorectal cancer: A multicenter, single-arm, prospective study.

First Author: Fan Wang, Department of Oncology, Peking University Shenzhen Hospital, Shenzhen, China

Background: Apatinib is an oral highly-selective tyrosine kinase inhibitor (TKI) that blocks vascular endothelial growth factor receptor 2 (VEGFR-2). This exploratory study evaluated the efficacy and safety of apatinib monotherapy in patients with chemotherapy-refractory metastatic colorectal cancer.

Methods: In this multicenter, single-arm, prospective study, 48 patients with metastatic colorectal cancer who had failed at least two lines of chemotherapy including fluorouracil, oxaliplatin and irinotecan were recruited from 14 centers in Guangdong, China. Apatinib at a 500mg dose was administered daily continuously. Each cycle was 4 weeks (28 days). The primary endpoint was progression free survival (PFS). Secondary end points included overall survival (OS), objective response rate (ORR), disease control rate (DCR), quality of life (QoL) and toxicity. Results: A total of 48 patients was enrolled in the study from September 3, 2015 to June 9, 2017. Four patients achieved a partial response, and 22 achieved stable disease, representing a response rate of 8.3% and a disease control rate of 60.4%. Median follow-up time was 10.3 months. Median progression-free survival (PFS) and overall survival (OS) of evaluable patients (n=41) were 4.7 months (95% confidence interval [CI] 3.7-5.9) and 9.7 months (95% CI 5.9-13.6). The most common grade 3 or 4 adverse events (AE) were hypertension (12.5%), hand-foot syndrome (10.4%), thrombocytopenia (10.4%), proteinuria (8.3%) and mucositis oral (6.3%).

Conclusions: Apatinib monotherapy shows promising efficacy and manageable toxicities in patients with chemotherapy-refractory metastatic colorectal cancer. Further phase 3 trial is warranted. Clinical trial information: ChiCTR190002503.

Genomic alterations after EGFR blockade in patients with RAS wild-type metastatic colorectal cancer: Combined tissue and blood-based analysis from SCRUM-Japan GI-SCREEN and GOZILA.

First Author: Yoshiaki Nakamura, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Anti-EGFR therapy (tx) in RAS wild-type (wt) metastatic colorectal cancer (mCRC) induces resistance through acquired genomic alterations. We aimed to define such alterations in Nationwide Cancer Genome Screening Project tissue and blood specimens, using next generation sequencing (NGS). Methods: Tumor specimens in patients (pts) with RAS wt mCRC were obtained from SCRUM-Japan GI-SCREEN (tissue) and GOZILA (circulating tumor DNA [ctDNA] from blood). Genomic alterations were compared using the Oncomine Comprehensive Assay (SCRUM) and Guardant360 (GOZILA), before anti-EGFR tx and after progression. Results: 373 total actionable alterations were identified in 71 pts with available matched tissue and ctDNA; 255 (68%) were acquired after anti-EGFR tx progression. Frequently seen acquired oncogenic alterations included KRAS mutations (27%) and amplifications (amps) of EGFR (41%), CDK6 (24%), BRAF (20%), MYC (17%), MET (14%), PIK3CA (11%), FGFR1 (11%), and KRAS (10%). Fusions of RET, ALK, and FGFR3 were newly acquired in 1-4%. Acquired alterations co-arose in multiple pathways, including the cell cycle, PI3K-AKT, and MAPK, although 29% of pts had none. Acquired mutations were less frequently clonal versus primary mutations (p<0.0001), but clonal acquired mutations were seen in several oncogenes, including EGFR, KRAS, and PIK3CA. A subset of acquired KRAS, MET, CCND2, and EGFR amps had high (>7) adjusted plasma copy numbers (ApCN). Acquired ERBB2 amps were identified in 3 pts (4%) with a median ApCN of 4, one of whom (ApCN=4.2), treated with dual HER2 blockade, progressed after 2 cycles. Conclusions: Our integrated analysis revealed the anti-EGFR tx of pts with RAS wt mCRC led to acquired genomic alterations in multiple oncogenic pathways. Although most acquired alterations were subclonal, a subset of oncogenic alterations had relatively high clonality and ApCN, suggesting potential targets for overcoming acquired resistance to anti-EGFR tx. Early progression in a pt with an ApCN of 4.2 suggests low-level/subclonal acquired alterations may not be effective treatment targets.
3529 Poster Session (Board #21), Mon, 8:00 AM-11:00 AM
Screening patients for fluoropyrimidine-related toxicity risk. First Author: Olivier Capitain, Institut de Cancérologie de l’Ouest, Site Paul Papin, Angers, France

Background: Severe, sometimes fatal, toxicity can occur during the 1st or 2nd course of chemotherapy using fluoropyrimidines (FPs), and poses a serious public health problem. FPs carry a 3-5% risk of grade ≥ 3 early toxicities and 0.2% risk of death linked to Dihydropyrimidine Dehydrogenase (DPD) deficiency. Methods: Of 29,000 patients screened since July 2000, 472 were referred to us due to severe toxicity linked to Dihydropyrimidine Dehydrogenase (DPD) deficiency. Toxicity evaluation was performed according to the NCI scale of adverse reactions to cancer drugs.

$\text{Plasma uracil (U) level, 3) Plasma dihydrouracil/uracil ratio (UH}_2/\text{U) 4) a multiparametric approach with genotyping, UH}_2/\text{U ratio and key patient factors (age, sex, etc.)}$

Results: Of the 472 referred patients, 169 had grade 4 or 5 toxicity, of which 41 died from toxicity. 98 had one or plus DPYD mutation (*2A,*2B,*7,13, HapB3) 2) Plasma dihydrouracil/uracil ratio (UH2/U) and a multiparametric approach with genotyping, UH2/U ratio and key patient factors (age, sex, etc.). McNemar’s test with Bonferroni correction was used for statistical analysis.

Conclusions: The multiparametric approach is statistically (p<0.0001) the most efficient in terms of preventing grade 4 and 5 toxicity (death) due to 5-FU treatment. Around 290,000 patients are treated with 5-FU per year in the USA. Assuming a 0.2% mortality rate due to toxicity, around 580 lives could be saved per year using the multiparametric pre-treatment test.

Grade 4-5 tox DPYD Mutations Uracil > 16ng/ml UH2/U < 0.5 Multimetric

<table>
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<th>False negative n (%)</th>
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Grade 5 tox DPYD Mutations Uracil > 16ng/ml UH2/U < 0.5 Multimetric

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<th>False negative n (%)</th>
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3530 Poster Session (Board #22), Mon, 8:00 AM-11:00 AM
Tumor dynamics with fluorouracil/folinic acid, irinotecan, and oxaliplatin (FOLFOXIRI) plus panitumumab (pmab) or FOLFOXIRI alone as initial treatment of RAS wildtype metastatic colorectal cancer (mCRC). Central radiologic review of VOLF—A randomized, open label, phase-2 study (AIÖ KKR0109). First Author: Dominik Paul Modest, Department of Medicine III, University Hospital, LMU Munich, Munich, Germany

Background: The VOLF trial demonstrated improved objective response rate (ORR) with the addition of pmab to modified triplet chemotherapy with FOLFOXIRI in a 2:1 (63 patients FOLFOXIRI plus pmab, 33 patients FOLFOXIRI) randomized, controlled, phase II trial in patients with untreated RAS wildtype mCRC. Methods: Radiographic images from the study were centrally examined according to RECIST 1.1. We further assessed early tumor shrinkage (=ETS: 20% shrinkage of tumor diameter at first re-assessment) and depth of response (=Drp=E maximum shrinkage of lesions defined as relation of smallest tumor diameter to baseline). Moreover, time to depth of response was calculated (randomisation to depth of response image). Results: Images were available for 88 of 96 patients (91.7%), 86 patients (89.6%) had at least one follow-up image and were included in the central review. According to central review, objective response rates were 89.2% vs 66.7% with FOLFOXIRI plus pmab versus FOLFOXIRI alone (P=0.02). ETS was also significantly more frequent (Fisher’s exact test; P=0.011) and Drp=R (Wilcoxon test; P= 0.004) significantly greater with pmab as compared to chemotherapy alone. See table for details. Time to Drp=R was similar in the panitumumab-vs chemotherapy alone arm (3.9 (95% confidence interval 2.8-4.7) vs. 4.2 (95% CI 3.6-5.7) months, respectively. P=0.63). ETS rates in this central review significantly improves ORR, the rate of ETS and also Drp=R when added to a mFOLFOXIRI regimen. Our findings underline the potential of this highly active regimen in patients with RAS wildtype mCRC that need to achieve early and profound shrinkage of the tumor. Additional analysis including molecular subgroups and tumor sidedness will be shown at the meeting. Clinical trial information: NCT01328171.

3531 Poster Session (Board #23), Mon, 8:00 AM-11:00 AM
Metastasectomy and BRAF mutation: An analysis of survival outcome in metastatic colorectal cancer. First Author: Thiru Prasanna, University of Canberra, Canberra, ACT, Australia

Background: Surgical resection of oligometastases improves survival in metastatic colorectal cancer (mCRC). It is unclear whether such benefit is consistently observed for BRAF V600E mutant (MT) and wild type (WT) mCRC. We conducted a retrospective analysis to explore the influence of BRAF mutation status on survival outcomes after metastasectomy.

Methods: Data collected from two large prospective population databases in Australia (Treatmetn of Recurrent and Advanced Colorectal Cancer (TRACC) and South Australian cancer registry). Overall survival (OS) and recurrence free survival (RFS) for BRAF MT and WT mCRC were evaluated by Kaplan-Meier method and compared by log-rank test. Results: 513 patients who had undergone metastasectomy were identified, 6% were BRAF MT. Median age 63. Metastasectomy rate was lower in BRAF MT (13 v 27%). In BRAF WT, 4% un-derwent metastasectomy versus none in BRAF MT. Median OS in BRAF MT v WT: 25.7 v 48.5 months (HR 1.95; 1.18-3.22). In a multivariate model adjusting for variables differ after metastasectomy between BRAF MT and WT in a multivariate model.

Recurrence free survival (RFS) for BRAF MT and WT mCRC were evaluated by Kaplan-Meier method and compared by log-rank test. Results: 513 patients who had undergone metastasectomy were identified, 6% were BRAF MT. Median age 63. Metastasectomy rate was lower in BRAF MT (13 v 27%). In BRAF WT, 4% underwent metastasectomy versus none in BRAF MT. Median OS in BRAF MT v WT: 25.7 v 48.5 months (HR 1.95; 1.18-3.22). In a multivariate model adjusting for variables differences were greatest for CD8 + CT (Table).

Clinical trial information: NCT01328171.

3532 Poster Session (Board #24), Mon, 8:00 AM-11:00 AM
Intratumoral CD3+ and CD8+ T-cell densities in patients with deficient DNA mismatch repair (dMMR) metastatic colorectal cancer (mCRC) receiving programmed death-1 (PD-1) blockade. First Author: Sakthi Chakraborti, Mayo Clinic, Rochester, MN

Background: Colorectal cancer with dMMR display heterogeneity in the extent of intratumoral T-cell infiltration which may explain their variable responsiveness to PD-1 blockade. We examined the association of intratumoral CD3+ and CD8+ T-cell densities (TCD) with objective response rate (ORR) and response duration in patients with dMMR mCRC receiving programmed death-1 (PD-1) blockade (PEM).

Methods: Record review was performed on 12 patients with dMMR mCRC treated with PEM (200 mg intravenously every 3 weeks) after failure of prior chemotherapy (median no. of regimens was 1 (range 1-4)) between 01/2015 and 12/2017. CD3+ and CD8+ TCDs were analyzed in the primary tumor core (CT) and at the invasive margin (IM) by immunohistochemistry and automated image analysis to determine density score (0 to 100) for each T-cell subtype and compartment (Ventana Medical Systems, Inc.). Patients were categorized as responders as well as in patients who had disease control for 12 months. If confirmed, TCDs may potentially predict responsiveness to PD-1 blockade in dMMR mCRCs.

Central review population

<table>
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<th>mFOLFOXIRI plus panitumumab (N=56)</th>
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<tr>
<td>ETS 20% (%)</td>
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<td>DPr median (range)</td>
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<th>p-value</th>
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Impact of gender on the safety profile of chemotherapy plus bevacizumab in mCRC. A pooled analysis of TRIBE and TRIBE2 studies. First Author: Gemma Zuccaelli, Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

Background: Based on retrospective experiences, gender seems to affect the safety profile of chemotherapy (CT), with a higher incidence of CT-related adverse events (AEs) among females than males. Here we focus on the impact of gender on the toxicity of FOLFOXIRI/bev (bevacizumab [bev]) combined with oxaliplatin (OX) or FOLFIRI/bev in two randomized phase III studies by GONO: TRIBE and TRIBE2. Methods: The risk of experiencing CT-related AEs in males and females was estimated in univariable analysis in the overall safety population and according to treatment arms (doublets/bev and FOLFOXIRI/bev). In contrast, we assessed the independent weight of gender on the risk of developing AEs, multivariable logistic regression models were built. Results: Among 1187 patients enrolled in TRIBE and TRIBE2 studies, 1176 684 males, 58%, and 492 females, 42% were included in the safety population. Overall, women had a significantly higher risk of CT-related AEs, in particular gastrointestinal and hematologic AEs, anemia and alopecia, independently of the treatment arm. The risk of CT-related AEs was increased with FOLFIRI/bev vs doublets/bev independently of gender (p = 0.029). Notably, among women treated with FOLFOXIRI/bev 50% and 68% experienced any grade of vomiting and nausea, respectively. Conclusions: Female mCRC patients have a higher risk to develop CT-related AEs. In women treated with FOLFOXIRI/bev the high incidence of nausea and vomiting may suggest the need for an intensification of the antiemetic prophylaxis.
A randomized, double-blinded, placebo-controlled multicenter phase II trial of adjuvant immunotherapy with tecemotide (L-BLP25) after R0/R1 hepatic colorectal cancer metastectomy. LICC Final results, First Author: Carl Otfried Schimanski, Klinikum Darmstadt GmbH and Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Darmstadt and Mainz, Germany

**Background:** Hepatic metastasectomy is the only potential curative treatment option for stage IV colorectal cancer (CRC) limited to liver metastases (LM). After R0 resection of LM the high recurrence rate remains a major challenge. L-BLP25 is an antigen-specific cancer vaccine targeting mucin 1 (MUC1). The LICC trial aimed to improve survival outcome in mCRC patients (pts) after R0/R1 LM resection. Methods: This LICC trial, a binational, multicenter, double-blinded, placebo controlled phase II trial, included pts with stage IV LM limited CRC after resection of primary tumor and LM (R0/R1) within the last 8 weeks, ECOG 0/1 and adequate organ function. Pts were randomized 1:1 to receive L-BLP25 placebo or L-BLP25 330 mg back administered as 8 weekly subcutaneous doses followed by 6 week maintenance intervals until recurrence or a maximum of 2 years. Cyclophosphamide 300 mg/m² (CP) or matching saline (NS) was given intravenously 3 days prior to first L-BLP25/placebo. Co-primary endpoints were recurrence-free survival (RFS) and OS. Secondary endpoints were RFS and OS in subgroups with different MUC1 expression and safety. Differences in RFS and OS were analyzed with exploratory log-rank tests on the intention-to-treat population. Results: Of 121 pts enrolled between Oct 2011 and Dec 2014, 79 pts received L-BLP25+CP, 42 placebo. Baseline characteristics were well balanced except for age cut-point 60 years (commonly used in breast cancers, 60.0±18.3 vs. 60.2±18.3, p=0.77). Median age was 60 (90% CI: 5.8-8.8) vs. 11.4 months (90% CI: 5-20.3) and estimated 3-year OS rate 69.1% vs. 79.1% for L-BLP25 and placebo, respectively. Two-factorial Cox regression models showed no impact of MUC1 expression or treatment on RFS or OS. The most common L-BLP25-related grade 3/4 adverse events were diarrhea, anemia and back pain. There was one death in the L-BLP25 arm due to Merkel cell carcinoma assessed by the investigator as being potentially related to vaccination. Conclusions: The LICC trial failed to meet its primary endpoint of significantly improving RFS and OS with L-BLP25. MUC1 expression was not associated with outcome. Clinical trial information: NCT01462513.

Evaluating gender as a predictive marker for response to bevacizumab (Bev) in metastatic colorectal carcinoma (mCRC). A retrospective analysis of 3369 patients (pts) in the ARCAD database. First Author: Ofer Margalit, Sheba Medical Center, Ramat Gan, Israel

**Background:** Previous studies suggest a possible gender-specific response to Bev in mCRC, showing a benefit in males, while the effect in females is less significant. Therefore, we evaluated response to Bev according to gender. Methods: Data from 3369 mCRC patients enrolled on 4 first-line randomized trials testing Bev (2000-2007) were pooled. Association between gender and progression-free survival (PFS) overall survival (OS) was evaluated by stratiﬁed Cox regression model, adjusted for potential confounders. Predictive value was evaluated by interaction (inter.) effect between gender and treatment. In a pre-planned secondary analysis, analyses were stratified by a tumor age cut-point of 60 years. Results: Of 121 pts enrolled between Oct 2011 and Dec 2014, 79 pts received L-BLP25+CP, 42 placebo. Baseline characteristics were well balanced except for age cut-point 60 years (commonly used in breast cancer trials) to evaluate the possible role of menopausal-related effects. Results: OS was not statistically different between males and females (median OS (mo), 18.8 vs. 17.6 mo (mo), adjusted hazard ratio (HR├ø) 0.93, 95% conﬁdence interval (CI), 0.84-1.03; p = 0.15) in the overall population. Bev was associated with an improved mOS in males and females, with a 2.3 and 0.6 mo benefit, respectively, as well as an improved PFS. There was no statistically significant interaction effect between gender and treatment (see table). Further stratified by age (< vs. 60 years, Bev resulted in improved PFS and OS in both genders, at all ages, except for the effect in young females which did not reach statistical signiﬁcance (see table). Conclusions: Our results conﬁrmed the mOS beneﬁt from addition of Bev to ﬁrst-line chemotherapy in mCRC in both genders, although the beneﬁt in females was < 1 mo. For males under the age of 60, there are uncertainties for mOS beneﬁt from addition of Bev and further evaluation is needed.

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<th>Bev</th>
<th>mPFS (mo)</th>
<th>HR(95% CI)</th>
<th>p</th>
<th>Inter.</th>
<th>mOS (mo)</th>
<th>HR(95% CI)</th>
<th>p</th>
<th>Inter.</th>
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<td>0.08</td>
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Efficacy of retreatment with anti-EGFRs in mCRC is not predictable by clinical factors related to prior lines of therapy: A multi-institutional analysis. First Author: Daniele Rossini, Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

**Background:** Retrospective analyses and phase 2 studies suggest that administering an anti-EGFR in advanced lines may be effective in mCRC pts who achieved beneﬁt from a 1st-line anti-EGFR containing regimen. The identiﬁcation of clinical features associated with beneﬁt from anti-EGFR re-treatment (re-tx) in pts experiencing PD during 1st-line anti-EGFR (chalenge) or after its interruption (rechallenge), is a major clinical need. Methods: A real-life data-base including a total of 5530 pts treated at 6 institutions from December 2010 to October 2018 was queried. Pts retreated with anti-EGFRs, with RAS/BRAF wild-type status on tissue samples, who had received a 1st-line anti-EGFR-based tx with at least SD as best response, and at least one further line of therapy before anti-EGFR re-tx, were included. The association with RECIST response (RR), PFS and OS was investigated for the following variables: RR (PR or CR vs SD) and PFS during 1st-line; time from the last anti-EGFR administration to 1st-line PD (i.e. re-introduction vs rechallenge); reason for anti-EGFR discontinuation in 1st-line (PD vs. other); number of anti-EGFR-free lines of therapy before re-tx; anti-EGFR free interval (time between the last anti-EGFR administration to 1st-line and the time of re-tx); primary tumor side; time from the diagnosis of metastatic disease to re-tx (≤ vs. > 18 mos). Results: Data from 86 patients were retrieved, 56 (65%) and 30 (35%) received anti-EGFR rechallenge or reintroduction, respectively. Median anti-EGFR free interval was 15.1 mos. The RR during re-tx was 19.8%, with a DCR of 46.5%. Median PFS and OS were 3.6 and 10.2 mos, respectively. No significant association of investigated features with RR and PFS was observed. Different numbers in RR or PFS were observed among patients receiving anti-EGFR re-tx as rechallenge or reintroduction (20.4% vs 23.1%; p = 0.99; median PFS: 3.49 vs 4.97 mos, p = 0.61). Patients with left-sided tumors had longer OS (HR: 0.50, 95%CI: 0.26-0.93, p = 0.005). Conclusions: Clinical factors that are generally believed to affect the efﬁcacy of anti-EGFR re-tx are not so therefore, other clinical features should be evaluated. To decide on re-treatment (anti-EGFR re-tx) and adequate studies for implementing liquid biopsy in clinical practice are urgently needed.
**3541** Poster Session (Board #33), Mon, 8:00 AM-11:00 AM

**Effect of patient age on efficacy of FOLFIRI plus cetuximab vs bevacizumab in 1st-line treatment of metastatic colorectal cancer: An analysis of FIRE-3 (AIO KRK 0306).** First Author: Volker Heinemann, University Hospital Munich, LMU Munich, Munich, Germany

**Background:** FOLFIRI compared 1st-line therapy with FOLFIRI plus either cetuximab or bevacizumab in 592 KRAS exon 2 wt mCRC patients. The subgroup of extended RAS wt patients consisted of 400 patients. The median age of patients treated in FIRE-3 was 64 years. Analyses of efficacy of doublet-chemotherapy in patients >70 years old were not shown in the overall results. Methods: As per this exploratory analysis, patients were grouped into cohorts with 65 years and 70 years as a cut-off for age-related analyses of the FIRE-3 study population. ORR was compared using Fisher's exact test, Survival analyses were done using Kaplan-Meier estimation and median survival times were compared using log-rank testing. Results: Within the RAS wt population, patients older than 70 years had a significantly shorter OS when compared to patients ≤70 years of age in both arms (p = 0.02 for cetuximab arm, p = 0.02 for bevacizumab arm). Patients ≤65 years and ≤70 years had a significantly longer OS when treated with FOLFIRI plus cetuximab compared to FOLFIRI plus bevacizumab (p = 0.01 and 0.02 respectively). The OS benefit of cetuximab treated patients compared to bevacizumab treated patients was consistent for patients ≤65 years (p = 0.005) and patients ≥70 years (p = 0.009) of age. In patients older than 70 years, however, comparable efficacy of bevacizumab and cetuximab could not be demonstrated. This effect of age on outcome appears to be affected by sidedness. RAS wt population (n=400). Conclusions: In the overall RAS wt population, younger patients have a significant OS benefit when treated with FOLFIRI plus cetuximab compared to FOLFIRI plus bevacizumab, while this was not the case in patients older than 70 years.

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**3542** Poster Session (Board #34), Mon, 8:00 AM-11:00 AM

**ctdNA for accurate determination of RAS and BRAF mutations using OncoBEAM liquid biopsy in metastatic colorectal cancer patients: Results of the real-world multicentric ColoBEAM study.** First Author: Alexandre Harle, Institut de Cancérologie de Lorraine, Service de Biopathologie, CNRS UMR 7039 CRAN Université de Lorraine, Nancy, France

**Background:** Determination of KRAS, NRAS (RAS) and BRAF mutations is a standard of care for the management of patients with metastatic colorectal cancer (mCRC). RAS mutations are well characterized resistance biomarkers to anti-EGFR antibodies and BRAF V600 mutations indicate poor prognosis. Therefore, they have traditionally been used to determine RAS and BRAF mutations, but liquid biopsy analysis of circulating tumor DNA (ctDNA) has demonstrated utility as a less invasive tool to expedite molecular testing results to the clinic. The ColoBEAM study reports the performance of plasma mutation testing in a real-life prospective series of 278 patients across 8 centers. Methods: Plasma derived ctDNA was prepared from 20ml blood samples prospectively collected from mCRC patients who had not received chemotherapy in the prior 15 days. ctDNA was centrally assessed using OncoBEAM and results compared to those obtained by routine analysis of tissue. Both tissue and blood samples with discrepant RAS results were blindly reassessed with OncoBEAM. Results: Of 278 patients enrolled, 202 blood samples were available for OncoBEAM testing. RAS and BRAF V600E mutations were detected in tissue in 132/202 (65.4%) and 4/198 (2.0%) patients, respectively. Analysis of the first ctDNA sample as compared to tissue DNA resulted in a kappa coefficient of (k) of 0.52 (0.41 – 0.63) and accuracy of 75.2% (61.5% sensitivity; 94.3% specificity). OncoBEAM testing of a second sample resulted in (k) of 0.60 (0.51 – 0.68) and accuracy of 83.2% (77.3% sensitivity; 94.3% specificity). Of the 4 samples with a BRAFV600E mutation in tumor tissue 2 were detected in blood. In the subgroup of patients with liver metastasis (n=136), accuracy was 88.2% (87.4% sensitivity; 90.2% specificity) for RAS and BRAF status with (k) of 0.66 (0.53 – 0.78). In subgroup of chemotherapy naive patients with liver metastasis (n=49), accuracy was 91.8% (93.3% sensitivity; 89.5% specificity) for RAS and BRAF status with (k) of 0.83 (0.67 – 0.99).

Conclusions: The results of the ColoBEAM study confirm plasma ctDNA as a credible surrogate marker to tissue DNA for RAS and BRAF status assessment and may be incorporated as a first-line theragnostic assessment. Nest testing on a second sample for wild-type status demonstrated 91.8% concordance between blood and tissue. Clinical trial information: NCT02751177.

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**3543** Poster Session (Board #35), Mon, 8:00 AM-11:10 AM

**Development and validation of a prognostic score for overall survival integrating baseline metabolically active tumor volume measured by 18F-FDG PET/CT and clinical factors for metastatic colorectal cancer patients.** First Author: Erwin Woff, Nuclear Medicine Department, Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium

**Background:** This study aimed to develop and validate a prognostic score integrating baseline metabolically active tumor volume (MATV) and clinical factors in metastatic colorectal cancer (mCRC) patients. Methods: The development cohort included a non-randomized real-world cohort of mCRC patients in a retrospective multicenter non-randomized trials evaluating soralen/5-fluorouracil as last line therapy. The validation cohort included mCRC patients from another center, treated with chemotherapy and bevacizumab as first line. Baseline MATV was defined as the sum of metabolically active volumes of all target lesions identified on the baseline 18F-FDG PET/CT. MATV optimal cutoff for OS prediction was determined from the development cohort with Contal and O’Quigley’s method. MATV, age, gender, BMI, ECOG PS, years since diagnosis, and KRAS status were included in a multivariate analysis. A prognostic score to predict OS was developed from the development cohort using Cox proportional hazards model. Results: MATV and clinical factors were evaluable respectively in 155 and 122 patients of the development and validation cohorts. In univariate analysis, MATV with cutoff set at 100 cm³ identified two risk groups in patients with different median OS (mOS) in both the development (4.5 vs 10.9 months, HR: 2.64; p < 0.001) and validation cohorts (20.9 vs 42.9 months, HR: 2.39; p < 0.001). A multivariate analysis identified four independent negative predictors of OS (high MATV, short time since diagnosis, poor PS, BMI < 25). Combining these factors in a prognostic score for OS (best cutoff: 2) allowed to identify two risk groups with different mOS in the development (4.4 vs 13.4 months, HR: 3.67; p < 0.001) and validation cohorts (25 vs 63.8 months, HR: 2.5; p = 0.001). Conclusions: In mCRC patients, the high prognostic value of baseline MATV found in the development cohort was confirmed by external validation, independently of patients’ treatment. In both the development and validation cohorts the prognostic score for OS allowed to identify two risk groups of mCRC patients with significantly different mOS. MATV and our prognostic score for OS should provide a firm basis for risk stratification, in clinical practice and research trials.

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**3544** Poster Session (Board #36), Mon, 8:00 AM-11:00 AM

**ctDNA as a potential prognostic marker for locally advanced rectal cancer patients in a ‘watch and wait’ approach.** First Author: Lifeng Yang, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

**Background:** ‘Watch and Wait’ policy has currently led to growing interest for organ-preservation before neoadjuvant chemoradiation (nCRT) to improve quality of life. However, how to predict and select patients who may achieve clinical complete response is still an unsolved issue. We conducted a pilot study to evaluate the role of circulating tumor DNA (ctDNA) as a biomarker to predict treatment outcome and improve risk stratification in locally advanced rectal cancer (LARC). Methods: In this study, we recruited 119 patients with LARC receiving nCRT. 595 serial plasma samples were collected at d0, d15, d25 of radiotherapy as well before and 7 days post surgery. The level of ctDNA was calculated by dynamic monitoring the mutant allele frequency of somatic mutations in plasma. Plasma and tissue samples were subjected to targeted-NGS using a 422 cancer-related genes panel. We followed up patients with concomitant CT until disease progression or death. Results: Detected mutation of TP53 and APC gene in pre-treatment samples was negatively correlated with patients’ response to nCRT. Alterations in homologous repair and adherens junction pathways were associated with a better response (P < 0.05). Detection of pre-treatment mutations in any time points during nCRT was significantly (P = 0.03) decreased from TRG3 to TRG0 group (33%, 29%, 22% and 4%, respectively); while detection of pre-treatment mutations in any time points was significantly (P = 0.05) increased from TRG0 to TRG3 group (56%, 53%, 50% and 36%, respectively). Further, detection of pre-treatment mutations after completion of nCRT was achieved a mean AUC of 0.85 assessed by repeated cross validation. Based on support vector machine was developed for prediction of pCR achieving a mean AUC of 0.85 assessed by repeated cross validation. Further, detection of pre-treatment mutations after completion of nCRT was significantly associated with worse disease-free survival (DFS) (P < 0.05). Through tracking clonal extinction, persistence and emergence, patients were grouped into four evolutionary subtypes with distinct TRG and DFS. Conclusions: Our data showed the prognostic value of ctDNA on DFS. Dynamic monitoring of ctDNA can be used to predict TRG and prognosis in LARC patients receiving nCRT. ctDNA sequencing depicts the evolutionary trajectories of sensitive and resistant clones during nCRT in colorectal cancer. ctDNA derived potential be used to guide patient selection for W&W strategy.

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Genetic variants in RNA binding protein (RBP) to predict outcome in metastatic colorectal cancer (mCRC): Data from FIRE-3, TRIBE, and MAVERRICC trials. First Author: Hiroki Arai, Chiba Cancer Center, Chibashi, Japan

Background: RNA binding proteins (RBPs) post-transcriptionally regulate gene expression by stabilizing or destabilizing target messenger RNA. Although alteration of RBPs affects many steps of cancer development, its clinical implication in mCRC remains unclear. Methods: We analyzed data from mCRC patients (pts) enrolled in three first-line randomized trials (FIRE-3, TRIBE, and MAVERRICC). Genomic DNA from blood samples of pts was genotyped through the OncoArray, a custom array manufactured by Illumina. Candidate 30 SNPs in 10 RBP genes (MSI2, RBM3, LIN28A, LIN28B, IGF2BP1, IGF2BP2, IGF2BP3, ZFP36) were tested on a central review committee. The best response was 40.5(15/37) % (95% CI: 24.8-57.9), and the disease control rate was 86.5 (32/37) % (95% CI: 71.2-95.5). The AEs which were frequent as grade 3 or 4 were leucopenia (9.5 %), neutropenia (7.1 %), anemia (12.8 %), febrile neutropenia (10.3 %), and fatigue (10.3 %). No treatment related death was reported. Conclusions: The combination of trifluridine/tipiracil plus bevacizumab is an effective and well-tolerated regimen for elderly patients with metastatic colorectal cancer. Hematological adverse events were need for caution. The primary endpoint of PFS will be presented in the end of this year. Clinical trial information: UMIN000025242

Who can benefit from a liver surgery for metastatic colorectal cancer in the era of modern chemotherapy? A post hoc analysis of the MIROX phase III trial. First Author: Samita Mahkoul, Medical Oncology Unit, Lille, France

Background: Despite improvement in colorectal liver metastasis (CLM) treatment, survival after liver surgery remains highly variable. Several clinicopathologic prognostic factors have been reported whose validity in the era of modern chemotherapy remains to be defined. This study aimed to analyze the prognostic factors associated with survival after CLM resection. Methods: Clinicopathologic data of patients included in the MIROX phase III trial who underwent surgery for isolated CLMs were analyzed. The primary endpoints were 5-year overall survival (OS) and disease-free survival (DFS). Univariate Cox analysis was performed to identify associations with OS and DFS and select variables included in a multivariate model to determine their independent prognostic value. Results: A total of 181 patients were analyzed. The median follow-up period was 5.4 years (95% CI: 5.1-5.7). 41 patients died and 35 were lost to follow-up. The 5-year OS and DFS rates were 67.1% and 35.4%, respectively. On multivariate analysis, Fong's clinical risk score (CRS) as a categorical variable (CRS 0-1 vs 2-3 vs 4-5, p = 0.036) and polymorphonuclear neutrophil (PMN) count (>6000/mm³ vs ≤6000/mm³, p = 0.006) before chemotherapy were found to be independent prognostic factors for OS. However, only Fong's CRS remained significantly associated with DFS (p = 0.027). The final OS model was used to establish a nomogram that allows individual OS estimations at 1, 3, 5, and 10 years. Conclusions: Fong's CRS and PMN count were independently associated with poor OS after CLM resection. Fong's CRS was also associated with DFS. The established prognostic nomogram could predict OS more accurately before CLM treatment.

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3550 Poster Session (Board #42), Mon, 8:00 AM-11:00 AM
Bevacizumab (BV) maintenance (M) after first-line chemotherapy (CT) plus BV for metastatic colorectal cancer (mCRC) patients (pts): A meta-analysis of individual pts data (IPD) from three (3) phase III trials. First Author: Salvatore, Oncologia Medica, Fondazione Policlinico Universitario “A. Gemelli”, IRCCS, Roma, Italy

Background: Although CAIRO3 and AIO KRK 0207 trials demonstrated the benefit of BV + fluoropyrimidine as a M regimen after induction CT + BV, the role of BV alone is not clear. Indeed, SAKK 41/06 and PRODIGE 9 trials failed to demonstrate the superiority of BV alone vs no M, while AIO KRK 0207 showed the non-inferiority of BV alone vs combo M. Thus, in order to evaluate the magnitude of the eventual benefit of M with BV alone vs no M, an IPD meta-analysis was performed. Methods: Trials whereas mCRC pts were prospectively randomized to receive BV M or not were considered eligible. Primary end-points were PFS and OS, both from the start of induction and M. Univariate and multivariate analyses for PFS and OS were performed, with the following variables: baseline ECOG PS; age (> vs ≤ 65 years); RAS and BRAF status; LDH and CEA baseline level; RR (PR or CR vs SD) during induction; induction CT (oxa- vs iri-based); resected primary tumor; primary tumor side; synchronous vs metachronous; adjuvant treatment; number (N) of metastatic sites; liver-only disease. Results: IPD of 1,064 pts enrolled in the PRODIGE 9, AIO KRK 0207 and SAKK 41/06 trials were collected. Considering the different timing of randomization in PRODIGE 9 (at the start of induction) vs AIO KRK 0207 and SAKK 41/06 (at the start of M), IPD of pts not progressed during induction and starting M phase entered the analysis. 500 pts were included, 437 (87%) received BV M. Median PFS from induction start was 9.6 and 8.9 months in BV group vs no M group, respectively (HR 0.78; 95%CI: 0.68-0.89; p < 0.0001). At the multivariate PFS analysis, BV M, resected primary tumor, N of metastatic sites and liver-only disease were significant. No difference in terms of OS between the 2 groups was observed. Conclusion: This is the first IPD meta-analysis investigating the role of BV alone vs no M after first-line induction CT+BV in mCRC pts. Despite the significant PFS improvement in favor of BV M, the absolute benefit appears limited, and without a clear clinical relevance. On these bases, a predictive nomogram to identify pts most likely to benefit from BV M is under evaluation and will be presented during the Congress.

3552 Poster Session (Board #44), Mon, 8:00 AM-11:00 AM
Blood-based genomic profiling of cell-free DNA (cfDNA) to identify metastasitability instability (Msi-H), tumor mutational burden (TMB) and Wnt/B-Catenin pathway alterations in patients with gastrointestinal (GI) tract cancers. First Author: James Isaacs, Duke University, Durham, NC

Background: MSI-H cancers are responsive to immune checkpoint blockade (ICB), but nearly half of all patients experience primary or early treatment resistance. Activation of the WNT/B-Catenin pathway can lead to immune resistance and may drive resistance to ICB. Methods: 12 patients had stage III (N = 1) or IV (N = 11) MSI-H GI tract (small bowel, colon, or rectal cancer). Blood samples were obtained after (N = 5) or during (N = 5) ICB. 2 patients did not receive ICB. Blood samples from 8 patients with microsatellite stable (MSS) metastatic colorectal cancer were included as controls. The Guardant Health (Redwood City, CA) Omni 2.0 mb panel was used to analyze cfDNA. We analyzed MSI-H status, TMB, and mutations within the WNT/B-Catenin pathway, including APC, RNF43 and CTNNB1. Results: Of 12 patients with MSI-H GI cancers, 1 sample failed enrichment due to hemolysis. MSI-H was not detected in 2 patients with a history of MSI-H in tissue; however these patients had a complete response to ICB at the time of blood collection. The Omni panel identified MSI-H in the remaining 9 patients with MSI-H disease in tissue. Among 8 control patients with MSS disease in tissue, MSI-H was not detected. Median TMB (mutations/Mb) was greater for MSI-H specimens (109; range 30-807) than for MSS specimens (13; range 6-24). All 8 patients with MSS GI cancers were identified to have APC mutations, and none were found to have CTNNB1 or RNF43 mutations. Of 9 evaluable MSI-H GI cancers, 2 had APC mutations alone. The remaining 7 carried RNF43 mutations (G659fs). All patients with RNF43 mutations were found to have disease progression while on ICB. Among these 7 patients with RNF43 mutations, 6 had additional mutations in APC or CTNNB1. Conclusions: Blood based genomic profiling can identify MSI-H cancers. Patients with MSI-H cancers resistant to ICB in this cohort have mutations in RNF43 as well as additional mutations in APC or CTNNB1, suggesting that co-activation of the WNT/B-Catenin pathway may be biologically important. Further study of the role of WNT/B-Catenin pathway activation in ICB resistance will be pursued using tumor tissue from this cohort.

3551 Poster Session (Board #43), Mon, 8:00 AM-11:00 AM
Modulation of autophagy: A phase II study of vorinostat (VOR) plus hydroxychloroquine (HCQ) or regorafenib (RGF) in chemo-refractory metastatic colorectal cancer (mCRC). First Author: Sukeshi Patel Arora, UT Health San Antonio Cancer Center, San Antonio, TX

Background: Agents targeting the angiogenic pathway have been a cornerstone therapy in mCRC. In chemo-refractory mCRC, RGF, an oral multikinase inhibitor with considerable angiogenic inhibition, has shown modest effects on survival. We reported that autophagy modulation using the autophagy inhibitor, HCQ, enhances the anti-tumor activity of the histone deacetylase inhibitor, VOR, via ubiquitin-protein accumulation in CRC. A phase 1b study confirmed VOR/HCQ is active and tolerated in refractory mCRC. We conducted a prospective randomized study to evaluate efficacy of VOR/HCQ vs RGF in mCRC patients (NCT2316340) and report a planned interim analysis. Methods: Randomized, controlled trial of VOR 400 mg and HCQ 600 mg PO daily vs RGF 160 mg PO daily (3 weeks on, 1 week off), Q4weeks, in advanced CRC patients. Crossover was optional after first progression. A total of 76 patients were planned. Primary endpoint: mPFS. Secondary endpoints: mOS; adverse events (NCI-CTCAE v3.0); PD analysis: 27-plex Human Cytokine Array, NGS analysis (Guardant Health) on cell-free, cfDNA. Results: At interim analysis, n = 42 patients enrolled from 2/2015-10/2017: n = 20 VOR/HCQ (5 crossed to RGF); n = 22 RGF (13 crossed to VOR/HCQ). 38 patients evaluable (at least 1 cycle completed). Median age 58.4, 40% Nv vs 60% H, mPFS on 0.90 mo VOR/HCQ vs 4.35 mo RGF [p = 0.032, HR: 2.277l, mOS: 6.77 mo VOR/HCQ vs 7.23 mo RGF [p = 0.90, HR: 1.05]. Grade 3/4 AEs (see table). In both arms, there was trend towards decreased IL-1b, IL-2, IL-6, IL-10, TNFα, IFNγ but an increase in GM-CSF after treatment. Responders (4+ cycles) had lower baseline Max MAF versus nonresponders for both arms. In responders, there was trend toward a decrease in Max MAF at C2 and then increase at progression. Conclusions: VOR/HCQ did not improve survival when compared to RGF. VOR/HCQ has a favorable safety profile, but further planned subgroup analysis is pending to identify biomarkers of efficacy in responders. Clinical trial information: NCT2316340.

3554 Poster Session (Board #46), Mon, 8:00 AM-11:00 AM
Clinical, pathological and prognostic features of rare BRAF mutations (MTs) in metastatic colorectal cancer (mCRC): A bi-institutional retrospective analysis (REBUS study). First Author: Brunella Di Stefano, Fondazione Policlinico Universitario A. Gemelli-IRCCS-UOC Oncologia Medica, Rome, Italy

Background: Recently, 3 classes of BRAF MTs have been described. BRAF V600 MTs, which identify mCRC with poor prognostic and not benefitting from anti-EGFR drugs, belong to class 1. Class 2 and include BRAF non-V600 MTs, occurring in about 1-2% in mCRC and are associated with favorable prognosis and specific clinicopathologic features. Class 2 and 3 differ in kinase activity and sensitivity to anti-EGFR: class 2 are activated and RAS-independent; MTs; class 3 are kinase-dead and sensitive to inhibition of EGFR. This study aims to retrospectively evaluate features and prognostic role of rare BRAF non-V600 compared to BRAF V600 MTs in mCRC pts treated at 2 Italian Institutions. Methods: mCRC pts harboring BRAF MTs, assessed by means of NGS, pyrosequencing or RT-PCR, treated between Jan-13 and Dec-18 at 2 Italian Institutions, were retrospectively analyzed. Clinico-pathological and treatment characteristics and survival data were collected. Results: 55 pts bearing BRAF MTs were identified. Of those, 46% (84/180) harbored a V600E and 9 (16%) a non-V600 MT. Within the non-V600 group, 3 MTs (K601E, G469A, G469R) belonged to class 2, while 5 MTs (G466E, G466A, 2 D594G, D594N), belonged to class 3. One pt harboured a T5991 MT, whose kinase activity is unknown. Compared to BRAF V600E mCRC, BRAF non-V600 mCRC were more frequently left-sided (p =0.017) and displayed a lower grade (p =0.045). In addition, non-V600 mCRC pts had a lower tumor burden (involving one metastatic site) (p =0.026) and underwent more frequently to resection of metastases with radical intent (77.7 vs 18%; p =0.00075). mOS was significantly longer in the non-V600 compared to the V600E group (61.3 vs 20.4 m; H2: 4.11, 95%CI 1.88-9.33; p =0.05). No difference in activity and efficacy of anti-EGFR agents was observed between class 2 and 3. Conclusions: Despite the small size of our retrospective analysis, the results were consistent with previous evidences. BRAF non-V600 MTs identified a subgroup of mCRC, differing both in terms of clinicopathologic characteristics and prognosis from BRAF V600 mCRC. Interestingly, the better prognostic features allowed more frequently radical resection of metastases, positively impacting on survival.
3555  Poster Session (Board #47), Mon, 8:00 AM-11:00 AM
Randomized phase II trial of adjuvant hepatic arterial infusion (HAI) + systemic FOLFIRI +/- panitumumab (Pmab) in patients with resected RAS wild type colorectal cancer hepatic metastases (CRLM). First Author: Nancy E. Kemény, Memorial Sloan Kettering Cancer Center, New York, NY
Background: HAI therapy has improved recurrence free (RF) survival in several randomized trials after resection of CRLM. The purpose of this trial was to determine whether systemic Pmab added to adjuvant HAI + FOLFIRI in RAS WT pts increases RF at 15 months. The two arms had similar pt characteristics and toxicity, with the exception of Pmab related rash (Table). In the median follow-up 79% and 67% in +/- Pmab arms, respectively. With a median follow-up of 45 months, 3-year RFS is 65% (CL 0.45-0.78) and 42% (CL 0.24-0.57), and 3-year survival is 96% and 90% in +/- Pmab arms, respectively. Conclusions: In this trial, the addition of Pmab to HAI and SYS showed promising activity without increase in biliary toxicity and should be further investigated in a larger study. Predictive biomarkers will be presented.
Clinical trial information: NCT01312857.

3556  Poster Session (Board #48), Mon, 8:00 AM-11:00 AM
Chemotherapy rechallenge or reintroduction (CTrr), regofenib (REG) and TAS-102 for metastatic pretreated colorectal cancer (mCRC) patients (pts). A propensity score analysis of treatment beyond second-line (PROSERpINA Study). First Author: Maria Alessandra Calegari, Oncologia Medica, Fondazione Policlinico Universitario “A. Gemelli”, IRCCS, Roma, Italy
Background: The optimal treatment for mCRC beyond 2nd line is still questioned. Recently, REG and TAS-102 showed to improve survival compared to BSC. While in real-world practice CTrir is often considered in this setting, supporting evidences are limited. In absence of studies comparing all three therapies, we aimed to compare the prognostic performance of CTrir, REG and TAS-102 in mCRC treated beyond 2nd line. Methods: mCRC pts progressing at least after 2 lines of CT, treated with CTrir, REG or TAS-102 between Jan-10 and Jan-19 were considered eligible. The primary endpoint was OS; secondary endpoints were PFS and RR. Cox’s proportional hazard models for survival were estimated. A propensity score (PS) adjustment for baseline characteristics was further accomplished for survival analysis. Results: The clinical data of 341 pts (CTrir 133, REG 150, TAS-102 58) were retrospectively collected. At multivariate analysis type of treatment, ECOG PS, number of metastatic sites and treatment line independently correlated with OS (p < .001). mOS was 18.5 (95% CI, 14.3-22.7), 6 (95% CI, 5.6-9.5) and 7.6 months (95%CI, 5.6-9.5), for CTrir, REG and TAS-102 group, respectively (log-rank p < .0001). mOS was significantly longer for pts receiving CTrir than for those treated with REG/TAS-102 (15.8 vs 7.1 months; adjusted HR 1.96, 95% CI 1.44-2.66; p < .0001) at the PS analysis, adjusted for ECOG PS, number of metastatic sites and treatment line; 2-ys OS was 34% and 11.6% for CTrir and REG/TAS-102, respectively. PFS was significantly longer for pts receiving CTrir than for those treated with REG/TAS-102 (5.5 vs 3.9 months; HR 1.45, 95% CI 1.11-1.91; p = .065) at the PS analysis. Accordingly, RR was higher in pts receiving CTrir compared to REG/TAS-102 (2.3 vs 1.5; HR 1.44, 95% CI 1.11-1.91; p = .0001). Conclusions: Our analysis, although underpowered, generates the hypothesis of a superiority of CTrir in comparison to REG or TAS-102, in both efficacy and activity. Given the retrospective nature of our analysis, and the potential role of selection bias in treatment assignment, a prospective validation is mandatory.

3557  Poster Session (Board #49), Mon, 8:00 AM-11:00 AM
A phase I study of PolyPEPI1018 vaccine plus maintenance therapy in patients with metastatic colorectal cancer with a predictive biomarker (OBERTO). First Author: Joleen Marie Hubbard, Mayo Clinic, Rochester, MN
Background: The goal of this study was to evaluate the safety, tolerability and immunogenicity of a single dose of PolyPEPI1018 as an add-on to maintenance therapy in subjects with metastatic colorectal cancer (mCRC). PolyPEPI1018 is a peptide vaccine containing 12 unique epitopes derived from 7 conserved cancer tests antigens (CTAs) frequently expressed in mCRC. These epitopes were designed to be Personal EPItopes (PEPIs), i.e. predicted by our novel PEPI test to bind to at least three autologous HLA alleles and more likely to induce T-cell responses than epitopes presented by a single HLA. Methods: mCRC patients in the first line setting receiving the vaccine (dose: 0.2 mg/peptide) just after the transition to maintenance therapy with a fluoropyrimidine and bevacizumab. Vaccine-specific T-cell responses were first predicted by the PEPI test (using the patient’s complete HLA genototype and antigen expression rate) and then measured by ELISPOT after one cycle of vaccination. Results: Eleven patients were vaccinated with PolyPEPI1018. The most common adverse events were transient skin reactions (local inflammation at the site of the injections, e.g. erythema, redness and itchingness) and flu-like syndrome. No grade 3 or higher adverse events related to the vaccine occurred. Initial analysis on 4 patients demonstrated that T-cell responses were elicited by 96% of vaccine peptides. The overall percentage agreement between PEPI test-predicted and Eispot-measured CD8+ T cell responses was 71%, consistent with our retrospective analysis on 64 vaccine clinical trials involving 1,790 patients. Two of these 4 patients had unexpected tumor size reduction. Based on these encouraging results, the trial was amended to administer 3 doses of PolyPEPI1018 given 12 weeks apart. Conclusions: PolyPEPI1018 combined with maintenance therapy was safe and well-tolerated in mCRC patients. Unprecedented immune responses were induced after single dose, with broad CRC-specific T cell responses and high accuracy prediction of CD8+ T cell responses. This promising activity in mCRC patients led to a trial amendment to administer 3 doses of PolyPEPI1018 in combination with systemic therapy. Clinical trial information: NCT03391232.

3558  Poster Session (Board #50), Mon, 8:00 AM-11:00 AM
Exosomes as novel prognostic biomarker in potentially resectable colorectal cancer (mCRC) patients (pTs). First Author: Ina Valeria Zurlo, Oncologia Medica, Università Cattolica del Sacro Cuore, Rome, Italy
Background: Target therapies and new surgical strategies deeply modify the history of CCLM patients (pts). Several prognostic scoring systems have been developed but no one is able to identify pts who should be excluded from a potentially useless surgery. Currently research is committed in identifying early biomarkers able to discern pts who could benefit from an aggressive approach. Exosomes are arising as promising biomarkers in cancer. The aim of this pivotal study was to analyze the association among exosome levels during CCLM-pTs treatment, clinical outcomes and the KRAS status. Methods: We enrolled 22 pts with CCLM candidate to preoperative chemotherapy (pCT) and subsequent liver surgery. A blood sample was collected before pCT, after surgery, monthly during follow-up and at progression (PD). Exosomes were isolated by ultracentrifugation and characterized by standard method. Exosomes concentration was assessed by Bradford assay. We adopted ddPCR™ KRAS G12G13 Screening Kit to evaluate the KRAS status in exosomal DNA (e-DNA). Results: 22 CCLM pts received pCT and underwent liver surgery: 5 major hepatectomies and 17 multiple liver resections. Changes in exosomes plasma levels were found to correlate with each treatment step, resulting reduced after pCT and surgery and increased at PD, respectively (p = 0.0026). Pts with higher baseline exosome levels experimented shorter PFS than those with lower levels (p = 0.0033 HR 2.02). No association was found between exosome levels after liver surgery and disease free interval or overall survival. KRAS status on e-DNA was evaluated on 10 pts in baseline, in pCT, after surgery, and in PD samples. In 8 out of 10 pts e-DNA displayed the same mutational status than the one detected on tumor DNA. Changes in e-DNA KRAS copies were found statistically significant in pCT vs surgery and pCT vs PD (p = 0.039; p = 0.04).
Conclusions: Our study suggests a prognostic role of exosomes levels in CCLM pts. Moreover, we showed that KRAS mutational status could be monitored during the post-surgery follow-up by analyzing e-DNA. Overall, our data confirm the potential role of exosomes in liquid biopsy tool to monitor molecular changes during the treatment of CCLM pts.
Gender and survival benefit from initial irinotecan in metastatic colorectal cancer: Analysis of the XELAVIRI (AI01KR0110) study. First Author: Katrin Heinrich, Department of Medicine III, University Hospital, Munich, Germany

Background: XELAVIRI compared initial vs sequential irinotecan (iri) in combination with fluoropyrimidine (FP) plus bevacizumab (bev) in patients (pts) with mCRC, trial identification: NCT01249638. In the full analysis set of the study, non-inferiority of time to failure of strategy (TFS) was not shown (primary endpoint). Pts with RAS/BRAF wildtype (wt) tumors benefitted from initial iri. Methods: The study endpoints objective response rate (ORR), progression-free survival (PFS), time to failure of strategy (TFS) as well as overall survival (OS) were evaluated in female vs. male pts as well as molecular subgroups (i.e. RAS mutational status). Interaction of treatment and gender was tested by likelihood ratio tests. Results: Of 421 patients, 281/140 were male/female. In male patients, ORR was 33.6% without and with 58.3% with initial iri (P < 0.001). PFS (HR: 0.54 (95% CI 0.42-0.69), P < 0.001) and OS (HR: 0.63 (95% CI 0.47-0.85), P = 0.002) were also significantly better with initial iri. In the subgroup analysis, this effect was especially pronounced in pts with RAS/BRAF wt tumors. In female pts, ORR was 4.3% in both arms, PFS was similar (HR: 1.09 (95% CI 0.76-1.55), P = 0.65) without and with initial iri. In OS, a strong trend for inferior outcome with initial iri was seen (HR: 1.46 (95% CI 0.95-2.24), P = 0.08) that reached significance in the multivariate analysis (HR: 1.73 (95% CI 1.04-2.86, P = 0.034). Female patients with RAS/BRAF wt tumors did not benefit from initial iri (HR 1.00 (95% CI 0.46-2.10), P = 0.99) although chemotherapy and interaction of treatment and gender was seen for ORR (P = 0.018), PFS (P = 0.002) and OS (P = 0.001). There were some trends for more pronounced toxicities in female pts treated with Irinotecan. Conclusions: This unplanned exploratory analysis suggests that gender might interact with efficacy of irinotecan when used in the context of FP and bev. While especially male RAS wild-type patients benefitted from initial iri when used in the context of FP and bev, no survival benefit was observed in female pts treated with Irinotecan. While especially male RAS wild-type patients benefitted from initial iri when used in the context of FP and bev, no survival benefit was observed in female pts treated with Irinotecan.

Predictive factors for early mortality after initiation of regorafenib or trifluridine/tipiracil in refractory metastatic colorectal cancer. First Author: Toshiki Masuzumi, Aichi Cancer Center Hospital, Nagoya, Japan

Background: Regorafenib (REG) and trifluridine/tipiracil (FTD/TPI) have been recognized as standard treatments for patients (pts) with refractory metastatic colorectal cancer (mCRC). Because these drugs have limits on efficacy benefit for some pts, we are necessary to select pts who may be better not to receive REG or FTD/TPI. However, no reports are available on how to predict pts with early mortality after initiation of these drugs. Methods: We retrospectively evaluated pts with mCRC who were registered in a multicenter observational study (the REGOTAS study). The main inclusion criteria were ECOG PS of 0–2, refractory or intolerant to fluoropyrimidines, oxaliplatin, irinotecan, and anti-VEGF and anti-EGFR therapy (if KRAS wild type), and no prior use of REG or FTD/TPI. Predictive factors for early mortality (<12 weeks from initiation of REG or FTD/TPI) were evaluated by multivariate analysis for survival with all variables with P values of <0.05 from the univariate analysis, using the Cox proportional hazards model. In this analysis, the pts who lived at first 15 weeks were defined as censored case. Results: A total of 523 pts (REG, 212; FTD/TPI, 311) were eligible. Predictive factors for early mortality without propensity matching were poor tumor-resectability (HR: 1.56 (95% CI 1.19-2.04), P = 0.002), the lack of meaningful patient-facing clinical trial matching, making ad-
Background: Colorectal cancer (CRC) incidence in patients younger than 50 years of age is steadily rising by 2% annually. Early-onset CRC usually presents with more aggressive features; however, data on prognosis are widely conflicting. Clinicians may hold an age-related bias in treating younger patients, but this proclivity and its effects have not been quantified.

Methods: Patients with a history of metastatic CRC who consented to a departmental chart review protocol were collected between 2014 and 2018 at Massachusetts General Hospital. The cohort was divided into two groups based on age at initial diagnosis: < 50 and ≥ 50. Data were gathered on treatments and clinicopathological features. A log-rank test compared survival from the diagnosis of metastatic disease between age groups. The distributions of clinicopathological features were compared using Wilcoxon rank sum tests. Results: 464 metastatic CRC patients were identified. 155 patients (33%) were < 50 (median age 43, 49% female) and 309 patients (67%) were ≥50 (median age 61, 45% female). Sex did not significantly differ between the two groups (p = 0.45). Patients < 50 received more lines of therapy after metastatic diagnosis than patients ≥50 (p = 0.002). Younger patients also received more resections of distant metastases (mean 0.62 v. 0.48; p = 0.01). A higher rate of enrollment in clinical trials for patients < 50 approached significance (p = 0.06). Even so, patients < 50 did not see a significant survival benefit over older patients (2-year survival for patients < 50 prior to diagnosis vs. ≥ 50 prior to diagnosis was 26% vs. 17%, respectively; p = 0.33). In patients < 50 who had a lower proportion of right-sided tumors (p = 0.0002) and BRAF mutations (p = 0.0009). There was no difference in MSI status (p = 0.28), RAS mutational status (p = 0.40), mucinous features (p = 0.53), or signet ring features (p = 0.26).

Conclusions: Overall survival in patients < 50 is lower compared to patients ≥ 50 receiving more aggressive therapy. Further study is warranted to better understand these differences. Potential areas of interest include performance status, age-related treatment bias, and biological factors.

**3565**

**Poster Session (Board #57), Mon, 8:00 AM-11:00 AM**

**Survival according to mutations in BRAF, KRAS, or microsatellite instability (MSI-H) after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal metastases from colorectal cancer.**

First Author: Stein G Larsen, Section for Surgical Oncology, Norwegian Radium Hospital; Department of Gastroenterological Surgery, Oslo University Hospital, Oslo, Norway

Background: Patients with metastatic colorectal cancer (mCRC) and mutations in BRAF V600E (mutBRAF) or KRAS (mutKRAS) have a worse prognosis after liver or lung surgery/ablation, whereas the impact of microsatellite instability (MSI-H) has not been well studied. Few patients with mutBRAF receive liver or lung surgery (1-4%), whereas mutBRAF is present in 5-12% of mCRC trial patients and in up to 20% of the general mCRC population. The frequency and prognostic role of mutBRAF, mutKRAS, and MSI has not been well studied after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal metastases from colorectal cancer. Methods: The Norwegian Radium Hospital is the only center offering CRS and HIPEC in Norway. From 2004 to 2015 257 patients with history proven peritoneal metastasis from colorectal cancer, appendiceal cancer excluded, were consecutively enrolled. Molecular analyses of KRAS, BRAF and MSS/MSI in mutBRAF were done. Fourteen patients were excluded due to missing tumour blocks (7), unsuccessful analysis (4) and other malignant disease (1). Results: 180 of 243 patients obtained complete cytoreductive surgery and received HIPEC for 90 minutes with Mitomycin C (45-70mg). Median survival for the 180 patients was 47 months and 5-year survival rate 40.1%. Median disease-free survival was 10 months. mutBRAF was found in 23.4% of cases, mutKRAS 35.1% and double-wild-type 41.5%, mutBRAF with MSS was found in 16.4%, mutBRAF with MSI-H in 7.0%. 3-year disease free survival (DFS) and median overall survival (OS) was 50.5% and 59 months with mutBRAF with MSI-H, significantly higher compared to 24.2% and 30 months in patients with double wild type, 13.2 % and 41 months in mutKRAS and 17.9% and 22 months in mutBRAF with MSS. Conclusions: A surprisingly high frequency of mutBRAF was seen in mCRC patients after CRS and HIPEC for peritoneal metastases. mutBRAF and MSI-H had a significantly better DFS and OS after CRS and HIPEC. DFS for patients with mutBRAF and MSS was numerically lower but not statistically different from patients with mutKRAS or double wild type.

**3566**

**Poster Session (Board #58), Mon, 8:00 AM-11:00 AM**

**Circulating tumor DNA dynamics, serial testing and evolution on treatment in 322 colorectal cancer patients.**

First Author: Pashtoon Murtaza Kasi, Mayo Clinic, Jacksonville, FL

Background: According to the American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP) joint review on circulating tumor DNA (ctDNA) issued in March 2018, widespread use of ctDNA assays in most patients with advanced cancer is still an area of ongoing research. However, multiple studies thereafter published and/or presented support its use in patients with metastatic colorectal cancer (CRC). This has led to several institutions adopting it as ‘clinical practice’. The aim of this study is to report on our institution’s adoption of ctDNA testing for every patient at the time of diagnosis and/or time of progression. Methods: We report on results of 322 CRC patients with 607 ctDNA tests at our center from January 2017 to February 2019 using a commercially available platform (Guardant360). Results: Among 322 patients of our cohort, a total of 607 ctDNA tests were done (Table). 127 (39.4%) of these tests were serial analyses. In the CRC patients who had serial testing, at progression, mechanisms of resistance included acquisition of KRAS, NRAS, EGFR mutations; and HER2- and MET-amplifications. The subclonal mutations were noted to disappear when the selective inhibition was stopped. This was seen in patients on targeted therapies/biologics rather than chemotherapy. This was of value in treatment modification, clinical trial selection and/or monitoring of disease progression in these patients. Conclusions: While ctDNA testing may not be ready for prime time in all advanced cancers, it is increasingly being adopted in practice for especially metastatic CRC. Of particular value is the serial ctDNA testing in the RAS/RAF wildtype subset and now BRAF V600E mutant CRC on anti-EGFR based therapies.

<table>
<thead>
<tr>
<th>Total number of patients</th>
<th>322</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of tests</td>
<td>607</td>
</tr>
<tr>
<td>Number of serial analyses</td>
<td>127</td>
</tr>
<tr>
<td>RAS/RAF wild-type</td>
<td>214 (66.4%)</td>
</tr>
<tr>
<td>Number of RAS mutations</td>
<td>83 (25.8%)</td>
</tr>
<tr>
<td>Number of V600E BRAF mutations</td>
<td>18 (5.6%)</td>
</tr>
<tr>
<td>Number of non-V600E BRAF mutations</td>
<td>7 (2.2%)</td>
</tr>
<tr>
<td>Number of HER2 amplifications</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Number of HER2 spikes</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

*Of note, 25(7.8%) of CRC were dMMR/MSI-High in the cohort. ctDNA testing company started reporting MSI-High later in 3rd quarter of 2018.*
Neoadjuvant chemoradiotherapy (nCRT) is nowadays the standard of care for the locally advanced rectal cancer (LARC). However, there is no effective method to predict patients’ possible benefits from nCRT and monitor the response to it. Methods: Patients with locally advanced middle and low rectal cancer of stage cT3-4N0M0 or cTanyN+M0 were enrolled from August 2017 to July 2018. All patients received nCRT with long-term radiation concomitant CT sessions of 5FU/MMC at RT weeks 1 and 5. Pmab was added if the tumor did not respond. Results: Forty-five patients (male: 9 (20%); female: 36 (80%); median age: 60.1 [41.5-81]) were enrolled in 15 French centers. All patients but one completed the CRT. Median duration of CRT was 52 days [30-76]. Fourteen patients had a RT interruption because of toxicity. Most common related grade 3-4 toxicities observed were diarrhea (51.1%), hematologic (lymphopenia: 73.4%; neutropenia: 11.1%), radiation dermatitis (28.8%) and asthenia (11.1%). On patient died because of treatment-related death. Panitumumab was continued for additional 2 weeks (8 weeks of panitumumab (Pmab) combined with MMC-5FU based CRT). The overall response rate (ORR) was 90% with continuous panitumumab treatment for 8 weeks. Fourteen patients had a RT interruption because of toxicity. Most common related grade 3-4 toxicities observed were diarrhea (51.1%), hematologic (lymphopenia: 73.4%; neutropenia: 11.1%), radiation dermatitis (28.8%) and asthenia (11.1%). On patient died because of treatment-related death. Panitumumab was continued for additional 2 weeks (8 weeks of panitumumab (Pmab) combined with MMC-5FU based CRT). The overall response rate (ORR) was 90% with continuous panitumumab treatment for 8 weeks. Fourteen patients had a RT interruption because of toxicity. Most common related grade 3-4 toxicities observed were diarrhea (51.1%), hematologic (lymphopenia: 73.4%; neutropenia: 11.1%), radiation dermatitis (28.8%) and asthenia (11.1%). 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Conclusion: Panitumumab in combination with CRT for locally advanced anal canal carcinoma as neoadjuvant therapy is feasible and associated with excellent outcomes with no severe toxicity beyond grade 3.

First Author: Jiaolin Zhou, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China

Background: Young-onset colorectal cancer patients disproportionately diagnosed with advanced disease. Patient self-reported journey of symptom duration and misdiagnosis. First Author: Ronit Yarden, Colorectal Cancer Alliance, Washington, DC

Background: Colorectal cancer (CRC) is the second leading cause of cancer-related death among males and females in the US. Despite a decrease in overall incidence and mortality, there has been an alarming increase of CRC diagnosis among young adults (20-49 years old). The Colorectal Cancer Alliance launched a comprehensive survey for young-onset CRC patients and survivors via social media to track the self-reported clinicopathological, financial and quality of life experiences of this often overlooked, group. Methods: The survey was completed by 1195 living patients and survivors. The majority of participants (57%) were diagnosed between the ages of 40 and 49, 33% of patients/survivors were diagnosed between the ages 30-39 and about 10% were diagnosed before the age of 30. Only 8% of the respondents were diagnosed with Lynch syndrome although about 28% reported some family history. Results: Our survey revealed a higher proportion of the young-onset patients and survivors (71%), diagnosed with advanced stage tumors, compared with ACS report for overall CRC patients (60%). The late stage diagnosis subjected young patients to aggressive therapies and a substantial decrease in quality of life including neuropathy, anxiety, clinical depression, and sexual dysfunctions. Most respondents (63%) waited 3-12 months before visiting a doctor, with a higher proportion of females waited more than 12 months compared with males (22% vs. 15% p = 0.02). Moreover, even when visited their doctors, most patients indicated that they were initially misdiagnosed. The majority of the respondents (67%) saw at least 2 physicians, and some more than 4 physicians, prior to their diagnosis. Patients that saw 3 or more physicians prior to diagnosis were more likely to be diagnosed with advanced disease. Interestingly, half of the patients that were initially misdiagnosed also claimed they were initially misdiagnosed. Conclusions: Our survey indicates that medical professionals and young adults need to be aware of the increasing incidence of young-onset CRC, and the importance of timely screening when signs and symptoms are present, regardless of age. Yet, 50% of physicians did not explain to the patients’ family members about their elevated risk of the disease and their need for screening.

First Author: Ronit Yarden, Colorectal Cancer Alliance, Washington, DC

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Following primary chemoradiotherapy for squamous cell carcinoma of the anal canal (A-SCCa), 10% of patients have persistent cancer, and 30% develop local recurrence after initial complete response. Both persistent and recurrent A-SCCa may be amenable to salvage surgery, which typically involves intense health care resource utilization. Because only small cohorts have been reported, we synthesized the evidence for salvage surgery to gain a comprehensive understanding of outcomes. Methods: We systematically searched MEDLINE, Embase, and Cochrane Library (until October 11, 2018) for studies reporting on persistent or recurrent A-SCCa treated with salvage surgery. Quality assessment was performed using the Institute of Health Economics Quality Appraisal Checklist. Overall survival (OS) and disease-free survival (DFS) were pooled using two approaches: survival curve meta-analysis, and exact binomial likelihood random-effects model for survival probabilities. We used meta-regression, subgroup and sensitivity meta-analyses to explore sources of heterogeneity. Results: We identified 39 observational studies that included 1386 patients. Pooled 5-year OS was 45.5% (95% CI 40.6 to 49.9; 33 studies; 1308 patients) and 5-year DFS was 53.3% (95% CI 48.8 to 58.3; 24 studies; 1308 patients). Rate of treatment interruption did not differ in patients resected for recurrent (14 studies; n=295 patients) vs. persistent (n=238 patients). There was no association of OS with study year, tumor size, or resection margin at the aggregate-level. Pooled 5-year DFS was 38.3% (95% CI 31.4-43.9; 14 studies; 554 patients). Pooled 30-day complication rate of 35.3% (95% CI 25.3% to 45.8% for solid tumors; 72% patients); major complications 27.7% (95% CI 22.3-33.8), reoperations 12.7% (95% CI 8.7-18.2), and mortality 1.7% (95% CI 1.1-2.6%). Pooled perineal complications were 32.2% (95% CI 25.0-41.4). Conclusions: Salvage surgery offers 5-year OS of ~45% and DFS of ~40% for recurrent/persistent A-SCCa. Major complications and perineal wound complications are common, but postoperative mortality is rare. Presently, there are no reports of patient-reported outcomes such as quality of life after salvage surgery for A-SCCa. Comparative effectiveness studies comparing surgery to other treatments are warranted.

Factors affecting differential outcomes in the definitive treatment of anal cancer between HIV+ and HIV- patients. First Author: Matthew Susko, University of California San Francisco Medical Center, San Francisco, CA

Background: Anal cancer is an uncommon malignancy with numerous factors that influence treatment outcomes. Historically, HIV+ patients were restricted from entering clinical trials, limiting data on their outcomes to small retrospective reports. This study seeks to understand the factors related to anal cancer outcomes, specifically the differences between HIV+ and HIV- patients. Methods: Inclusion criteria was non-metastatic anal squamous cell carcinoma treated with definitive course of chemotherapy and radiation between 2005 and 2018 at a single institution. Clinical data related to baseline characteristics, treatment parameters, and post-treatment follow-up were extracted for calculation of freedom from local recurrence (FFLR) and overall survival (OS). Univariate analysis (UVA) and multivariate analysis (MVA) were done using cox proportional hazard model, and FFLR and OS were calculated using the Kaplan-Meier method. Results: During the study period, 111 patient initiated definitive treatment for anal cancer. Median age was 56.7 years (IQR: 51.4-63.5), and 47% (N=52) were HIV+. At median follow-up of 28 months, 12 and 24-month FLLR was 84.1% and 78.2% respectively, with 24-month OS of 87.3%. A demonstrated significant association between FFLR and T-stage HR 4.02 (95% CI: 2.14-7.55) p < 0.001, elapsed treatment time (median of 50 days) 1.08 (95% CI: 1.04-1.12) p < 0.001, and diagnosis to treatment start (median time of 15 weeks) 1.05 (95% CI: 1.01-1.08) p = 0.005. Additional analysis with log-rank test for FLLR demonstrated significant difference between patients taking FOLFOX or FOLFOX plus cetuximab. OS on log-rank test (p = 0.016), with pretreatment CD4 values being non-significant. Conclusions: This study represents the largest single institution report on HIV positive patients treated for anal cancer. We identified factors associated with local recurrence or overall survival between HIV+ and HIV- patients was elucidated; however, HIV+ patients with lower pretreatment CD4 counts had worse OS. The most significant predictors of local recurrence were advanced T-stage, increased time from diagnosis to treatment initiation, and prolonged treatment time.
Prognosis and chemosensitivity of non-V600E BRAF mutations in metastatic colorectal carcinoma (mCRC). An AGEO French multicenter retrospective cohort. First Author: Aline Derosiere, Amiens University Hospital, Amiens, France

Background: BRAF mutations are present in 5-15% of mCRC. V600E BRAF mutations account for ~80% of cases and are mostly found in right-sided tumors. Non-V600E BRAF mutations are rare (~2% of mCRC), mostly left-sided. Although BRAF V600E mutations are associated with a dismal prognosis, some studies suggest that non-V600E BRAF mutations may be associated with a favorable outcome. The chemosensitivity of non-V600E BRAF-mutated mCRC has never been studied. Methods: From 2017 to 2018, all consecutive patients (pts) with non-V600E BRAF-mutated mCRC (next generation sequencing) treated in the participating centers were included. Survival analyses were performed using Kaplan-Meier method and LogRank test. Results: A total of 108 pts in 34 centers in France were included between October 2017 and August 2018 (median age, 66 years [range, 58-77]; ECOG performance status 0-1, 86%). The primary was mostly left-sided (66%). Main metastatic sites were the liver (73%), lungs (33%), lymph nodes (39%) and peritoneum (26%). D594 (34%), G469 (15%), K601 (31%), N581 (7%) and L597 (7%) were the most frequent mutations. A concomitant RAS mutation was found in 22% of pts. Microsatellite instability (MSI) was found in 3/67 pts (4.5%). First-line chemotherapy (CTx) (n = 69) efficacy was overall response rate/disease control rate 49%/77% (anti-EGFR-containing CTx [n = 20], 75%/85%; antiangiogenic-containing CTx [n = 22], 75%/73%). Median overall survival (mOS) was 25.6 months (95% CI: 17.1-43.8) overall; it was 8.0 months with best supportive care alone (n = 10), 16.0 months with palliative CTx alone (n = 63), and attained 105.1 months with curative-intent management of metastases (n = 35). mOS did not differ according to sidedness (p = 0.12), type of mutation (p = 0.52), or its functional impact on BRAF (p = 0.19). Conclusions: Non-V600E BRAF-mutated mCRC retain sensitivity to CTx + biologics and harbor a good prognosis (especially when amenable to curative-intent surgery), regardless of the type of mutation and its impact on BRAF kinase function. Contrarily to BRAF V600E mutations, non-V600E mutations may occur along with RAS mutations, but uncommonly with MSI.

Association of TGF-β expression with intratumoral infiltration of cytotoxic T lymphocytes in patients with metastatic colorectal carcinoma. First Author: Amir Mehrvaer Sarshekeh, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Transforming growth factor-β pathway (TGF-β) has an established role in promoting growth, invasion, metastasis as well as epithelial to mesenchymal (EMT) transition. Among 4 different described molecular subtypes of colorectal cancer (CRC), consensus molecular subtype 4 (CMS4) comprises to 25% of CRC pts, distinguished by activation of this pathway, and is associated with higher relapse rate and poor prognosis. Recently, it has also been proposed that TGF-β activation drives immune evasion in murine models, but these findings have not been clinically validated. Methods: Using multi-gene RNA expression profiling, fresh-frozen paraffin-embedded samples of 35 patients with CRC were analyzed to determine TGF-β and EMT expression levels. Multiplexed IHC staining was performed on FFPE tumor blocks by using the Opal 7-Color fIHC Kit and the stained slides were scanned by a Vectra multispectral microscope (PerkinElmer) to measure infiltration of immune cells (i.e., T lymphocytes, cytotoxic T lymphocytes (CTL), T cell antigen-experienced, macrophages, etc.) in the tumor, stroma, and both components. TGF-β and EMT expression levels – as continuous variables - were compared with the infiltration of various immune cells using Spearman’s rank correlation analysis. Results: Among 35 pts, 28 pts had non-CMS1/MSS CRC. TGF-β RNA expression in the tumor microenvironment of these samples was inversely associated with the infiltration of CTL into the tumor (r = -0.43, p = 0.022). In contrast, there was no association of TGF-β with non-cytotoxic T-cells or macrophage infiltration. The tumor and stromal CTL infiltration differed substantially by CMS (p = 0.04, p = 0.02, respectively) with tumor infiltration lowest in CMS4 (n = 7). Consistent with this, EMT gene signature, which includes TGF-β expression, showed a similar inverse correlation with CTL infiltration (r = -0.48, p = 0.009). Conclusions: TGF-β and EMT gene signatures have important roles in the exclusion of CTL in the tumor microenvironment of CRC pts. Inhibiting TGF-β pathway may potentially increase the intratumoral infiltration of CTL, which is a necessary (but not sufficient) step for immunotherapeutic response in MSS CRC. Clinical trials evaluating this hypothesis are currently ongoing (NCT03436563).

High incidence of advanced stage cancer and prolonged rectal bleeding history before diagnosis in young-onset patients with colorectal cancer. First Author: Gurprataap Singh Sandhu, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: In contrast to the older population, the incidence of colorectal cancer (CRC) in younger patients (aged < 50 years) has been increasing in the last three decades. Younger patients tend to present with more advanced disease, thought to be in part related to lack of routine screening colonoscopies. The goal of this study was to examine characteristics of young-onset CRC and potentially identify factors that may aid in earlier diagnosis and treatment. Methods: We collected data for patients available through the University of Colorado Cancer Center Cancer Registry. Inclusion criteria included: 1) Diagnosis of colon or rectal cancer between the years 2012-2018 and 2) age at diagnosis of less than 50 years. Pertinent data including baseline characteristics, clinical presentation, family history, pathology, molecular testing, staging, and treatment were collected. Results: 211 patients with young-onset CRC were available for review. Mean age at diagnosis was 42.4 years and 55.5% were males. A total of 42.1% had rectal cancer and a majority of the colon cancer diagnoses had left-sided tumors (66%). Regarding clinical presentation, 52.2% presented with rectal bleeding prior to diagnosis. Of those who presented with rectal bleeding, the average time from the onset of bleeding to diagnosis was 271.17 days. 42.9% of young-onset CRC were stage IV at the time of initial diagnosis. Evaluation of the pathology specimens showed that 89.6% were adenocarcinomas and 63.5% were grade 2 or higher. At diagnosis, the mean BMI was 26.6 and the mean CEA was 135.5. A total of 72.5% of young-onset patients had a positive family history of any cancer. KRAS or NRAS mutations were present in 49.6% of patients, BRAF V600E mutations were present in 3.8%, and 10.8% were MSI-H. Conclusions: Prolonged rectal bleeding history prior to diagnosis was noted in a significant proportion of young-onset patients with colorectal cancer. Patients and primary care physicians should be made aware of this finding in order to facilitate timely referral for colonoscopy which may lead to earlier diagnosis, less advanced disease at diagnosis, and improved outcomes.

Dissection of the lateral lymph nodes with short axis of ≥ 5 mm affects the prognosis in rectal cancer patients: A central role of 73R BRAF mutation on magnetic resonance images. First Author: Koya Hida, Kyoto University, Kyoto, Japan

Background: The usefulness of lateral lymph node dissection (LLND) for lower rectal cancer has been discussed. Concerning relapse-free survival (RFS), in the JCOG0212 trial, the non-inferiority of avoiding LLND for rectal cancer without LLN enlargement of ≥ 10 mm was not shown; however, the superiority of LLND was also not demonstrated. Methods: To examine whether the difference in dissection effect could be demonstrated by the size of LLN, magnetic resonance imaging (MRI) for the central review of pre-registered patients with stages III/IV lower rectal cancer below the peritoneal reflection was performed, and the prognosis of the patients were prospectively investigated as a cohort. The relationship between LLND and RFS was also evaluated. Results: MR images of 738 cases (mean distance from anal verge: 4.5 cm) were evaluated. Twenty patients with LLN enlargement of ≥10 mm were excluded from the analysis. Overall, of 718 patients, 310 did not undergo LLND (non-LLND group), whereas the other 408 underwent LLND (LLND group). The lymph node sizes of ≥5 mm were observed in 10.0% and 21.1% of patients in the non-LLND and LLND groups, respectively. Although there was some bias in the background characteristics of the two groups (non-LLND vs. LLND); median age 66 vs. 61 years; laparoscopic surgery 64.2% vs. 17.9%; preoperative treatment 39.4% vs. 27.9%; circumferential resection margin evaluated by MRI 37.3% vs. 49.9%; and postoperative complications 33.2% vs. 44.4%), almost no difference in the 5-year RFS was observed (63.4% vs. 67.5%). The LLND group had significantly more favorable with ≥5 mm LLN (non-LLND 51.6% vs. LLND 69.0% P = 0.023) than with non-LLND (P = 0.001). Almost no difference in the 5-year RFS was observed (9.6% vs. 10.8%). Conclusions: Oncological benefit of LLND was suggested in patients with enlarged lateral nodes on MRI using a large cohort of clinical stage II/III lower rectal cancer.
Background: BRAF mutations (mts) portend poor prognosis in mCRC and patients (pts) may die before ascertainment. Since 2014, Vancouver Coastal Health (VCH) has performed reflex hereditary screening of CRCs with BRAF and mismatch repair (MMR) immunohistochemistry (IHC). We evaluated this BRAF mCRC population-based cohort (BRAF-pop) to establish the true prognosis of BRAF mts in mCRC pts: We reviewed all mCRCs from VCH between 4/2014 and 12/2018. BRAF by IHC (VE1 antibody). Overall survival (OS) from stage IV diagnosis was compared to mCRCs with next generation sequencing (NGS) determined BRAF mts (BRAF-V600E) from BC Cancer & MD Anderson. BRAF-V600E OS did not differ by center (p = 0.77). Results: See table for BRAF cohort baseline characteristic comparison. BRAF-pop pts had worse OS than BRAF-NGS pts (HR 2.5, 95% CI 1.6 – 3.9, P < 0.0001). Median OS for all BRAF mt pts was 17.9 mos. Both groups had worse OS than wild type pts (P < 0.001). 52 (81%) of BRAF-pop pts were referred to oncology, 40 (63%) received chemotherapy, and 12 (19%) had NGS testing. BRAF-pop pts who had NGS testing with BRAF mts had OS comparable to other BRAF-pop pts (P = 0.89) and better OS than BRAF-NGS pts that never had NGS testing (HR 0.37, 95% CI 0.18-0.76, P = 0.030). Pts with BRAF mts and MMR deficiency (dMMR) (n = 20) had worse OS than MMR proficiency (pMMR, n = 202) (1.6, 95% CI 1.0-2.5, P = 0.011). This was driven by BRAF DMMR-pmmR (HR 1.9, 95% CI 0.9-4.0, P = 0.036) as no difference was seen by MMR in BRAF-pMMR pts (HR 1.3, 95% CI 0.8-2.2, P = 0.30). Conclusions: Current estimates of prognosis for mCRC with BRAF mts likely underestimate its impact due to referral bias for NGS testing; BRAF mts with dMMR are associated with worse prognosis than pMMR. This appears driven by BRAF-pop pts.

**3580**

**Poster Session (Board #72), Mon, 8:00 AM-11:00 AM**

Retrospective analysis of overall survival (OS) by subsequent therapy in patients (pts) with RAS wild-type (wt) metastatic colorectal cancer (mCRC) receiving cetuximab + irinotecan as a second-line (2L) therapy in pts with EGFR-detectable mCRC. A retrospective analysis in the EPIC RAS wt population showed improved overall response rate (29.4% vs. 5.0%) and progression-free survival (5.4 vs. 2.6 mo) upon the addition of cetuximab to irinotecan. Median OS (mOS) was similar in both treatment arms, possibly due to differences in subsequent therapies. We present OS by post-study therapy in the RAS wt population. Methods: 1298 RAS-unselected pts were enrolled from May 2003 to February 2006. The primary endpoint was OS. RAS status was determined retrospectively in 2018 from existing DNA samples using BEAMing technology, wt status was defined as having a sum of mutated RAS allele frequencies of ≤5%, with all relevant alleles being analyzable. Results: Among the 452 pts with RAS wt mCRC, 231 received cetuximab + irinotecan and 221 received irinotecan. Baseline characteristics were similar in both arms. OS data by post-study therapy are summarized in the Table. No new or unexpected safety signals were observed. Conclusions: Post-study cetuximab was associated with improved OS in both treatment arms compared with post-study therapy without cetuximab and no subsequent therapy, suggesting that cetuximab-based therapy may be suitable as a standard treatment for pts with RAS wt mCRC in the rechallenge setting. Study limitations include a potential bias due to the differences in proportion of subsequent therapies with and without cetuximab arms between (almost) 50% of pts in the irinotecan arm received post-study cetuximab) as well as the likelihood for pts who live longer to receive cetuximab in any subsequent therapy line.

**3582**

**Poster Session (Board #74), Mon, 8:00 AM-11:00 AM**

Germline multigene panel testing in colorectal cancer: Precision therapy and clinical management implications. First Author: Edward D. Esplin, Invitae, San Francisco, CA

Background: Recent studies suggest that the prevalence of abnormalities in homologous recombination deficiency (HRD) genes and other cancer genes not traditionally associated with colorectal cancer (CRC) may be more common in patients with CRC than previously appreciated. Herein, we investigate the efficacy of comprehensive multigene panels in patients with CRC to identify candidates for colorectal cancer (CRC) germline testing. Methods: This study has identified a relationship between Fnr and cancer pain in CRC patients. We investigated the associations between pre-treatment Fnr and cancer pain in CRC patients. We reviewed all mCRCs from VCH between 4/2014 and 5/2018 for patients. We investigated the associations between pre-treatment Fnr and cancer pain in CRC patients. When a comprehensive multigene panel was utilized P/LP variants in 2101 of 9669 pts (21%), 1838 (19%) pts when MUTYH heterozygous. Conclusions: DNA sequencing and exon-level copy number analysis were performed in over 9000 patients (pts) referred because of personal history of colon cancer between 2013 and 2018 at a commercial diagnostic laboratory. The genes required varied but consistently included 14 genes on a hereditary CRC panel; the patient data were de-identified and further analyzed for all 83 genes on a large hereditary cancer syndrome panel under an IRB-approved protocol. Results: Pathogenic/likely pathogenic (P/LP) findings were identified in 2101 of 9669 pts (21%), 1838 (19%) pts when MUTYH heterozygotes are excluded. When restricted to the Lynch syndrome (LS) genes, only 9% of patients had a P/LP finding, which increased to 15% of patients when 19 guidelines-based CRC genes were assessed. 137 pts (1.4%) had two or more P/LP variants. P/LP variants were in MLH1, MSH2, MSH6, PMS2, CHEK2, APC, MUTYH, BRCA2, ATM, BRCA1, PALB2, RAD50, BRF1, TP53, EPCAM, among others, of which 1.4% were BRCA1/2. When a comprehensive multigene panel was utilized P/LP variants in genes with known therapeutic implications, such as in HRD and mismatch repair deficiency (MMRD), were detected in 1408 (14%) of patients, and 1670 (17%) had P/LP variants in genes with established clinical management guidelines. Conclusions: This study suggests that 1 in 5 patients with CRC harbors actionable germline variants, up to one-half of which remain undetected when only LS genes are tested. Comprehensive panel testing identified candidates for precision treatment and established management recommendations, and have clinical implications for both pts and their at-risk family members.
Is the predictive and prognostic impact of sporadic and familial microsatellite instable stage III colon cancer different? A pooled analysis of the PETACC8 and NCTCG14718 (Alliance) trials.

**First Author:** Aziz Zaanan, Hospital Européen Georges Pompidou, Paris, France

**Background:** The Microsatellite instability (MSI) or deficient mismatch repair (dMMR) phenotype is usually taken as a single biological entity whereas no data are available concerning prognosis and response to chemotherapy between sporadic and familial dMMR cases.

**Methods:** Resected KRAS exon 2 wild-type (WT) tumor stage III colon cancers (N = 4596) from patients (pts) randomly assigned to FOLFOX +/- cetuximab in two adjuvant large phase III trials were prospectively analyzed for MSI status and dMMR mechanism (sporadic vs familial). Stratified Cox models were used to assess prognostic and predictive values of dMMR mechanism by treatment arms, adjusting for age, gender, tumor grade, EGCG PS, pT/PIp stage and primary tumor location.

**Results:** Among dMMR patients with complete data for dMMR mechanism analysis (N = 354), there were 255 (72%) sporadic (BRAF mutated or WT with MLH1 methylation and 99 (28%) familial (loss of MS2H or MS6H, or loss MLH1 with BRAF WT and unmethylated MLH1) cases. A large proportion of dMMR sporadic cases were mutated for BRAF (n = 200; 80%). In pts treated with FOLFOX, the disease-free survival (DFS) was not statistically different by dMMR mechanism, while for pts treated with FOLFOX + cetuximab, the sporadic cases did worse than familial cases (DFS; adjusted (adj) HR, 2.69; 95% CI, 1.02-7.08; P = 0.04). Considering the predictive value, a deleterious effect of adding cetuximab to FOLFOX was observed in sporadic (adjHR, 1.68; 95% CI, 1.01-2.79; P = 0.03) and not in familial dMMR pts (interaction P value regarding treatment effect = 0.03). Furthermore, a non-significant trend to a deleterious effect of adding cetuximab to FOLFOX was observed in BRAF mutant (HR: adj, 1.66; 95% CI, 0.95-2.52; P = 0.07) but not in BRAF WT pts. Conclusions: The additional benefit of cetuximab to FOLFOX was associated with reduced DFS in patients with sporadic dMMR cases. Further studies including the methylation status of the CIMP are needed to validate these results.

Clinical trial information: NCT00265811 and NCT00079274.

**Conclusions:** In unresectable metastatic colorectal cancer (mCRC) patients receiving oxaliplatin-containing regimen. In unresectable mCRC patients, mutations in APC were associated with poorer outcomes; absence of an APC alteration or the occurrence of other WT pathway alterations was associated with shorter survival.

**Methods:** Patients with unresectable mCRC treated at Memorial Sloan Kettering with genomic tumor profiling between 2014 and 2017 were included. Patients who underwent upfront resection were excluded. Clinical information was retrieved from electronic medical records, and we evaluated associations between genomic profiles with progression free survival (PFS) on first-line chemotherapy and overall survival (OS). Categorical data were analyzed by Fisher exact test and time-to-event data were analyzed by Cox proportional hazards models. Results: Of 1453 mCRCs profiled in this period, 471 patients met the study criteria. Median age was 59 years (range, 18 to 95), and 73% of patients were stage IV at diagnosis. Most tumors (91%) were microsatellite stable (MSS). The most frequent first-line regimen was FOLFOX +/- bevacizumab (66%). Among MSS patients treated with oxaliplatin-containing regimens (n = 305), 7% harbored alterations in genes associated with DNA damage response (DDR) (BRCA1, BRCA2, ATM, PALB2). DDR gene alterations were not associated with PFS (P = 0.94) nor were different quartiles of large-scale transitions (P = 0.54). Genomic alterations that significantly varied by duration of response included BRAF (16%, 10%, and 5% for PFS < 6 months, 6-12 months, and > 12 months, respectively) and APC (62%, 74%, and 80% for PFS < 6 months, 6-12 months, and > 12 months, respectively). APC mutation, single or dual, was associated with significantly longer PFS (HR 0.67) and OS (HR 0.59) in multivariate analysis versus no WT pathway alteration or alterations in other WNT pathway genes (HRF43, AXIN2, CTNNB1).

**Conclusions:** In unresectable mCRC patients, mutations in APC were associated with better outcomes; absence of an APC alteration or the occurrence of other WT pathway alterations was associated with shorter survival. Genomic alterations in DDR genes were not associated with outcomes. mCRCs with MAPK3/12 associated with prognosis.
3587 Poster Session (Board #79), Mon, 8:00 AM-11:00 AM
Identifying anti-EGFR (EGFRi) response subgroups using evidence of ctDNA selective pressure. First Author: Christine Mengederich, Parshaugan, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: Metastatic colorectal cancers (mCRC) that respond to EGFRi display a robust circulating tumor DNA (ctDNA) signature that reflects selective pressure and clonal evolution. Conversely, non-responding tumors do not exhibit this signature. On this basis, we developed a novel method that defines EGFRi sensitivity with improved biological confidence with fewer patients (pts), and does not rely on clinical trial outcomes where responses may be confounded by concurrent chemotherapy. We used this method to further elucidate the association of several features that have been previously reported to be associated with EGFRi resistance, namely tumor sidedness, BRAF, PIK3CA, or ERBB2 (HER2) MTs, and the absence of APC/TP53–.

Methods: We analyzed 112 pts with baseline tissue based RAS/PIK3CA mCRC who had progressed following EGFRi, and with plasma samples available for ctDNA sequencing using a blood based NGS assay. Using our previously validated EGFRi exposure signature, we identified pts with evidence of selective pressure. Results: Pre EGFRi ctDNA found 37% and 33% of pts with left sided and transverse tumors displayed evidence of selective pressure, respectively. 0 pts with right sided tumors displayed evidence of selective pressure; p = 0.01. Similarly, BRAF/VEGFOEAT– displayed no evidence of selective pressure vs 30% of WT pts; in contrast, selective pressure was evident in pts with PIK3CA– and ERBB2– and pts with absence of APC/TP53– (42% vs 28%, 67% vs 28%, 24% vs 43%, respectively for MT vs WT, p = NS for all). BRAF, PIK3CA, ERBB2 and APC/TP53 MT were present in 4/117, 12/108, 3/118 and 30/91 pts, respectively. ctDNA shedding was similar for all subgroups, as was time from previous EGFRi, indicating that these factors were not confounders. Conclusions: Consistent with prior large randomized studies, no pts with right sided tumors or BRAF– had evidence of EGFRi benefit, and benefit was not related to presence of PIK3CA/ERBB2– or absence of APC/TP53– had evidence of EGFRi selective pressure, confirming that these are not absolute predictors of EGFRi resistance and suggesting a subset of these pts were deriving benefit from EGFR inhibition. This plasma based approach has the potential to more efficiently evaluate biomarkers of targeted therapy in the future without reliance on large randomized datasets.

3588 Poster Session (Board #80), Mon, 8:00 AM-11:00 AM
Molecular landscape of colorectal cancers harboring R-spondin fusions. First Author: Andreas Seeber, Department of Internal Medicine V (Hematology and Medical Oncology), Innsbruck Medical University, Innsbruck, Austria

Background: Gene fusions involving R-spondin (RSPO) family members have been shown to drive Wnt-dependent tumor initiation in colorectal cancer (CRC). Therapies targeting Wnt pathway are being actively investigated for tumors harboring RSPO2/3 fusions. Here we set out to characterize the molecular features of CRC with and without RSPO fusions to gain insight into potential rationale combination therapy strategies. Methods: Tumor DNA sequencing of 592 genes (NextSeq, Illumina), RNA sequencing of 53 gene fusions (ArcherDxPlex) and immunohistochemistry for PD-L1 on tumor cells (SP142) were tested on CRC tumors at Caris Life Sciences, Phoenix, AZ. Molecular profiles of RSPO2/3 positive (pos) were compared with negative (neg) tumors, Fisher-Exact was used for comparative analysis.

Results: A total of 1356 CRC samples were analyzed. RSPO3 and RSPO2/3 fusions were detected in 42 (3.1%) and 4 (0.3%) samples, respectively, including 5 fusion events not previously reported (e.g., IFNGRI-RSPO3). A female predominance was seen in RSPOfusion pos vs. neg tumors (71.7 vs 45.0%, p < 0.001); no association with age or tumor sidedness was seen. RSPO3 fusions were mutually exclusive of MSI-high (0 vs. 5%), ERBB2 alterations (0 vs. 1%, mutation, 4% amplification) and other Wnt pathway activation drivers including APC (2 vs. 75%), CTNNB1 (0 vs. 1.4%) and RNF43 (0 vs. 5.3%) mutations. Significantly higher BRAF (26 vs 7%, RAF1 (4.5 vs 0.4%) and SMAD3 (30 vs 11%) mutation rates were seen in RSPO pos vs. neg tumors (p = 0.001). A universal co-activation of MAPK pathway (KRAS, NRAS or BRAF) was seen with RSPO fusions. There was a significantly elevated PD-L1 expression in RSPO3 pos tumors (14%) compared to RSPO neg (6%, p = 0.04) and APC-mutated (5%, p = 0.02) tumors that are NGS. Conclusions: This is the largest series of CRC cases harboring an RSPO rearrangement reported to date. Comprehensive molecular analyses asserted the unique molecular landscape associated with RSPO fusions in CRC and suggested potential combinatorial approach to target Wnt/MAPK pathway. The immune modulatory effects specific to RSPO2/3 fusion revealed by PD-L1 expression suggest co-targeting Wnt pathway with PD1/PDL1 inhibitors in RSPO pos tumors.

3589 Poster Session (Board #81), Mon, 8:00 AM-11:00 AM
Performance comparison of the methylated BCA71/IKZF1 ctDNA test (COLVERA) with the CEA assay for detection of recurrent colorectal cancer. First Author: Erin L. Symonds, Flinders University, Adelaide, SA, Australia

Background: Early detection of recurrent colorectal cancer (CRC) will improve treatment options, but the current standard blood test of carcinoembryonic-antigen (CEA) has suboptimal sensitivity for recurrence. This study compared performance of a quantitative circulating tumor DNA (ctDNA) assay for methylated BCA71 and IKZF1 (COLVERA) with that of CEA. Methods: 301 patients were radiologically or endoscopically confirmed to have recurrent CRC. Blood was collected at scheduled intervals and concentrations of CEA and ctDNA were measured using the LIASON CEA test (DiaSorin) and the COLVERA ctDNA test (Clinical Genomics). Surveillance for recurrent disease was examined using regular CT scans. Sensitivity of each blood test for recurrence was assessed in the sample collected closest to the time of imaging confirming recurrence status. Absence of recurrence was defined as at least two consecutive clear CT scans. Receiver operator characteristic (ROC) analyses were used to determine optimal positivity threshold for Colvera. Results: 131 patients underwent satisfactory assessment for recurrence and had blood testing performed within 12 months of determining recurrence status (61.8% male, mean age 62.6 ± 12.2(SD) y). Of the 47 recurrence cases, 37 (74%) were distant. The areas under the ROC curves were 0.7761 and 0.8188 for CEA and COLVERA, respectively (each p < 0.001). An optimal cut-off of 12.8pg/sample was determined for COLVERA and the standard 5mg/mL cut-off was selected for CEA. COLVERA had a significantly higher sensitivity for detecting recurrence as compared to CEA (68.1% vs 31.9%, p < 0.001) with a similar specificity (97.6% vs 96.4%, p = 0.6547). A multivariate analysis determined COLVERA to be a predictor of recurrence independent of CEA presence, and in the sample from patients with CEA below the cut-off score. COLVERA was more likely to have recurrence confirmed within the study timeframe, whereas CEA was not a significant predictor of recurrence (p = 0.228). Conclusions: These findings indicate that COLVERA, reporting in quantitative mode, is a more sensitive test than CEA. It provides a viable alternative for sensitive and early detection of recurrent CRC. Clinical trial registration: 12611000319897.
3591 Poster Session (Board #83), Mon, 8:00 AM-11:00 AM
Preoperative platelet leukocyte ratio as an independent risk factor for postoperative outcomes in colorectal cancers. First Author: Carrie E Ryan, University at Buffalo, Department of Surgery, Buffalo, NY

Background: Although preoperative platelet/leukocyte ratio (PLR) is a predictor of postoperative outcomes in various neoplasms, data is lacking for colorectal cancer (CRC). We hypothesized that elevated preoperative PLR would be an independent risk factor for postoperative complications and increased 30-day mortality in patients with surgically resected CRC. Methods: Patients undergoing resection for CRC were identified from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) from 2005 to 2016 dataset. Logistic regression models for 30-day morbidity and mortality for PLR ≥28.4 and >28.4 (calculated from ROC analyses) were completed. Univariate log-rank test, and multivariate Cox proportional hazards regression were used for time-to-event analyses and data are presented as odds/hazard ratio with confidence interval. Results: 98,398 patients were included in the study. Elevated PLR was an independent predictor of 30-day morbidity and mortality. Patients with high PLR were more likely to have a wound infection (1.022, 1.011-1.04), pneumonia (1.17, 1.17-1.23), require reintubation (1.23, 1.19-1.27), prolonged ventilation (1.31, 1.26-1.36), have renal insufficiency (1.17, 1.11-1.22), and have a postoperative myocardial infarction (1.23, 1.9-127). PLR value > 28.4 was among independent predictors of mortality (1.67, 1.47-1.87), along with the ASA class, age, perioperative transfusion, albumin and INR. (Table). Conclusions: Elevated PLR is a significant preoperative risk factor for 30-day morbidity and mortality. PLR may be considered as a potential risk assessment tool that predicts postoperative outcome following CRC resections. Multivariate analysis...

3592 Poster Session (Board #84), Mon, 8:00 AM-11:00 AM
Exploring the genetic basis of Lynch-like syndrome through paired germline and tumor exome sequencing. First Author: Jason Willis, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Lynch-like syndrome (LLS) is characterized by a diagnosis of mismatch repair deficient (dMMR) malignancy where somatic bi-allelic mutations in canonical MMR pathway genes (MLH1, MSH2, MSH6, PMS2) have been identified as the main cause. Yet, a substantial proportion of cases remain unexplained by MMR somatic bi-allelic events or germline mutations. We hypothesize that LLS cases with young-onset cancers carry cryptic germline alterations in other pathways. To explore this contribution, we performed analyses of the germline and tumour mutation landscapes in LLS patients diagnosed with dMMR cancers. Methods: 18 probands with young-onset (age <50 years) dMMR colorectal or uterine cancers were selected from a familial cancer registry. The absence of deleterious germline MMR mutation and/or somatic MLH1 inactivation was confirmed by standard genetic testing. We performed whole-exome sequencing (Illumina HiSeq) of germline (peripheral blood) DNA. Variant calls, quality-control, allele-frequency filtering (<1% in reference cohorts), and in silico annotation were performed using the GATK and polymorphSIFT tools. Pathway analysis was performed using the DAVID (Huang da et al.). Results: 237,055 rare germline variants were detected in our cohort. We enriched a subset of 758 variants with putative frameshift (45.1%), stop gain or loss (25%), or splice site alterations by (29.9%). Pathway analysis of these variants revealed excess events in DNA damage repair (e.g. ERCC5, POLM, POLN, EXO5) and mRNA splicing (e.g. SCAF1, SRSF4) pathways. Preliminary analysis of somatic mutations profiles shows frequent alteration of known drivers including APC(66%) and NOTCH1(36%). Conclusions: Our exploratory analysis provides novel evidence that LLS patients may harbor an excess of deleterious germline mutations in DNA damage repair- and mRNA splicing-related genes. Future studies will identify genes which are targeted by both germline and somatic mutation with the goal of nominating putative causal genes. Defining additional mechanisms of dMMR in LLS cancers may help to refine prevention strategies for unaffected individuals.

3593 Poster Session (Board #85), Mon, 8:00 AM-11:00 AM
Association of microRNA-21 with efficacy of cetuximab in RAS wild-type patients in the FIRE-3 study (AIO KRK 0506) and microRNA-21 expression on gene expression in the EGFR signaling pathway. First Author: Lisa Miller-Philips, Department of Medicine III, University Hospital, LMU Munich, Munich, Germany

Background: FIRE-3 compared first-line therapy with FOLFIRI plus cetuximab (cet) or bevacizumab (bev) in KRK exon 2 wild-type (wt) patients with metastatic colorectal cancer. Recent analyses showed microRNA-21 (miR-21) level in a predictive biomarker for anti-EGFR treatment and raising the question whether miR-21 influences gene expression in the EGFR signaling pathway. Methods: Reverse-transcription quantitative polymerase chain reaction assay identified quantitative miR-21 expression. Median expression was defined as a threshold value to discriminate FIRE-3 population into miR-21 low and high groups. Differential gene expression based on additional mRNA microarray data (Almac Inc. Xcel Array) was calculated by linear models adjusted for multiple testing followed by single sample gene set enrichment analysis (ssGSEA) to compare differentially enriched hallmark of cancer gene sets. Overall response rate (ORR) was compared using Fisher’s exact test. Median progression-free (PFS) and overall survival (OS) were analyzed using Kaplan-Meier estimation and log-rank test. Results: 333 RAS wt patients provided material for miR-21 expression analysis. In these patients, low miR-21 expression was associated with higher ORR (80.0% vs. 57.9%; p = 0.005) and longer OS (35.8 months (mo) vs. 25.9 mo; p = 0.001) when cet vs bev was added to FOLFIRI. High miR-21 expression was associated with comparable ORR (74.6% vs. 64.0%; p = 0.21) and OS (24.5 mo vs. 23.8 mo; p = 0.4). There was no significant difference in PFS in either group. By comparing miR-21 low and high groups using normalized mRNA microarray data, 538 genes were found to be significantly differentially expressed in RAS wt patients after adjusting for multiple testing. Including data from the two groups into ssGSEA yielded 23 hallmark of cancer gene sets that were significantly differentially enriched; among them, KRAS-signaling showed higher enrichment in the miR-21 high group (adjusted p = 2.09E-13). Conclusions: MI21 expression level might be a predictive biomarker for anti-EGFR therapy by modulating KRAS signaling in FIRE-3 patients.

3594 Poster Session (Board #86), Mon, 8:00 AM-11:00 AM
Comparison of HER2 overexpression with total HER2 mutation on resistance of EGFR-targeted therapy in RAS wild-type mCRC patients. First Author: Wenju Chang, Institute of General Surgery, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Cetuximab has shown clinical benefit in patients with metastatic colorectal cancer (mCRC) harboring wild-type Ras, however, only partial patients respond to cetuximab treatment. The effect of human epidermal growth factor receptor 2 (HER2) protein expression on the treatment is not well elucidated in patients with wild-type unresectable mCRC. Methods: From June 2008 to December 2014, we identified 216 patients with Ras wild-type unresectable liver-metastatic mCRC base on our previous study (ClinicalTrials. NCT01564810), whose Her2 wild-type treatment was not well elucidated in patients with Ras wild-type unresectable mCRC. Results: Of these 216 patients, 103 were received cetuximab plus chemotherapy (cetuximab group) and 113 were received chemotherapy alone (chemotherapy group). The total rate of HER2 overexpression was 8.8%, including 9.7% in cetuximab group and 7.9% in chemotherapy group. HER2 overexpression caused impaired survival compared with HER2 non-overexpression patients in cetuximab group, with a median progression-free survival (PFS) of 4 months (95% CI 2.482-5.518) versus 10 months (95% CI 8.963-11.037; P< 0.0001), and a median overall survival (OS) of 15 months (95% CI 17.5-22.2) versus 36 months (95% CI 31.4-40.5; P< 0.0001). While, HER2 overexpression effect on treatment efficacy in chemotherapy group, when comparing with HER2 positive patients, with a median PFS of 5 months (95% CI 2.228-7.772) versus 5 months (95% CI 4.004-5.996; P= 0.615), and a median OS of 21 months (95% CI 6.975-35.025) versus 21 months (95% CI 17.772-24.228; P= 0.629), Meanwhile, we observed 25.5% of total Her2 mutant (24.2% in cetuximab group and 26.5% in chemotherapy group), among of them 5 patients are HER2 overexpression. Total Her2 mutation has no impact on survival compared with Her2 wild-type ones in neither cetuximab group nor chemotherapy group. In further bioinformatics analysis is underdying, and which subgroup or type of the different potential to response to anti-EGFR antibodies data confirm. Conclusions: We show HER2 overexpression versus total Her2 mutant contribute to resistance of cetuximab treatment in patients with mCRC harboring wild-type Ras. Next, the subgroup mutant in total Her2 mutant needs further analysis to confirm their roles in survival after cetuximab treatment.
Background: PD is one of the most common age-related neurodegenerative disorders. Large epidemiological studies have consistently reported a reduced risk of CRC in PD patients (pts), but the biology behind this evidence is unclear. The methylation status of SNCA, one of the causal PD genes, has been identified as a tool for CRC screening and early diagnosis when evaluated in stool samples, and alterations in core PD genes are prevalent across human malignancies including CRC. Methods: The impact on outcome of 13 SNPs within 6 core PD genes (SNCA, PRKN, UCHL1, PINK1, DJ-1, LRRK2) was analyzed in pts enrolled in the randomized FIRE-3 trial. Genomic DNA from blood samples of pts treated with first-line FOLFIRI-ceuximab (n = 129) and FOLFIRI-bevacizumab (n = 107) was genotyped through the OncoArray, a custom array manufactured by Illumina. Gene expression levels were measured from 102 tumor samples of pts in the ct arm by HTG EdgeSeq Oncology Biomarker Panel. Results: In the ct cohort, pts carrying the YA genotypes of SNCA rs3561655 and rs2736990 had significantly shorter mOS (30 vs 41.1 mo) compared to any A genotype in both uni- and multivariable analysis (adjusted R^2 = .047 and .042, respectively). LRRK2 rs3761863 T/T allele carriers showed shorter mPFS (9.5 vs 13.3 mo, Padj = .001), while rs11564148 any A carriers had longer mPFS (14.2 vs 10.2 mo, Padj = .01) compared to reference genotypes. LRRK2 rs11564148 any A carriers also showed longer mOS in multivariable analysis (43.7 vs 33.2 mo, P = .044). Any C allele carriers of PINK1 rs1043424 showed longer mPFS in uni- and multivariable analysis (P = .001). No significant interaction was found with gender, tumor location and RAS status. These associations were not observed in bev arm. High SNCA expression was associated with worse mPFS (log_{2}(7.89, 5.9 vs 11.2 mo) and mOS (log_{2} > 7.68, 17.9 vs 31.1 mo) in FIRE-3 ct arm (P < .05). Conclusions: We provide the first evidence that gene expression and genetic variants in PD genes may have a predictive value in mCRC pts receiving first-line cetuximab-based treatment. Our findings open new perspectives on the role of PD genes in CRC biology warranting further investigation.

3596 Poster Session (Board #88), Mon, 8:00 AM-11:00 AM
Differences in pathology and mutational status among colorectal cancer (CRC) patients pre-, post-, and during screening age. First Author: Gustavo Dos Santos Fernandes, Hospital Sírio-Libanês, Brasília, Brazil

Background: Screening protocols for CRC are broadly recommended and effective in reducing mortality. However, populations from different age groups can harbor distinct pathological and molecular profiles that can also be influenced by screening and polyp resection, especially in older ages. Methods: We retrospectively analyzed patients from stage IV CRC patients from a central pathology laboratory in Brazil that is responsible for mutational counseling of patients. Patients were classified into age groups as the following: pre-screening (PsA; <45yo), screening(SA; 45-75yo) and post-screening (PsA; >75yo). Every tumor has been centrally reviewed by the pathologist. Groups were compared regarding clinicopathologic features and presence of RAS and BRAF mutations. Results: We included 1244 pts (164 PsA, 919 SA and 161 PsA). There were no difference among groups regarding side-effect(p = .681) and KRA mutations(p = .007). Stage IV at diagnose (p = .001), presence of signet-ring cell component (p <.001) along with poorly differentiated tumors (p = .006) were most found on young patients, while BRAF and NRAS mutations where significantly more common among PosSa (table). Conclusions: PsSa and PreSa CRCs seem to present a distinct profile from SA populations, including differences in the molecular and pathologic aspects. This could impact the frequency of screening tests among different age groups.

3597 Poster Session (Board #89), Mon, 8:00 AM-11:00 AM
The 55 STAR study: Prognostic and predictive value of the 55-gen classifier (55GC) in stage III colon cancer. First Author: Toshiaki Ishikawa, Tokyo Medical and Dental University, Tokyo, Japan

Background: Patient prognosis can be predicted based on cancer subtypes classified according to DNA microarray results. The most robust classification system involves the consensus molecular subtypes, which uses over 600 genes classified according to DNA microarray results. The most robust classification is CRC. Patient prognosis can be predicted based on cancer subtypes. Methods: We retrospectively identified stage III CC patients aged 20-79 years who underwent curative surgery and reported to be a useful and reproducible grading system for stage II CC reduced risk of CRC in PD patients (pts), but the biology behind this evidence is unclear. The methylation status of SNCA, one of the causal PD genes, has been identified as a tool for CRC screening and early diagnosis when eval- uated in stool samples, and alterations in core PD genes are prevalent across human malignancies including CRC. Methods: The impact on outcome of 13 SNPs within 6 core PD genes (SNCA, PRKN, UCHL1, PINK1, DJ-1, LRRK2) was analyzed in pts enrolled in the randomized FIRE-3 trial. Genomic DNA from blood samples of pts treated with first-line FOLFIRI-ceuximab (n = 129) and FOLFIRI-bevacizumab (n = 107) was genotyped through the OncoArray, a custom array manufactured by Illumina. Gene expression levels were measured from 102 tumor samples of pts in the ct arm by HTG EdgeSeq Oncology Biomarker Panel. Results: In the ct cohort, pts carrying the YA genotypes of SNCA rs3561655 and rs2736990 had significantly shorter mOS (30 vs 41.1 mo) compared to any A genotype in both uni- and multivariable analysis (adjusted R^2 = .047 and .042, respectively). LRRK2 rs3761863 T/T allele carriers showed shorter mPFS (9.5 vs 13.3 mo, Padj = .001), while rs11564148 any A carriers had longer mPFS (14.2 vs 10.2 mo, Padj = .01) compared to reference genotypes. LRRK2 rs11564148 any A carriers also showed longer mOS in multivariable analysis (43.7 vs 33.2 mo, P = .044). Any C allele carriers of PINK1 rs1043424 showed longer mPFS in uni- and multivariable analysis (P = .001). No significant interaction was found with gender, tumor location and RAS status. These associations were not observed in bev arm. High SNCA expression was associated with worse mPFS (log_{2}(7.89, 5.9 vs 11.2 mo) and mOS (log_{2} > 7.68, 17.9 vs 31.1 mo) in FIRE-3 ct arm (P < .05). Conclusions: We provide the first evidence that gene expression and genetic variants in PD genes may have a predictive value in mCRC pts receiving first-line cetuximab-based treatment. Our findings open new perspectives on the role of PD genes in CRC biology warranting further investigation.

3598 Poster Session (Board #89), Mon, 8:00 AM-11:00 AM
Urban/rural disparities in stage at presentation of colorectal cancer among young adults in the United States, 2007-2015. First Author: Victoria Nguyen, Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA

Background: The overall incidence rate of colorectal cancer (CRC) has declined in recent decades but is rising in young adults (YA). Disparities also exist in CRC presentation and geographical residence. We examined associations between urban/rural residence and CRC stage at presentation among YA 18-50 years old, using the Surveillance, Epidemiology, and End Results (SEER) 1973-2015 registry. Methods: Retrospective cohort study using SEER patients (pts) diagnosed with CRC between 2007-2015, aged 18-50. Urban/ rural status was defined at the county level as large metro, small metro, urban non-metro, and rural. Pts were grouped by age: 18-30, 31-40, and 41-50 years old. Stage was defined as in situ/localized and regional/distant. We used multivariable logistic regression to describe associations between urban/rural status with stage at presentation, adjusting for tumor location, histology, grade, and patient attributes (e.g. insurance status). Results: 27,198 CRC pts were analyzed: 62.2% large metro, 27.4% small metro, 9.4% urban non-metro, and 67.1% regional/distant stage. In multivariable analysis, YA in urban non-metro counties had lower odds of regional/distant stage at presentation compared to YA in large metro counties (OR = 0.87, 95% CI = 0.79-0.97). Associations between small metro and rural status with stage at presentation were not significant (OR = 0.94, 95% CI = 0.89-1.01 and OR = 0.84, 95% CI = 0.64-1.10, respectively). YA with Medicaid or no insurance had higher odds of regional/distant CRC (OR = 1.28, 95% CI = 1.17-1.39 and OR = 1.34, 95% CI = 1.20-1.51, respectively) compared to YA privately insured. Other factors in YA associated with higher odds of regional/distant CRC included signet-ring histology, poorly- moderately-, and undifferentiated grade, and younger age (30-39 vs 40-49 years old). Conclusions: Younger age in urban non-metro areas had lower odds of regional/distant CRC at presentation compared to YA in large metro areas. YA with Medicaid, no insurance, signet-ring histology, poorly- moderately-, and undifferentiated grade, and younger age had higher odds of regional/distant CRC at presentation. Further research is needed to explore the etiology of these differences.
**Background:** Existing tools for post-treatment CRC surveillance and monitoring are insensitive and expensive. MDMs are broadly informative for early detection of CRC but have not been extensively studied for diagnostic or monitoring. As a first step, we sought to assess the concordance of novel CRC-associated MDMs in pCRC and mCRC. Methods: A panel of 14 MDMs previously identified to be highly discriminant for pCRC was selected on the basis of high median fold-change of MDM levels relative to buffy coat (682 [IQR: 132-19347]). Surgically resected pCRC and paired mCRC were identified from institutional pathology databases. Quantitative methylation-specific PCR was used to assay MDMs. 30 paired samples per metastatic subtype were calculated to be sufficient. MDM levels were compared using two-sample and paired Wilcoxon rank sum tests. Results: 87 patients with paired pCRC and mCRC including 57 synchronous and 30 metachronous metastases were included. 41/87 (47%) had neoadjuvant and 59/87 (68%) had adjuvant chemotherapy. All synchronous metastases were to liver in 19/30 (63%) and to lung in 11/30 (37%). The levels of 14 selected MDMs were remarkably similar between paired pCRC and mCRC (Table). Individual MDM levels and the average level (37%). The levels of 14 selected MDMs were remarkably similar between paired pCRC and mCRC (Table). Individual MDM levels and the average level were not significantly different (p > 0.0018 by Bonferroni correction). Conclusions: MDM levels are highly concordant in pCRC and mCRC. Thus, MDMs discovered from pCRC should be further studied for non-invasive surveillance after surgical resection and monitoring of treatment response in mCRC.

### MDMs

<table>
<thead>
<tr>
<th>MDM</th>
<th>pCRC vs Sym-mCRC</th>
<th>pCRC vs Meta-mCRC</th>
<th>pCRC vs Meta-Sym-mCRC</th>
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</thead>
<tbody>
<tr>
<td>VAV3</td>
<td>1.0 (0.2, 4.4)</td>
<td>1.2 (0.3, 4.1)</td>
<td>1.0 (0.3, 2.6)</td>
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<td>1.0 (0.5, 2.2)</td>
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<td>0.7 (0.3, 2.0)</td>
<td>0.8 (0.2, 2.6)</td>
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<td>0.4, 1.8</td>
<td>0.9 (0.2, 0.4)</td>
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<tr>
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<td>1.0 (0.4, 1.7)</td>
<td>1.0 (0.4, 1.7)</td>
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</table>

**Table:** Median fold change (IQR) for MDMs in pCRC vs Sym-mCRC, pCRC vs Meta-mCRC, and pCRC vs Meta-Sym-mCRC.

### Association between gene mutations and SWI/SNF complex

<table>
<thead>
<tr>
<th>Gene</th>
<th>SWI/SNF genes</th>
<th>MDM</th>
<th>TMB-high (S)</th>
<th>TMB-high (H)</th>
<th>pCRC vs Syn-mCRC</th>
<th>pCRC vs Met-mCRC</th>
<th>pCRC vs Meta-Syn-mCRC</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>MDM</td>
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<td>VAV3</td>
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<tr>
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</tbody>
</table>

**Table:** Median fold change (IQR) for SWI/SNF genes in MDMs in pCRC vs Sym-mCRC, pCRC vs Meta-mCRC, and pCRC vs Meta-Sym-mCRC.

**Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.**
Background: HLA-A*02, a common allele in the Scandinavian population, is a common allele in the Scandinavian population, is a positive prognostic factor in epithelial ovarian cancer. It is a strong predictor of patient outcome, only inferior to clinical staging. This prognostic trait in epithelial ovarian cancer is stronger by the presence of the gene compared to the expression of its protein, MHC class I. Microsatellite instability (MSI) is used as a biomarker for prognosis and suggested an increased tumor mutational burden which can make the tumor more susceptible for T cell mediated immunotherapy. Our aim was to analyze the prognostic markers HLA-A*02 genotype, MHC class I on tumor cells, the CD8+ lymphocyte infiltration and MSI status in colon cancer patients with randomized treatment. Methods: Clinical information and primary tumors were collected from 520 colon cancer patients and followed for overall survival for 120 months. Patients who stage II and III colon cancer and were randomized to surgery alone or surgery and adjuvant chemotherapy. HLA-A*02 genotype was determined by conventional PCR. MHC class I, status and CD8+ lymphocyte infiltration were determined by immunohistochemistry. Results: For patients who stage III tumor and HLA-A*02 genotype had a better outcome if they had received adjuvant chemotherapy instead of just surgery (p = 0.03), whereas this was not the case for patients with other HLA-A genotypes or in the male patients where HLA-type did not correlate to outcome. MHC class I expression did not act as a prognostic factor, however, a positive correlation between MSI and HLA-A*02 was observed (p = 0.03). In the invasive margin and the size of the tumor was a positive prognostic factor for overall survival (p = 0.01), although only statistically significant in the male patients (p = 0.03). 21% patients had a tumor with MSI (23% of the female and 19% of the male patients respectively). MSI tumors had a slightly better outcome and this was irrespective of gender and HLA-type. Conclusions: The prognostic traits of HLA-A*02 appear in this colon cancer cohort to act differently in men and female patients. Also CD8+ infiltration is different between genders. These findings suggest that men and women may have two different immune responses to malignancy.

Conclusions: Differences in clinical outcomes in young-onset colorectal cancer based on ethnicity in an NCI-designated comprehensive cancer center. Background: Ethnic disparities can impact clinical outcomes of young-onset colorectal cancer (CRC) patients. We aimed to determine if differences in outcomes based on ethnicity exist in young-onset CRC treated at an NCI-designated comprehensive cancer center program. Methods: A retrospective chart review for stage II – IV young-onset CRC patients ≤45 years old was performed between 04/2011 and 11/2015. Patients had to undergo treatment at safety-net Parkland Hospital (PH) or at the Simmons Comprehensive Cancer Center (SCC) in Dallas, TX. Demographic data, dates of surgery, adjuvant chemotherapy, recurrence or death were obtained. Results: Of 423 patients that met inclusion criteria, 15 were excluded due to incorrect dates of surgery, adjuvant chemotherapy, recurrence or death were obtained. Of the remaining 408 patients, 36 (33%) and 72 patients (67%) were treated at SCC and PH respectively. Sixty (55%) were non-Hispanic vs 48 (44%) Hispanic. There were more Stage IV patients at SCC vs Parkland (58.3% vs 30.6%, p < 0.01) but there was no difference regarding age. Also, no significant difference was seen between non-Hispanic White (NHW), Hispanic, and Black patients in median days to colostomy (1 vs 13 vs 0; p = 0.420) or adjuvant chemotherapy (55.5 vs 53.0 vs 64.0 days, p = .820). Hispanic patients had significantly better overall survival (OS) than Black or NHW patients (p = 0.025). The OS benefit was driven by improved 5-year OS in stage II/III Hispanic vs NHW vs Black patients (95% vs 62% vs 60%; p = 0.06). Multivariate Cox Regression analysis showed stage III/IV (p < 0.001) and Hispanic ethnicity (p < 0.001) were independent predictors of overall survival and OS. Conclusions: Young-onset CRC patients who stage II and III CRC. The causes for these ethnic differences in young-onset CRC patients needs further exploration.
Background: To date, large-scale genomic sequencings of colorectal cancers (CRC) have been reported mainly from Western countries. However, ethnic diversities, differences by stage, and the prognostic impact of the genomic landscape in CRC remain poorly identified. Methods: The subjects were 534 patients (pts) with stage III CRC from the JCOG0910 study—a randomized phase-III trial conducted in Japan on 1564 pts to assess the efficacy of S-1 versus capecitabine as adjuvant chemotherapy. Targeted-genome sequencing of 171 potentially CRC-associated genes was performed on both normal tissue and tumor samples, and somatic single-nucleotide variants and insertion/ deletions were determined. Tumors with MSIsensor scores > 7 and ultra-mutated tumors with POLE mutations were grouped as hypermutated tumors.

Genes whose alterations were associated with recurrence-free survival (RFS) were evaluated using multivariable Cox regression models. Results: Of the 534 pts (right-sided: 184, left-sided: 350), 109 pts had recurrences or died during the study. Mutation frequencies were as follows: TP53, 73.5%; APC, 75.1%; KRAS, 43.6%; PIK3CA, 19.7%; FBXW7, 18.5%; SOX9, 11.8%; COL6A3, 8.2%; NOTCH3, 4.5%; NRAS, 4.1%; and RNF43, 3.7%. Thirty-one tumors were hypermutated (5.8%) (right: 14.1%, left: 1.4%). None of the 49 genes with mutation frequencies > 3% showed a significant association with RFS based on Bonferroni’s adjustment for multiple testing. The following modest associations were observed: mutant KRAS (HR, 1.66; p = 0.011) and mutant RNF43 (HR, 2.17; p = 0.055) had poorer RFS, whereas mutant COL6A3 (HR, 0.35; p = 0.040) and mutant NOTCH3 (HR, 0.18; p = 0.093) had better RFS. RFS tended to be better for hypermutated than for non-hypermutated tumors (HR, 0.53; p = 0.229).

Conclusions: The overall mutation spectrum of our stage III CRC was generally similar to that of Western countries. However, the mutation frequencies of TP53, SOX9, and FBXW7 were higher, and the proportion of hypermutated tumors was lower. Multiple gene mutations tended to impact RFS, indicating that tumor genomic profiling has a high potential to support precision medicine for pts with CRC.

Background: Mucinous adenocarcinoma and signet-ring cell carcinoma were uncommon in locally advanced rectal cancer. And it has been reported that both mucinous adenocarcinoma and signet-ring cell carcinoma showed poor response to standard neoadjuvant chemoradiotherapy. Here, we tried to compare the efficacy of different neoadjuvant treatment regimen on locally advanced mucinous adenocarcinoma or signet-ring cell carcinoma (M/S).

Methods: We enrolled patients with locally advanced rectal cancer from 3 prospective clinical trials (NCT01211210, NCT02217020 and NCT02887831), including FOWARC study (NCT00994864), mFOLFOXIRI neoadjuvant chemotherapy alone (N = 103), and the neoadjuvant treatment with FOLFOX and radiotherapy (N = 129). Among the 541 patients, 41 (7.6%) patients were M/S and 500 were non-M/S. Totally, 7 M/S patients and 84 non-M/S patients received FOLFOX concurrent with radiotherapy (Group A), 20 M/S patients and 208 non-M/S underwent FOLFOX concurrent with radiation or total neoadjuvant treatment (Group B), 11 M/S patients and 92 non-M/S patients underwent mFOLFOXIRI neoadjuvant chemotherapy alone (Group C).

Conclusions: The pCR rate was 14.3% and 11.9% (p = 0.85), and the tumor downstaging rate was 14.3% and 36.5% (p = 0.22) in M/S and non-M/S patients, respectively. In Group B, the pCR rate was 15.0% and 34.6% (p = 0.07), and the tumor downstaging rate was 25.0% and 60.1% (p = 0.002) in M/S and non-M/S patients, respectively. However, in group C and group D with chemotherapy alone as neoadjuvant treatment, no M/S patients showed pCR or tumor downstaging, while in non-M/S patients higher tumor downstaging rate was observed. M/S patients showed resistance to neoadjuvant chemotherapy along regimens. Even with chemoradiotherapy, M/S patients showed poorer response than that of non-M/S patients. Further study was warranted to explore the new regimen for M/S patients.
3611 Poster Session (Board #103), Mon, 8:00 AM-11:00 AM
Long-term outcomes after high-dose chemoradiotherapy for non-surgical management of distal rectal cancer. First Author: Edina Dzidarevic, Vejle Hospital, Vejle, Denmark.

Background: Surgery is standard treatment for rectal cancer, but neoadjuvant chemoradiotherapy (CRT) may result in clinical complete response (cCR) in selected patients, allowing for non-surgical management (NSM). Prospective studies of NSM strategies are sparse however, and long-term data on quality of life (QoL) are limited. We conducted a single-arm phase II trial of high-dose CRT for NSM of distal rectal cancer; we report secondary long-term patient-reported outcomes (PROs), local regrowth and overall survival (OS) in patients managed non-surgically. Methods: Fifty-one patients with resectable, T2 or T3, NO–N1, low adenocarcinoma received 65Gy (IMRT, brachytherapy boost) and oral tegafur-uracil. Patients with cCR 6 weeks after treatment (clinical examination, MRI, biopsy) were referred for observation, and followed closely with clinical examinations, endoscopies, PET-CTs, and PROs for 5 years. Overall colorectal cancer specific QoL and specific symptom scores were compared between timepoints using paired Wilcoxon tests. Local regrowth was estimated using cumulative incidence; overall survival using Kaplan-Meier estimates. Results: Forty patients achieved cCR after treatment; 28 were in follow-up at 24m, 21 at 36m, 18 at 60m. Patients left the trial due to local tumor regrowth (n=12), distant metastases (n=3), new primary cancers (n=6) and loss to follow-up (n=1). Average QoL score did not differ between baseline (median 11.1) and 24m (13.7), 48m (11.1) or 60m (6.9). See Table for individual scores; only rectal bleeding deteriorated from baseline (significantly worse at 24m). At median follow-up of 5 years, local recurrence rates were 31% (95 CI 15%-47%) and 85% (95 CI 75%-97%), respectively. Conclusions: Long term follow-up after NSM of early rectal cancer showed excellent general colorectal cancer QoL and local symptom scores. (NCT00952962), EORTC QLC – CR 29. Proportion reporting ‘quite a bit’ or ‘very much’ on symptom scales. Clinical trial information: NCT00952962.

Baseline (n=24m) 24m (n=28) 48m (n=22) 60m (n=18)
Daytime urinary frequency 27% 12% 18% 17%
Urinary incontinence 0% 0% 9% 0%
Rectal pain 0% 4% 0% 4%
Bowel in stools 8% 27% 23% 11%
Faecal incontinence 3% 7% 0% 0%
Daytime bowel movement frequency 14% 17% 17% 12%

3613 Poster Session (Board #105), Mon, 8:00 AM-11:00 AM
Pathway analysis of hypoxia-related factors in early colorectal cancer patients with poor prognostic factors. First Author: Yingxin Tan, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: Colorectal cancer is one of the most common malignancies with a high mortality rate. Patients with stage I and stage II colorectal cancer have limited options for treatment. Hypoxia affects the activation and regulation of colorectal cancer cells and participates in its invasion and migration. However, there is lack of an accurate and non-invasive method for assessing tumor hypoxia. The aim of this study was to identify validated a hypoxia gene signature for predicting the outcome in stage I/II colorectal cancer patients. At the same time, we hypothesized that analysis of database of CIT microarray dataset could identify important biomarkers for stage I/II colorectal cancer patients. Methods: A total of 309 colorectal cancer patients of early stage with complete clinical information were enrolled for construction generation of hypoxia-related gene signature (HRGS) based on the CIT microarray dataset. 1877 colorectal cancer patients with stage I/II colorectal cancer were divided into a training cohort and two validation cohort (TCGA and meta-validation). Prognostic analysis was assessed in these cohort to evaluate the predictive value of HRGS. Results: A model of prognostic HRGS containing 14 hypoxia-related genes was developed. In training cohort and two validation cohorts, patients in hypoxia high-risk group satisfied by our HRGS had significant poor disease free survival compared with those in the in the low risk group (HR=4.35, 95% CI=2.30-8.23, P<0.001 in training cohort, HR=2.14, 95% CI=1.09-4.21, P=0.024 in TCGA cohort, HR=1.91, 95% CI=1.08-3.39, P=0.024 in meta-validation cohort). When compared with Oncotype DX, HRGS achieved an improved survival correlation in the training cohort (mean C-index, 0.80 vs 0.65, P<0.05) and the validation cohort (mean C-index, 0.70 vs 0.61 in the TCGA cohort, mean C-index, 0.68 vs 0.73 in meta-validation cohort). Analysis of the data found that patients with low survival rates have significant relationships with genes regulated by the cell cycle pathway, such as mTORC1, E2F, G2-M, mitotic, oxidative phosphorylation, MYC, PI3K-AKT-mTOR (P<0.005). Conclusions: HRGS was a satisfactory prognostic signature model on colorectal cancer patients. Hypoxia-related genes that regulate the cell cycle pathway were associated with prognosis in patients with stage I and stage II colorectal cancer. Further researches are needed to assess the clinical effectiveness of the system and the treatment options for biological targets.

3612 Poster Session (Board #104), Mon, 8:00 AM-11:00 AM
Simultaneous versus staged resection for synchronous colorectal cancer liver metastases: A population-based cohort study. First Author: Pablo Emilio Serrano, Aybar, McMast University, Hamilton, ON, Canada

Background: Simultaneous resection of colorectal cancer primary and liver metastases is not performed routinely due to concerns about safety. We hypothesized that simultaneous resection has steadily increased overtime and that the outcomes are similar. Methods: Population-based cohort study of patients undergoing resection for synchronous (resection of the primary colorectal cancer and liver metastases within six months) liver metastases from 2006-2015 by linking administrative datasets in Ontario, Canada. Outcomes: post-operative complications, length of hospital stay, and overall survival. Survival for the staged group was measured from the last surgical resection to death and estimated using Kaplan Meier and compared with the log-rank test. Cox proportional hazard models were used to calculate risks for death. We aimed to identify practice patterns, outcomes of simultaneous vs. staged resections for these patients. Results: Of 2,738 patients undergoing colorectal and liver resection for colorectal cancer, 1,168 were synchronous, of which, 442 underwent simultaneous resection. Rate of synchronous disease presentation increased on average by 3% per year (p = 0.02). Median length of stay was shorter (9 vs. 11 days, p < 0.001), rate of major liver resections were lower (17% vs. 65%, p < 0.001), and 90-day post-operative mortality was higher (6% vs. 1%) for simultaneous resections. Major postoperative complications were higher in the synchronous group (28% vs. 23%, p = 0.067), mostly due to a higher reoperation rate (6% vs. 3%, p = 0.034). Median overall survival was worse with synchronous resection (HRGS = 4.35, 95%CI 2.35-8.23 vs. 78 months, 95%CI 59-86). Risks factors for worse survival were comorbidities, rurality, right-sided primary and simultaneous resection. There is selection bias that favours survival in the staged group, as patients must have survived the first operation and have stable disease in order to undergo the second operation. Conclusions: Simultaneous resection is associated with worse post-operative outcomes. Considering selection bias, randomized studies would be necessary to determine the role of simultaneous.

3614 Poster Session (Board #106), Mon, 8:00 AM-11:00 AM
Clinical features and survival among patients with standard-onset versus early-onset colorectal cancer by age groups. First Author: Ana Aucuna Villardron, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY

Background: Colorectal cancer (CRC) incidence is increasing in patients younger than 50 years old. Currently, there are discordant recommendations regarding CRC screening; while the American Cancer Society favors to start at age 45, the National Comprehensive Cancer Network and the US Preventive Task Force suggest starting at age 50. This study is aimed to compare the incidence, clinical characteristics and survival of patients diagnosed with standard-onset CRC (SO) versus early-onset colorectal cancer by age groups. Methods: Patients diagnosed with CRC at ages older than 35 were identified using the SEER registry and categorized into four groups based on age at diagnosis. EO1 (35-39), EO2 (40-44), EO3 (45-49) and SO (>50) years, respectively. Incidence, clinical features and survival were compared among groups. Results: 178,678 patients were identified. 9.2% were diagnosed before 50 years. Of these, 14%, 2.8% and 5.1% were EO1, EO2 and EO3; respectively. Patients with early-onset CRC (EO) had higher frequency of Hispanics (13.9% vs. 8.4%, p<0.01), stage IV (24.8% vs. 17.3%, p<0.01), left-sided tumors (74.1% vs. 56.9%, p<0.01) and better survival compared to SO. Among EO groups, the frequency of poor/anaplastic grade was inversely proportional to age; stage IV was similar between EO2 and EO3 and lower in EO1. Black race, stage and grade were predictors of mortality for all EO groups; laterality was a mortality predictor in EO2 and EO3. Conclusions: Simultaneous resection is associated with worse post-operative outcomes. Considering selection bias, randomized studies would be necessary to determine the role of simultaneous.

<table>
<thead>
<tr>
<th></th>
<th>EO1</th>
<th>EO2</th>
<th>EO3</th>
<th>SO</th>
<th>p*</th>
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<tbody>
<tr>
<td>Incidence (per 100,000)</td>
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<td>16.5</td>
<td>30.1</td>
<td>146.8</td>
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<tr>
<td>Male (%)</td>
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<td>51.4</td>
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<td>NH (%)</td>
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<td>Hispanic (%)</td>
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<td>4.3</td>
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<td>Stage IV (%)</td>
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<td>26.6</td>
<td>27.4</td>
<td>24.6</td>
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*Comparison between EO groups.
**TPS3615**  
Poster Session (Board #107a), Mon, 8:00 AM-11:00 AM  
POLEM: Avelumab plus 5-fluoropyrimidine-based chemotherapy as adjuvant treatment for stage III dMMR or POLE exonuclease domain mutant colorectal cancer—A phase III randomized study.  
First Author: David Lui, Royal Marsden NHS Foundation Trust, Sutton, United Kingdom  

**Background:** Colon cancer with deficient mismatch repair (dMMR) and POLE mutations are characterised by a high tumor mutational burden (TMB) and an immunogenic lymphocyte infiltrate. Approximately 12% of stage III colon cancer have dMMR. POLE mutations occur in 1% of colon cancers, but is enriched in patients 50 years of age. Colon cancer with high TMB have demonstrated to be sensitive to immune checkpoint inhibition in the metastatic setting. We are conducting a phase III randomised trial to determine if the addition of the anti-PD-L1 antibody, avelumab following adjuvant chemotherapy can improve disease free survival (DFS) in patients with stage III colon cancer with dMMR or POLE mutations.  

**Methods:** We are recruiting patients with curatively resected, stage III colon cancer which are dMMR or have a centrally confirmed POLE exonuclease domain mutation. Eligible patients are randomised in a 1:1 ratio to standard 5-fluoropyrimidine-based chemotherapy (CAPOX [capecitabine, oxaliplatin] for 12 weeks or capecitabine for 24 weeks) or chemotherapy followed by avelumab (10mg/kg, 2 weekly for 24 weeks). Stratification is by chemogenetic MMR status. The primary endpoint is DFS. Secondary endpoints include overall survival, toxicity, quality of life, and health resource use. Exploratory objectives will investigate circulating, tumor and stool based biomarkers of avelumab benefit. The 3-year DFS rate in the control arm is expected to be ~75%. Avelumab is expected to improve the 3-year DFS rate by 12% (i.e., 87%). Target accrual is 402 patients which provides 80% power to detect a hazard ratio of 0.48 for DFS at a two-sided alpha of 0.05. This trial is a national, multi-centre phase III trial and it is anticipated that approximately 40 centres in the UK will participate. This study opened to recruitment in August 2018. Clinical trial information: NCT03827044.

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**TPS3616**  
Poster Session (Board #107b), Mon, 8:00 AM-11:00 AM  
The Global POLAR program: Two pivotal placebo-controlled studies of calmanagafodipir as add-on therapy for oxaliplatin-induced peripheral neuropathy (CIPN). First Author: Alan F. Parmley, The Ohio State University Comprehensive Cancer Center, Division of Medical Oncology, Columbus, OH  

**Background:** Oxaliplatin (OXA), is approved in combination with 5-FU/FA (5-fluorouracil/leucovorin; FOLOX) for metastatic as well as in adjuvant colorectal cancer (CRC) treatment. CIPN is a common adverse event, after OXA treatment. The incidence of chronic CIPN is approximately 15% after a cumulative dose of 780 to 850 mg/m² and 50% after a cumulative dose of 1170 mg/m². OXA induced neuropathy, results in greatly reduced nitrated manganese superoxide dismutase (MnSOD) activity. Treatment with a superoxide dismutase mimetic, such as calmanagafodipir (CAL), prevents and reverses oxaliplatin-induced neuropathies. This has been demonstrated in the PROLIFI study, with CAL (Gilmeilus et al. 2017). The POLAR program is a Phase 3, multicenter, placebo (PLC)-controlled program of CAL to prevent CIPN, recruiting in US, Europe (B, D, ES, F, ES, I and UK) and Asia (J, SK, TW and HK) and is described below; POLAR A Patients with CRC, treatment of patients with Stage III or high-risk Stage II who are indicated for adjuvant chemotherapy with FOLOX (mFOLFOX) chemotherapy for up to 6 months, randomized in a 1:1 ratio, each arm n = 140: A: CAL (5 µmol/kg) + mFOLFOX chemotherapy B: PLC + mFOLFOX chemotherapy POLAR M Patients with metastatic colorectal cancer (mCRC), who are indicated for first-line mFOLFOX chemotherapy for at least 3 months, without any pre-existing treatment breaks, randomized in a 2:1:1 ratio: A: CAL (2 µmol/kg) + mFOLFOX chemotherapy B: CAL (5 µmol/kg) + mFOLFOX chemotherapy C: PLC + mFOLFOX chemotherapy  

**Primary objective:** is to compare CAL vs PLC for the proportion of patients with moderate or severe chronic CIPN. The primary endpoint is: Patient reported symptoms as a proportion of patients scoring 3 or 4 in at least 1 of the first 4 items of the FACT/GOG-NTX-13 (i.e., FACT/GOG-NTX-4), targeting numbness, tingling or discomfort in hands and/or feet, assessed 9 months after the first dose of chemotherapy. In addition to conventional safety endpoints, Progressive Free Survival and Overall Survival are assessed in the POLAR M study. In the POLAR A study, Disease Free Survival is one additional safety endpoint assessed. Results are expected during second half 2020. Clinical trial information: NCT03654729.

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**TPS3617**  
Poster Session (Board #108a), Mon, 8:00 AM-11:00 AM  
A phase Ib study of ramucirumab in combination with TAS102 versus TAS102 monotherapy in metastatic, chemotherapy refractory colorectal cancer patients: The RAMTAS trial of the German AIO (KRK-0316). First Author: Stefan Kasper, University Hospital Essen, Essen, Germany  

**Background:** Patients with metastatic colorectal cancer (mCRC) with progressive disease on/after or who are intolerant to fluoropyrimidines, oxaliplatin, irinotecan, anti-angiogenic and anti-EGFR therapies have limited therapeutic options and a dismal prognosis, with a median survival below 6 months. Recently, Trifluridin/Tipiracil (TAS102) significantly improved survival in patients with refractory mCRC and ramucirumab has been approved in combination with FOLFIRI for the treatment of patients with mCRC after prior FOLFIRI/bevacizumab first line therapy. Previous studies on both components provide a strong rationale to conduct a randomized study evaluating the efficacy and safety of ramucirumab in combination with TAS102 in patients with refractory mCRC to improve efficacy and prevent resistance.  

**Methods:** This is an interventional, randomized, open label, multicenter, phase Ib study in patients with advanced mCRC. Eligible patients will be randomized 1:1 and receive either ramucirumab and TAS102 (ramucirumab 8 mg/kg on d1-15, q4w and TAS102 35 mg/m² on d1-5 and d8-12, q4w) or TAS102 alone. Primary endpoint is overall survival as assessed by the Kaplan-Meier method, assuming a 6 months survival probability of 70% with ramucirumab in combination with TAS102 and 58% with TAS102 alone. Treatment groups are compared using the log-rank test. A total of 144 patients will be enrolled at 30 sites (1-sided alpha 0.10, power 0.80). Main secondary endpoints are overall response rate, disease control rate, progression free survival and quality of life. In addition, a large comprehensive translational research program will be conducted to identify novel predictive and prognostic biomarkers. The study started in December 2018. By February 2019, a total of 3 patients have been enrolled. Clinical trial information: NCT03520946.

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**TPS3618**  
Poster Session (Board #108b), Mon, 8:00 AM-11:00 AM  
Phase III randomized sequential open-label study to evaluate the efficacy of FOLFIRI + panitumumab followed by FOLFIRI + bevacizumab (Seq. 1) versus FOLFIRI+ bevacizumab followed by FOLFIRI + panitumumab (Seq. 2) in untreated patients with wild-type RAS metastatic, primary left (L)-sided, unresectable colorectal cancer (CRC): The CR-SEQUENCE. First Author: Ramon Salazar, Oncobell Program IDIBELL Institut Català d’Onkologia Hospital Duran i Reynals, CIBEROncol, Hospitalitat, Spain  

**Background:** Both anti-EGFR and anti-VEGF therapies have shown clinical benefit when they are given sequentially in patients with stage IV CRC. The conflicting results in anti-VEGF vs. anti-EGFR studies (FIRE-3, PEAK and CALGB/SWOG 80405 studies) suggest that the sequence of targeted therapies added to FOLOX or FOLFIRI regimens in first- and second-line treatment could be an important factor in the overall survival (OS) of mCRC patients. Currently, there are no randomized data on the sequential use of an anti-EGFR followed by an anti-VEGF or vice versa. Therefore, the aim of this randomized clinical trial is to compare the efficacy of two treatment sequences, panitumumab followed by bevacizumab versus bevacizumab followed by panitumumab in combination with FOLFOX chemotherapy in first-line and with FOLFIRI in second-line in patients with wild-type RAS, primary L-sided, metastatic colorectal cancer (mCRC).  

**Methods:** A phase III, multicentre, open-label and randomized two-arm clinical trial. Untreated patients with wild-type RAS mCRC (determined locally), primary L-sided and unresectable will be screened for this trial. Eligible patients will be randomized 1:1 to receive first-line (1L) panitumumab plus FOLOX and then bevacizumab plus FOLFIRI as second-line (2L) treatment (Seq. 1) or bevacizumab plus FOLFIRI as 1L and then panitumumab plus FOLFIRI as 2L treatment (Seq. 2). Randomization will be stratified by number of metastatic organs involved (1 vs > 1). Primary objective is the comparison of the progression free survival (PFS) rate at 35 months (m) of Seq 1 vs Seq 2. Secondary objectives: will be randomized to 2nd progression or death, OS rate at 35 months and OS of Seq 1 vs Seq 2; PFS, objective response rate, disease control rate, early tumour shrinkage, Depth of Response, duration and time to response and safety in 1L treatment and in 2L treatment in each Sequence arm. Exploratory objectives: impact of baseline biomarkers predictive of the efficacy in each Sequence arm and the clinical impact of factors.  

**Background:** By longitudinal analysis of circulating tumour deoxyribonucelic acid (ctDNA) in plasma. The trial is in progress; 28 of up to 370 planned patients have been recruited at the end of January 2019 (first patient in 31 October 2018). Clinical trial information: NCT03653021.
PRODIGE 53-UCGI 30 (SULANT): A randomized phase II study comparing treatment intensification with hepatic arterial infusion chemotherapy plus systemic chemotherapy to systemic chemotherapy alone in patients with liver-only colorectal metastases considered still not resectable after at least two months of systemic induction chemotherapy. First Author: Valerie Boige, Digestive Oncology, Gustave Roussy, Villejuif, France

Background: In the first-line setting, current combination chemotherapy (CT) achieve high objective response rates (ORR) ranging from 40% to 80% and leads to complete resection rate (CRR) of colorectal cancer liver metastasis (CRLM) in 25% to 50% of patients with initially non-resectable CRLM. However, when patients with CRLM are still not amenable to resection after induction CT, ORRs (5–30%) and CRRs (< 10%) obtained with second-line systemic CT are much lower. Combining hepatic arterial infusion (HAI) and systemic (SYS) CT for unresectable CRLM lead to high ORR and the potential of cure in the second-line and further setting. Methods: This multicenter randomized phase II trial conducted in 20 centers in France plans to include 140 patients with CRLM still not amenable to a curative intent-treatment after at least two months of first-line induction SYS CT whatever the tumor response. Patients are randomized (1:1) between intensified biweekly regimen combining oxaliplatin (100 mg/m²) and SYS FOLFIRI (leu-introtecan 180 mg/m², and 5-FU 2.4 g/m² over 48 h) plus cetuximab 500 mg/m² or bevacizumab 5 mg/kg (according to RAS status and prior response/ tolerance to SYS induction CT) or SYS CT alone according to current guidelines. The primary endpoint is to evaluate and compare the curative-intent (R0-R1) resection (and/or ablation) rate (CRR) of CRLM in both arms. A gain of 20% in R1 and/or ablation rate (CRR) of CRLM in both arms is expected (30% in the experimental arm vs. 10% in the control arm; α 5% [two-sided]; β 20%). Stratification factors at randomization are prior adjuvant or SYS induction oxaliplatin-based CT, tumor response to SYS induction CT, and center. Secondary endpoints include progression-free (overall, hepatic, and extrahepatic), overall survival, and safety. This trial is required to enroll 140 patients scheduled to be followed for 2 years after last treatment. An interim analysis is planned at the 12-month follow-up to determine whether the trial should be stopped for futility or unfavourable results. This study is registered with ClinicalTrials.gov (NCT03164655).

DEEPER trial is completed. Clinical trial information: UMIN000018412.

Methods: 

A randomized phase II trial, DEEPER (JACCRO CC-13) (NCT02515734), is on-going to evaluate FOLFIRI plus cetuximab (cet) vs. FOLFIRI plus bevacizumab (bev) in terms of depth of response as primary endpoint in 360 mCRC patients (pts) with RAS wild-type tumors, comparing cet vs. bev. The clinical utility of circulating tumor DNA (ctDNA) analysis has been largely validated for monitoring during treatment and companion diagnostics after chemotherapy. However, there are few published results regarding ctRNA in cancer treatment. Use of ctRNA from liquid biopsies would enhance tumor profiling through the trending of actionable biomarkers not found in ctDNA, and allow for patient monitoring by measuring dynamic changes in levels of gene expression. Methods: This study will enroll pts with willing to undergo biopsies of both tissue and blood among participants of the DEEPER trial. The estimated number is 250. The main purpose is to find novel predictors for efficacy of cet or bev in mCRC using liquid biopsies, which are performed to obtain ctDNA and ctRNA at 6 time points: pre-treatment, 8 weeks after treatment start, beginning of maintenance phase in FOLFIRI-regimen, progression, before and 8 weeks after 2nd-line treatment. The tissue samples collected before chemotherapy will be used for analyzing intra-tumoral genetic alterations. Associations between analytes in blood/tissue and the clinical outcomes of each treatment (with cet or bev) will be assessed using Fisher’s exact test, Kaplan–Meier curves, and log-rank tests in univariate analyses. We will evaluate on whether transcriptomic analysis in ctRNA could predict treatment efficacy more accurately compared to genomic analysis in ctDNA, and verify the clinical utility of ctRNA testing in mCRC treatment. Accrual will continue until the DEEPER trial is completed. Clinical trial information: UMIN000018412.

First Author: Yu Sunakawa, Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan

Methods: 

Background: A randomized phase II trial, DEEPER (JACCRO CC-13) (NCT02515734), is on-going to evaluate FOLFIRI plus cetuximab (cet) vs. FOLFIRI plus bevacizumab (bev) in terms of depth of response as primary endpoint in 360 mCRC patients (pts) with RAS wild-type tumors, comparing cet vs. bev. The clinical utility of circulating tumor DNA (ctDNA) analysis has been largely validated for monitoring during treatment and companion diagnostics after chemotherapy. However, there are few published results regarding ctRNA in cancer treatment. Use of ctRNA from liquid biopsies would enhance tumor profiling through the trending of actionable biomarkers not found in ctDNA, and allow for patient monitoring by measuring dynamic changes in levels of gene expression. Methods: This study will enroll pts with willing to undergo biopsies of both tissue and blood among participants of the DEEPER trial. The estimated number is 250. The main purpose is to find novel predictors for efficacy of cet or bev in mCRC using liquid biopsies, which are performed to obtain ctDNA and ctRNA at 6 time points: pre-treatment, 8 weeks after treatment start, beginning of maintenance phase in FOLFIRI-regimen, progression, before and 8 weeks after 2nd-line treatment. The tissue samples collected before chemotherapy will be used for analyzing intra-tumoral genetic alterations. Associations between analytes in blood/tissue and the clinical outcomes of each treatment (with cet or bev) will be assessed using Fisher’s exact test, Kaplan–Meier curves, and log-rank tests in univariate analyses. We will evaluate on whether transcriptomic analysis in ctRNA could predict treatment efficacy more accurately compared to genomic analysis in ctDNA, and verify the clinical utility of ctRNA testing in mCRC treatment. Accrual will continue until the DEEPER trial is completed. Clinical trial information: UMIN000018412.

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First Author: Yu Sunakawa, Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan

Methods: 

Background: A randomized phase II trial, DEEPER (JACCRO CC-13) (NCT02515734), is on-going to evaluate FOLFIRI plus cetuximab (cet) vs. FOLFIRI plus bevacizumab (bev) in terms of depth of response as primary endpoint in 360 mCRC patients (pts) with RAS wild-type tumors, comparing cet vs. bev. The clinical utility of circulating tumor DNA (ctDNA) analysis has been largely validated for monitoring during treatment and companion diagnostics after chemotherapy. However, there are few published results regarding ctRNA in cancer treatment. Use of ctRNA from liquid biopsies would enhance tumor profiling through the trending of actionable biomarkers not found in ctDNA, and allow for patient monitoring by measuring dynamic changes in levels of gene expression. Methods: This study will enroll pts with willing to undergo biopsies of both tissue and blood among participants of the DEEPER trial. The estimated number is 250. The main purpose is to find novel predictors for efficacy of cet or bev in mCRC using liquid biopsies, which are performed to obtain ctDNA and ctRNA at 6 time points: pre-treatment, 8 weeks after treatment start, beginning of maintenance phase in FOLFIRI-regimen, progression, before and 8 weeks after 2nd-line treatment. The tissue samples collected before chemotherapy will be used for analyzing intra-tumoral genetic alterations. Associations between analytes in blood/tissue and the clinical outcomes of each treatment (with cet or bev) will be assessed using Fisher’s exact test, Kaplan–Meier curves, and log-rank tests in univariate analyses. We will evaluate on whether transcriptomic analysis in ctRNA could predict treatment efficacy more accurately compared to genomic analysis in ctDNA, and verify the clinical utility of ctRNA testing in mCRC treatment. Accrual will continue until the DEEPER trial is completed. Clinical trial information: UMIN000018412.

First Author: Atsuo Takashima, Division of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: Adjuvant chemotherapy is the current standard treatment for stage III colorectal cancer after curative resection. However, the prognosis of stage III colorectal cancer is still poor even after curative resection and adjuvant chemotherapy. Recently, several observational studies suggested the anti-tumor effect of aspirin for advanced colorectal cancer. The main mechanism of the anti-tumor effect by aspirin may be to suppress cyclooxygenase activity in the arachidonic acid cascade and to inhibit the production of prostaglandins involved in tumor growth. So far, aspirin showed a prolongation of survival for colorectal cancer in several retrospective studies. However, in these studies, aspirin was given not to be evaluated the effect on prognosis of colorectal cancer in adjuvant setting but to prevent cardiovascular event. In addition, baseline patient characteristics were imbalanced between aspirin group and non-aspirin group and both dosage amount and dosing period of aspirin were different among patients.

Methods: We planned a randomized double-blind placebo-controlled phase III trial commenced in Japan in March 2018 to confirm the superiority of aspirin in terms of disease-free survival (DFS) over placebo for stage III colorectal cancer patients after curative resection. Patients receive aspirin (100 mg/day) or placebo for 3 years with the standard adjuvant chemotherapy of mFOLFOX6, CAPOX or capecitabine until relapse or unacceptable toxicities. The primary endpoint is DFS and the secondary endpoints are overall survival, relapse-free survival, relative dose intensity, adverse events, and serious adverse events. We assumed the 3-year DFS of aspirin arm as 74% based on two previous trials conducted by JCOG and expected a 6% increase in the 3-year DFS with aspirin adding to the standard adjuvant chemotherapy after curative surgery. A total of 880 patients will be accrued from 20 Japanese institutions within 3 years, and 47 patients were enrolled as of Jan 31, 2019. Both aspirin and placebo are provided by Bayer Yakuhin Ltd. This trial has been registered at Japan Registry of Clinical Trials as jRCTs031180009 (https://jRCT.niph.go.jp/detail/589). Clinical trial information: jRCTs031180009.

Aspirin as adjuvant treatment for colorectal cancer: Rationale and progress of the Add-Aspirin trial.

First Author: Ruth E Langley, Medical Research Council Clinical Trials Unit at University College London, London, United Kingdom

Background: There is now a body of evidence indicating a potential role for aspirin in colorectal cancer (CRC) prevention. In cardiovascular trials, effects on incidence of cancer metastases and short-term mortality suggest further possible roles in the treatment setting, supported by observational studies of aspirin use after cancer diagnosis. In the prevention setting, aspirin use has been limited by toxicity concerns, particularly of serious bleeding. In the adjuvant setting, benefits associated with reducing recurrence and subsequent treatment may outweigh these risks. The Add-Aspirin trial will investigate this, and will also consider possible mechanisms of action for aspirin effects, including the impact of PIK3CA mutations, where there are currently several theories and conflicting data.

Methods: Add-Aspirin (ISRCTN74358648) is an international, phase III, double-blind, randomised, placebo-controlled trial recruiting patients who have undergone surgery and relevant adjuvant treatment for stage II or III CRC, as well as those with completely resected CRC liver metastases. Parallel randomised cohorts will address the question in breast, gastro-oesophageal and prostate cancer. Participants take aspirin 100mg daily for an 8-week run-in, to assess adherence and toxicity, and those suitable to proceed are randomised (1:1:1) to aspirin 100mg, aspirin 300mg or placebo daily for at least 5 years. A number of measures – including blood pressure control and PPI use where relevant - are in place to reduce bleeding risk. The primary outcome is disease-free survival (target hazard ratio = 0.8, n = 2600 in 5 years) with a long term analysis of survival planned across the tumour groups. Translational work includes a sub-study monitoring urinary thromboxane B2 as a marker of platelet activation in a subgroup (n = 500) to investigate mechanisms of action. Add-Aspirin opened in 2015 and recruited 1505 CRC patients during the first 3 years from 137 UK centres. 1282 (85%) proceeded to randomisation. A pre-planned feasibility analysis of run-in data (n = 2253 across all 4 tumour groups) provided reassuring data on safety, tolerability and adherence, and recruitment continues with centres in India and Republic of Ireland recently joining. Clinical trial information: 74358648.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
4000  Oral Abstract Session, Sun, 9:45 AM-12:45 PM
APACT: phase III, multicenter, international, open-label, randomized trial of adjuvant nab-paclitaxel plus gemcitabine (nab-P/G) vs gemcitabine (G) for surgically resected pancreatic adenocarcinoma. First Author: Mark S. Tempero, University of California, San Francisco, San Francisco, CA

Background: In metastatic pancreatic cancer (PC), nab-P/G demonstrated significantly longer overall survival (OS) vs G. APACT assessed efficacy & safety of nab-P/G vs G in surgically resected PC. Methods: Treatment (tx)-naive patients (pts) with histologically confirmed PC, macroscopic complete resection, ECOG PS 0/1, & CA19-9 < 100 U/mL were eligible. Stratification factors: resection status (R0/R1), lymph node status (LN/-/+), & geographic region. Tx was initiated ≤ 12 wks post surgery. Pts received nab-P 125 mg/m² + G 1000 mg/m² or G 1000 mg/m² on days 1, 8, 15 of 28-dx cycles. Primary endpoint was disease-free survival (DFS) by independent reviewer (IR); IRs received baseline clinical data & scans. Secondary endpoints were OS & safety. -433 DFS events were needed for 90% power to detect an HR of 0.73 with nab-P/G vs G at a 2-sided significance level of 0.05. Results: 866 pts were randomized. Median age was 64 y (range, 34 - 86); most pts had ECOG PS 0 (60%), LN+ (72%), & R0 (76%). 69% of pts completed 6 tx cycles (nab-P/G, 66%; G, 71%). Median follow-up for OS was 38.5 mo. Median IR-assessed 3-y OS rate for nab-P/G was (94% vs 88%) for R0 pts; (94% vs 89%) for LN- pts; (96% vs 96%) for geographic region. There was no difference in DFS (primary endpoint) between nab-P/G vs G (hazard ratio [HR] 0.96, 95% CI 0.92 - 1.00; stratified log-rank P = 0.41). Clinical trial information: UMIN000001795.

4001  Oral Abstract Session, Sun, 9:45 AM-12:45 PM
ARTIST 2: Interim results of a phase III trial involving adjuvant chemotherapy and/or chemoradiotherapy after D2-gastrectomy in stage II/III gastric cancer (G). First Author: Seung-Hyuk Kim, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: Adjuvant chemotherapy and/or chemoradiotherapy have been the standard of care in GC for years, supported by randomized trials. We compared the efficacy of different chemotherapy regimens and chemoradiotherapy in patients with D2-resected, stage II/III, node-positive GC. Methods: From Feb 2013 through Nov 2018, we randomly assigned, in a 1:1:1 ratio, patients with pathologically-stage II or III, node-positive, D2-resected GC, to receive adjuvant S-1 (40 - 60 mg twice daily 4-weeks-on/2-weeks-off) for one year, S-1 (2-weeks-on/1-week-off) plus oxaliplatin 130 mg/m² for six months, or SOX plus chemoradiotherapy 45 Gy (SOXRT). Randomization was stratified according to the type of surgery (total or subtotal gastrectomy), stage (II or III), and Lauren histologic classification (diffuse or intestinal). The primary endpoint was disease-free survival (DFS). A total of 90 patients had to be enrolled to demonstrate superiority of SOX or SOXRT to S-1 (hazard ratio [HR] 0.67), with 90% power at a two-sided significance level of 5%. Results: A total of 538 patients were included for this interim efficacy analysis. Median age was 58 years, men constituted 65%, and stage II and III were 31% and 69%, respectively. Baseline tumor and patient characteristics were balanced between treatment arms. Adverse events were anticipated in each arm, generally well-tolerated and manageable. DFS in the control arm (S-1) were significantly shorter than in SOX and SOXRT arms (stratified HR for recurrence S-1 vs. SOX, 0.699; 95% CI 0.633 - 0.770; P = 0.00168). Interim OS (427 events) was 40.5 mo (95% CI 36.9 - 43.9; P = 0.057). The DFS at 3-yrs was found to be 65%, 78% and 73% in S-1, SOX and SOXRT arms, respectively. No difference in DFS between SOX and SOXRT was found (HR 0.910, P = 0.667). Based on the results after the observation of 145 recurrence events at the cutoff date of Dec 27, 2018, the independent data monitoring committee considered the results sufficient to meet the endpoint of the trial and recommended early stopping of the trial. Conclusions: In patients with curatively D2-resected, stage II/III, node-positive GC, adjuvant SOX or SOXRT was effective in prolonging DFS, when compared to S-1 monotherapy. Clinical trial information: NCT0176146.

4002  Oral Abstract Session, Sun, 9:45 AM-12:45 PM
A multicenter randomized controlled trial to evaluate the efficacy of surgery vs. radiofrequency ablation for small hepatocellular carcinoma (SURF trial). First Author: Namiki Izumi, Musashino Red Cross Hospital, Tokyo, Japan

Background: Surgery (SUR) and radiofrequency ablation (RFA) are both known to be effective therapy for treating patients with small oligonodular hepatocellular carcinoma (HCC), however there is only insufficient evidence about which therapy is more preferred approach. This randomized controlled trial was designed to prospectively compare the efficacy of SUR and RFA as the first approach to primary HCC. Methods: In this open-label trial, patients were assigned to receive SUR (primary treatment) or RFA (first-line secondary treatment). Patients were then randomly assigned in a 1:1 ratio to undergo SUR or RFA, stratified by age, infection of hepatitis-C virus, number of tumors, tumor size and in-stitution. The primary endpoint was recurrence free survival (RFS) and overall survival (OS). Results: Between April 2009 and August 2015, total 308 patients were enrolled to this trial. Because of ineligibility 15 patients were excluded, therefore 145 patients underwent SUR and 148 patients underwent RFA finally. There was no perioperative mortality. Under the median follow-up of 5 years, the 3-year RFS of patients underwent SUR and RFA was 49.8%, 47.7%, respectively (hazard ration [HR] 0.96, 95% CI 0.721-1.28; p = 0.793). OS will be analyzed and published after two years. Conclusions: SUR and RFA were both safe therapeutic approaches and provided equally RFS for early stage HCC smaller than 3 cm. Clinical trial information: UMIN000001795.

4003  Oral Abstract Session, Sun, 9:45 AM-12:45 PM
ABC-06 I A randomised phase III, multi-centre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC+mFOLFOX) for patients (pts) with locally advanced / metastatic biliary tract cancers (ABC) previously-treated with cisplatin/gemcitabine (CisGem) chemotherapy. First Author: Angela Lamerac, Department of Medical Oncology, The Christie NHS Foundation Trust / Institute of Cancer Sciences, University of Manchester, Manchester, United Kingdom

Background: Level A evidence supports use of CisGem as first-line chemotherapy for ABC; no robust evidence is available for second-line chemotherapy. Methods: Pts diagnosed with ABC with disease progression after prior CisGem were randomised (1:1) to either ASC+mFOLFOX or ASC. Randomisation was stratified by serum albumin levels (< 35 vs. ≥ 35 g/L), platinum sensitivity (determined by first-line CisGem) and disease extent (locally advanced vs metastatic), Pts with CCG PS 0-1, adequate haematological, renal and liver function, and adequate biliary drainage were eligible. Primary end-point was overall survival (OS) (multicovariable Cox regression adjusted for stratification factors); sample size: 162 pts delivering 148 events were required (80% power; 5% two-sided alpha) for a hypothesised hazard ratio (HR) of 0.63. Assumed median survival for ASC was 4 months. Results: 162 pts (81 in each arm) were randomised (27 March '14 - 04 Jan '18); median age 65 yrs (range 26-84); sex: 80 (49%) male, 82 (51%) female; primary site: intrahepatic 72 (44%), extrahepatic 45 (28%), gallbladder 34 (21%) and ampullary 11 (7%). Baseline characteristics were balanced between arms except platinum sensitivity (ASC+mFOLFOX 7 pts (33%); ASC 34 pts (42%). After 150 OS events, the adjusted HR was 0.69 (95% CI 0.50-0.97; p = 0.031; ASC+mFOLFOX vs ASC). Median OS (months) (m), 6m and 12m OS-rate (%) were 6.2m, 50.6% and 25.9% for the ASC+mFOLFOX and 5.3m, 35.5%, 11.4% for the ASC arm, respectively. Grade 3/4 toxicities were reported in 12% (59%) in the ASC+mFOLFOX and 17% (39%) in the ASC arms, respectively; these were balanced between arms except for fatigue and neutropenia (more frequent in ASC+mFOLFOX arm); data cleaning is ongoing. No chemotherapy-related deaths were reported. Conclusion: Survival with ASC was greater than assumed; ASC+mFOLFOX improved OS after progression to CisGem with a clinically meaningful increase in median OS of 1.0m (12.0 months). ASC+mFOLFOX should become standard of care in second-line for ABC. Clinical trial information: NCT01926236.
Results of KEYNOTE-240: phase 3 study of pembrolizumab (Pembro) vs best supportive care (BSC) for second line therapy in advanced hepatocellular carcinoma (HCC). First Author: Richard S. Finn, University of California, Los Angeles, Los Angeles, CA

Background: Pembro received accelerated approval based on results of KEYNOTE-224, a phase 2 trial in pts with advanced HCC in the second line setting. KEYNOTE-240 (NCT02702401) was a randomized, placebo (Pbo) controlled, phase 3 study of Pembro vs BSC in pts with previously treated advanced HCC. Methods: Eligible pts had a radiographic or pathologic diagnosis of HCC, radiographic progression on/tolerance to sorafenib, Child-Pugh A disease and ECOG PS ≤1. Pts were randomized 2:1 to receive Pembro 200 mg × BSC or Pbo × BSC IV every 3 wk, stratified by geographic region, macrovascular invasion and α-fetoprotein levels for ≤35 cycles or until confirmed PD/untolerable toxicity. Response was assessed every 6 wk per RECIST v1.1 by central imaging review. Co-primary endpoints were OS and PFS. Secondary endpoints included ORR, DOR and safety. Data cutoff was Jan 2 2019 for OS; Mar 26 2018 for PFS and ORR. Results: 413 patients were randomized; 278 to Pembro and 135 to BSC. After a median follow up of 13.8 mo, 10.1% of pts remained on Pembro and 3.0% on Pbo. Pembro improved OS (HR: 0.78; one sided p = 0.0238) and PFS (HR: 0.78, one sided p = 0.0209) vs Pbo; these differences did not meet significance per the pre-specified statistical plan. ORR was 16.9% (95% CI 12.7-21.8%) for Pembro vs 2.2% (95% CI 0.5-6.4%) for Pbo (nominal one sided p = 0.00001). A stratified log-rank test based on the intend-to-treat (ITT) principle was used. Unblinding and crossover were allowed if PD confirmed by central review. Results: 171 (97 PZ, 74 PBL) pts were randomized between 6/2013-10/2015: median age 63; 56% female; 66% small bowel primary; 87% concurrent SSA. Median follow-up of 31 mo; 112 (56 PZ, 56 PBL) PFS events observed. 6 pts (4 PZ, 2 PBL) remain on initial treatment. Median PFS was 11.6 and 8.5 mo in PZ and PBL, respectively (HR = 0.53, 1-sided 90% upper confidence limit [UCL] 0.69, p = 0.0005) which crossed the pre-specified protocol efficacy boundary. 49 PL pts received PZ after PD. Median OS was 41 and 42 mo in PZ and PBL, respectively (HR = 1.13, 1-sided 90% UCL 1.51, p = 0.70). RR data will be presented. Notable grade 3+ adverse events were (PZ v. PL %) hypertension (35 v. 8), fatigue (11 v. 4), ALT (10 v. 0), AST (10 v. 0), and diarrhea (7 v. 4).

Conclusions: PZ compared to PL was associated with significant improve-ment in PFS in patients with progressive CARC. The results confirm that VEGF signaling pathway is a valid target for therapy in CARC. Support: U10CA180821, U10CA180882 https://acknowledgments.alliancefound.org. Clinical trial information: NCT01841736.

Background: Many pts with aGOAC are elderly and/or frail. We previously compared epirubicin/ oxaliplatin/ capcitabine (ECODp) vs Ocap vs Cap in a pick-the-winner study and found Ocap best. GO2 was designed to find the optimum dose of Ocap and to explore the use of an objective baseline geriatric assessment to individualize doses for maximum Overall Treatment Utility (OTU), a composite of clinical benefit, tolerability, QL and patient value.

Methods: Pts with aGOAC were eligible if unsuitable for full-dose ECODp due to age or frailty, but fit for Ocap; GFR ≥ 30, bili <2x UFLN. Baseline assessment included global QL; symptoms; functional scales; comorbidity; frailty. Randomization was 1:1:1 to dose Level A (Ox 130 mg/m² d1, Cap 625 mg/m² bd d1-21, q21d), B (80% Level A doses) or C (60% Level A doses). Pts with GFR 30-50 ml/min or bili 1.5-2.0 xULN received 75% of the allocated dose of Cap. At 9 wks, pts were scored for OTU. Continuation thereafter was based on clinical judgement. Non-inferiority (vs A) was assessed using PFS censored at 12 months, with boundary HR 1.34 (based on discussion with pts and clinicians), needing 284 PFS events per 2-way comparison. Baseline fitness was assessed as predictive of OTU, overall and by interaction with dose level.

Results: 514 pts were randomised, 2014-17, at 61 UK centres. Clinical trial information: 44687907. Non-inferiority of PFS is confirmed for Level B vs A (HR 1.09, CI 0.89-1.32) and for Level C vs A (HR 1.0, CI 0.90-1.33). Level C pts had less toxicity and better OTU outcomes than A or B. When analysed by baseline age, frailty and PS, Level C produced the best OTU even in younger, less frail and better PS patients; no group was identified who benefit more from the higher dose levels. Conclusions: This is the largest RCT to date specifically investigating frail and/or elderly aGOAC pts, and should guide future treatment. The lowest tested dose was inferior in terms of PFS and produced less toxicity and better overall treatent utility.

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Efficacy and safety of pembrolizumab (pembro) alone or in combination with chemotherapy (chemo) in patients (pts) with advanced gastric or gastroesopha-
geal (G/G) cancer: Long-term follow up from KEYNOTE-059. First Author: Zev A. Wainberg, David Geffen School of Medicine at UCLA, Los Angeles, CA

Background: Interim analysis of a global, phase 2 KEYNOTE-059 study (NCT02335411) reported manageable safety and promising antitumor activity for pembro alone or pembro + chemo in pts with G/G cancer. Here we report long-term efficacy and safety data of all 3 cohorts. Methods: pts with recurrent or metastatic G/G adenocarcinoma were enrolled in 3 cohorts. Cohort 1 pts (PD-L1 positive or negative) received pembro alone after 2 prior lines of therapy. Cohort 2 pts (PD-L1 positive or negative) received pembro + cisplatin (80 mg/m^2 day) 1 + 5-fluorouracil (800 mg/m^2 days 1-5) Q3W or capecitabine (in Japan only, 1000 mg/m^2 twice daily) as first-line. Cohort 3 pts (PD-L1 positive, combined positive score ≥1% using the PD-L1 IHC 22C3 pharmDx assay) received pembro alone as first-line. All pts received pembro 200 mg Q3W for up to 2 years. End points included safety, ORR, DOR, and OS. Results: At data cutoff (Aug 6, 2018), median (range) follow-up was 6 (1-38), 14 (2-40), and 21 (2-36) months for cohorts 1 (n = 259), 2 (n = 25), and 3 (n = 31), respectively. In cohort 1, confirmed ORR (95% CI) was 11.6% (8.16) overall, 15.5% (10.22) in PD-L1-positive, and 6.4% (3.13) in PD-L1-negative tumors. In cohort 2, confirmed ORR was 60.0% (39-79) overall, 73.3% (45-92) in PD-L1-positive, and 37.5% (9-76) in PD-L1-negative tumors. In cohort 3, confirmed ORR was 25.8% (14-45). Median (range) DOR in months was 16.1 (2.35) , 4.6 (3-37+) , and not reached (2.3-21.5) in cohorts 1, 2, and 3, respectively. OS at 1 year/2 years was 24.6%/12.5%, 52%/32%, and 63.6%/40% in cohorts 1, 2, and 3, respectively. In cohorts 1, 2, and 3, 3 grade 5 treatment-related adverse events (TRAEs) led to discontinuation in 6 (2%) and 3 (12%) pts in cohorts 1 and 2, respectively, and to death in 2 (1%) pts in cohort 1. No TRAEs led to discontinuation or death in cohort 3. Conclusions: These updated results demonstrate manageable safety, durable clinically meaningful activity of pembro in heavily pretreated pts, and promising efficacy of first-line pembro (alone or + chemo) in pts with advanced G/G cancer. Clinical trial information: NCT02335411.

4011 Poster Discussion Session; Displayed in Poster Session (Board #116), Mon, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:30 PM

First-line pembrolizumab (P), trastuzumab (T), capecitabine (C) and oxaliplatin (O) in HER2-positive metastatic esophagogastric adenocarcinoma. First Author: Yelena Yury-Janjigan, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Trastuzumab stimulates HER2-specific T cell responses and enhances tumor PD-L1 expression, and anti-PD-1 antibody can help enhance T cell-specific immunity of trastuzumab. We conducted a phase I trial of pembrolizumab with chemotherapy/trastuzumab. Methods: Patients (pts) with previously untreated HER2 IHC 3+ or FISH+ tumors irrespective of PD-L1 status received intravenous P 200 mg flat dose, T 6 mg/kg (after 8 mg/kg load), and C 850 mg/m^2 2 weeks on/1 week off. 22 pts received pembrolizumab with chemotherapy/trastuzumab. Results: Median PFS was only 6.6 mo. In pts with available material, 14/36 (40%) had PD-L1 CPS ≥10. Median PFS was 11.3 months (mo), with 67% 6 mo PFS. Median OS was 7.1 mo, 12-mo OS rate was 40%. In the ITT, median OS was 7.1 mo vs 7.1 hr, HR 0.89; 95% CI 0.75-1.05; P = 0.0560. Updated OS will be presented. Grade 3-5 drug-related AEs (≥10% incidence in either arm) included decreased white blood cells (0% vs 10%), decreased neutrophils (0.3% vs 10%). In CPS ≥10, HRQoL improved with pembrolizumab vs chemo only for EQ-5D VAS (difference in LS mean change from baseline 5.57, 95% CI 0.58-10.56). Conclusions: Pembrolizumab significantly improved OS vs chemo as second-line therapy for advanced esophageal cancer with PD-L1 CPS ≥10; more than a favorable safety profile and stable and similar QOL. These data support pembrolizumab as a new second-line standard of care for esophageal cancer with PD-L1 CPS ≥10. Clinical trial information: NCT02564263.

4012 Poster Discussion Session; Displayed in Poster Session (Board #117), Mon, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:30 PM

Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): Results from CheckMate 040. First Author: Thomas Yau, The University at Hong Kong, Hong Kong, China

Background: NIVO monotherapy (mono) is approved for sorafenib (SOR)-treated pts with HCC based on data from CheckMate 040 (NCT01658878), which reported an overall response rate (ORR), disease control rate (DCR), median OS, median progression-free survival (PFS), and median duration of response (DOR) of 16 months (mo). This is the first report of efficacy and safety of the NIVO + IPI combination in SOR-treated pts with aHCC. Methods: Pts were randomized to 3 arms: (A) NIVO 1 mg/kg + IPI 3 mg/kg Q3W (4 doses) or (B) NIVO 3 mg/kg + IPI 1 mg/kg Q3W (4 doses), each followed by NIVO 240 mg Q2W, or (C) NIVO 3 mg/kg + IPI 1 mg/kg Q6W. Treatment continued until intolerable toxicity or disease progression. Primary endpoints included safety and tolerability. Secondary endpoints included ORR (BICR per RECIST v1.1), duration of response (DOR), disease control rate (DCR), and OS. Cutoff was 25 Sep 2018. Results: 148 SOR-treated pts were randomized. Median follow-up for OS from last pt randomization date to data cutoff was 24 mo. At baseline, 88% had vascular invasion or extrahepatic spread, 91% had BCLC stage C, 84% discontinued SOR due to disease progression and 14% due to toxicity. Overall, ORR was 31% (7 had a complete response [CR]) with a median DOR of 17 mo, DCR was 49% and 24-mo OS rate was 40%. Pts in arm A had a mOS of 23 mo and pts in arm B had a mOS of 10.1 mo. The table shows additional efficacy results by arm. At 18 mo, 63% in arm A had PD-L1 CPS ≥10. The table shows additional efficacy results by arm. At 18 mo, 63% in arm A had PD-L1 CPS ≥10. Conclusions: NIVO + IPI led to clinically meaningful responses and had an acceptable safety profile in SOR-treated pts, with an ORR twice that of NIVO mono and a more favorable safety profile and stable and similar QOL. These data support pembrolizumab as a new second-line standard of care for esophageal cancer with PD-L1 CPS ≥10. Clinical trial information: NCT02564263.
Randomized phase II study of second-line modified FOLFIRI with PARP inhibitor ABT-888 (Veliparib) (NSC-737664) versus FOLFIRI in metastatic pancreatic cancer (mPC): SWOG S1513, First Author: E. Gabriela Chioran, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA

Background: PC is characterized by DNA Damage Repair (DDR) deficiencies, including in BRCA1/2, ATM, and FANC genes. Given preclinical synergism between veliparib with irinotecan, safety and preliminary efficacy, we designed a randomized phase II study of mFOLFIRI (no 5-FU bolus) + veliparib vs FOLFIRI alone for 2nd line mPC patients (pts). Methods: Eligible pts had mPC, adequate organ function, ECOG PS 0-1, and 1 prior non-irinotecan systemic therapy. 143 pts were to be randomized (1:1) to veliparib vs control. Primary endpoint was overall survival (OS). All pts had blood and tumor biopsies at baseline to assess germline and somatic BRCA1/2 mutations (in-integrated), and homologous recombination (HR) or DDR biomarkers (exploratory). Results: 123 pts were accrued between 09/2016 to 12/2017, and 108 were included in this analysis. 117 pts were biomarker evaluable: 109 blood/106 tumors. 11 cancers (9%) had HR deficiency (HRD), including 4 germline (BRCA1, BRCA2, ATM) and 7 somatic mutations (BRCA2, PALB2, ATM, CDK12). Additional 24 cancers (20%) had germline (n = 11, e.g., FANC, BLM, SLX4, CHEK2) or somatic mutations (n = 13, e.g., FANC, BLM, POLE, RIF1, MSH2, MSH6) in other DNA repair genes, not classified as HRD. A plateau of veliparib efficacy was seen at 35% of expected PFS events detected, implying the veliparib arm was unlikely to be superior to control. Most common grade 3/4 treatment related toxicities were neutropenia (33% vs 20%), fatigue (19% vs 4%), and nausea (11% vs 4%), for veliparib vs control. Treatment exposure was similar for veliparib vs control: median 4 cycles (range 1-3 vs 1-32). Median OS was 15.7 vs 19.3 mos (HR 1.3, 95%CI 0.9-1.8, p = 0.21), and median PFS was 2.1 vs 2.9 mos (HR 1.5, 95%CI 1.0-2.2, p = 0.05) for veliparib vs control arms, respectively. Correlations of gene mutations and signatures with efficacy outcomes will be presented. Conclusions: Nearly 30% of mPC pts had DNA repair gene abnormalities, including 9% with HRD. Veliparib treatment did not improve OS when added to mFOLFIRI in biomarker unselected pts, BRCA1/2 and DDR biomarkers will be correlated with efficacy to inform patient selection for future PARP inhibitor clinical trials. Clinical trial information: NCT02890355.

Rivaroxaban thromboprophylaxis in ambulatory patients with pancreatic cancer: Results from a prespecified subgroup analysis of the CASSINI study, First Author: Saroj Vadhan-Raj, The University of Texas MD Anderson Cancer Center, Department of Sarcoma Medical Oncology, Section of Cytokines and Supportive Oncology, Houston, TX

Background: Rivaroxaban thromboprophylaxis has been shown to reduce venous thromboembolism (VTE) in patients receiving anticoagulation in a recent randomized trial. Pancreatic cancer patients are at substantial risk for VTE; value of thromboprophylaxis has not been definitively established. Methods: CASSINI was a double-blind placebo-controlled trial of cancer patients initiating a new regimen, at high risk for VTE (Khorana score ≥2), randomized to rivaroxaban 10 mg daily or placebo up to 180 days. Patients were stratified by presence or absence of pancreatic cancer. Patients had screening ultrasound and blood drawn at baseline and every 8 wks. Primary efficacy endpoint was a composite of symptomatic DVT, asymptomatic proximal DVT, any PE and VTE-related death. Primary safety endpoint was International Society on Thrombosis and Hemostasis (ISTH)-defined major bleeding. Results: Of 1080 patients enrolled, 49 (4.5%) failed screening due to VTE. Median age was 66 y; 57% male and 155/273 (57% in each arm) completing the double-blind period. During intervention (on-treatment) period, 5/35 (3.7%) pancreatic cancer patients in the rivaroxaban arm and 14/138 (10.1%) in placebo arm had primary endpoint events (HR 0.35, 95%CI 0.13, 0.97, p = 0.03; number needed to treat, NNT = 16). Major bleeding was not increased, occurring in 2 (1.5%) patients in rivaroxaban arm and 3 (2.3%) in placebo arm. Further benefit with rivaroxaban was observed when including primary and secondary endpoints (arterial/visceral events): 6/35 (4%) events in rivaroxaban vs 17/313 (12%) in placebo (HR, 0.34, 95%CI 0.14, 0.87, P = 0.02; NNT = 13). Correlative biomarker studies demonstrated significant decline in D-dimer values over time (weeks 8 and 16) in patients without VTE randomized to rivaroxaban prophylaxis compared to placebo (P = 0.03). Conclusion: Increased safety and efficacy of rivaroxaban substantiates the need for reduced VTE in pancreatic cancer patients during intervention period. Given no increase in major bleeding, our findings suggest benefit to rivaroxaban thromboprophylaxis in pancreatic cancer patients initiating systemic therapy. Clinical trial information: NCT02595878.

4017 Oral Abstract Session, Sun, 9:45 AM-12:45 PM
S-1 plus oxaliplatin versus S-1 plus cisplatin as first-line treatment for advanced diffuse-type or mixed-type gastric/gastric-oesophageal junction adenocarcinoma: A randomized, phase 3 trial, First Author: Rui-hua Xu, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Diffuse-type or mixed-type gastric adenocarcinoma is associated with poor prognosis, and more effective treatment is needed. In Asia, S-1 plus cisplatin (SP) is the standard first-line chemotheraphy regimen for advanced gastric cancer. Nevertheless, some clinical data suggested that oxaliplatin-based chemotherapy might be more effective and well-tolerated, and shows promising efficacy particularly in naive-pancreat-ic cancer patients who are FHC- and/or harbor DDR mutations. A randomized trial to assess the contribution of Vel to the regimen is warranted. Clinical trial information: NCT01489865.
Background: We evaluated a PET-guided treatment stratification for improvement in obtaining negative surgical margins (RO) in resectable gastroesophageal junction (GEJ) adenocarcinoma. According to sequential 18F-FDG PET, only 40–50% of patients (pts) respond to neoadjuvant chemotherapy (CTX). PET non-responders (P-NR) after induction CTX might benefit from changing to chemoradiation (CRT).

Methods: 75 pts with resectable GEJ adenocarcinomas were enrolled in this interventional, prospective, non-randomized multicenter trial. Pts underwent baseline 18F-FDG PET scan followed by 1 cycle of CTX (physicians' choice, e.g. EOX, XP, mFOLFOX6). PET was repeated at day 14–21 and responders (R), defined as: ≤35% decrease in SUVmax from baseline, continued with CTX. P-NR switched to CRT (41.4 Gy/23 fractions with weekly carboplatin/paclitaxel). Pts underwent surgery 4–6 weeks post-CTX/CRT. Primary objective was an improvement of R0 resection rates in P-NR above a proportion of 70% based on results from the MUNICON1/2 trials. Secondary endpoints include disease-free survival (DFS), overall survival (OS), measured from randomization to death from any cause, and translational endpoints.

Results: Between 12/2014 and 07/2018 160 pts with resectable GEJ adenocarcinomas were prospectively screened with PET in three German university centers. Overall, 75/160 (47%) P-R could not be upstaged to RO on initial PET. PET non-responders (P-NR) had 40% (20/50) locally recurrent/metastatic disease prior to CTX. P-NR after induction CTX had: 20% (10/50) non-responders (pCR), 80% (40/50) responders (pCR), pCR: < 10% vital tumor cells, was 33% (15/46) in P-R and 55% (12/22) in P-NR. With a median follow-up time of 19 months (mo), estimated 18 mo DFS was 71%/61% for P-R/P-NR, respectively. Observed median 18 mo OS was 95% for P-R and 75% for P-NR.

Conclusions: Alternative CRT for GEJ adenocarcinoma improved R0- and pCR rates compared to pts who were P-NR after induction CTX. PET response was prognostic for a prolonged OS and DFS. Clinical trial information: 2014-00860-16.

Background: The number of patients undergoing laparoscopy-assisted distal gastrectomy (LADG) has been increasing worldwide. Several retrospective studies have demonstrated equivalent survival after LADG compared to open distal gastrectomy (ODG). However, no controlled randomized trials has been published in a peer review journal to evaluate the efficacy of LADG compared with ODG, ensuring strict surgical skill and quality control of surgery. We conducted phase III study to confirm that LADG is not inferior to ODG in efficacy. Methods: Eligibility criteria included histologically proven adenocarcinoma in the middle or lower third of the stomach; clinical stage I-III gastric cancer. This report focused on the chemo-refractory AGC cohort receiving toripalimab (3 mg/Kg d1, Q2W) as a single agent therapy. Primary endpoint was ORR. Biomarkers including tumor PD-L1 expression, TMB, microsatellite instability (MSI) and Epstein-Barr virus (EBV) infection status were evaluated for their correlation with clinical efficacy as preplanned. Tumor PD-L1 expression was assessed with the SP142 immunohistochemistry assay, and the other biomarkers were assessed with whole exome sequencing based on tumor samples. Results: There were 58 subjects included in this cohort. The ORR was 12.1% and the disease control rate was 39.7%. Only 1 subject was MSI-H and achieved partial response. One out of 4 EBV positive subjects achieved partial response. Significant higher ORR was observed in subjects with positive PD-L1 expression (ORR 37.5%, 3/8) or TMB ≥12 Mutations/Mb (ORR 33.3%, 4/8) than those with negative PD-L1 expression (ORR 8.5%) or TMB < 12 Mutations/Mb (ORR 7.0%). The TMB-high subgroup showed significant superior OS than the TMB-low subgroup (HR = 0.48 [96% CI 0.24 to 0.96], p = 0.038), while PD-L1 expression status failed to differentiate OS.

Conclusions: This trial showed that LADG is not inferior to ODG in efficacy and demonstrated promising anti-tumor activity in chemo-refractory AGC patients. TMB might serve as a better predictive marker for OS than PD-L1 expression for chemo-refractory AGC patients receiving PD-1 blockade immunotherapy. Clinical trial information: NCT02915432.

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Impact of age and sex on chemotherapy (CTx) efficacy, toxicity and survival in early oesophageogastric (OG) cancers: A pooled analysis of 3265 patients from four large randomised trials (ECOG, OEDS, MAGIC, STO 3). First Author: Avani Athauda, The Royal Marsden Hospital, Surrey, United Kingdom

Background: No large scale randomised data exists evaluating the impact of age and sex in pts (pts) undergoing potentially curative surgery and CTx for OG cancer. However, differences in age and sex may be contributing factors to variability in CTx dose-response and toxicity which could also impact survival.

Methods: Data from four prospective randomised controlled trials were pooled using a two-stage meta-analysis. For survival data, hazard ratios were calculated for pts <70 vs ≥70 years and between males and females. Pts were allocated to receive neoadjuvant platinum and fluoropyrimidine +/- anthracycline and bevacizumab. Mandard tumour regression grade (TRG) and prevalence of ≥3 toxicities were compared across the same subgroups using Chi-squared test. Results: 3265 pts were included for survival analysis (2668 (82%) M, 597 (18%) F; 2626 (80%) <70, 639 (20%) ≥70). A significant improvement in disease specific survival (DSS) (HR 0.78; P = 0.001) and OS (HR 0.78; P = 0.001) was observed in females vs males. Although OS was worse in older vs younger pts (HR 1.15; P = 0.02) no significant difference in DSS was observed (HR 1.04; P = 0.52). For those pts who underwent resection following neoadjuvant CTx, older patients (19% vs 13%; P = 0.01) and female patients (19% vs 13%; P = 0.02) were more likely to achieve a more favourable Mandard TRG 1&2 scores. Older pts experienced significantly more ≥3 toxicity (30 vs 22%; P = 0.004). Females experienced significantly more ≥3 nausea/vomiting (5% vs 3%; P = 0.001) and diarrhoea (9% vs 4%; P = 0.001). Conclusions: This study represents the largest pooled analysis of age and sex differences on safety of neoadjuvant CTx and survival in early OG cancer. Female pts had significantly improved survival while experiencing more GI toxicities. Older pts achieved comparable DSS and thus, dependent on fitness, should be offered the same treatment paradigm as younger pts.

Background: Human epidermal growth receptor 2 (HER2) is considered as an oncogenic driver gene in gastric cancer (GC). Immunotherapy has been proven to be effective in GC patients. Previous studies indicated that patients harboring driver mutations were considered as poor candidate for immunotherapy. But the efficacy of immunotherapy for HER2 positive GC has not been defined. We therefore analyzed the immunogenicity of HER2 alterations in GC.

Methods: Genomic profiling of DNA from 448 GC was performed using next-generation sequencing on 381 cancer associated genes. The expression of PD-L1 protein was evaluated in 192 GC with the use of an automated immunohistochemical assay (Ventana, SP263). Whole-exome sequencing, copy number variations, RNA-seq and clinical data of 443 GC from The Cancer Genome Atlas (TCGA) were also analyzed to further evaluate the immunogenicity of HER2 alterations. TMB was defined as number of somatic non-synonymous mutations in coding regions. HER2 amplification in TCGA was defined as ≥2 derived from the copy-number analysis algorithms GISTIC.

Results: HER2 alterations including amplification, missense and fusion were present in 19.2% (85/443) of TCGA cohort and 11.4% (51/448) of clinical cohort. 14.0% (62/443) of TCGA cohort and 6.0% (27/448) of clinical cohort harbored HER2 amplification. Higher TMB was observed in MSS/MSI-L patients carrying any HER2 alterations in TCGA cohort (P = 0.018), MSS/MSI-H patients carrying any HER2 alterations in TCGA cohort (P = 0.018) and MSS/MSI-L patients carrying any HER2 alterations in clinical cohort (P = 0.018). Meanwhile, 14.2% (51/356) of patients who were at stage T4, 22.8% (51/226) of patients with PD-L1 expression and 40.9% (23/56) of patients with HER2 amplification in clinical cohort were found to be in Cohort I. For the first-line treatment, the median OS in Cohort I was 22.4 months, and the median PFS was 9.5 months.

Conclusions: This study highlights the clinical and biological significance of HER2 alterations in GC and is an opportunity for developing novel strategies for the treatment of HER2-overexpressing GC patients.
A phase II study of S-1, oxaliplatin, and nab-paclitaxel, and itraconazole aimed at conversion surgery for advanced and recurrent gastric cancer. First Author: Yoshikazu Akamatsu, Meisei University, Tokyo, Japan

**Background:** Preclinical and clinical studies demonstrated that itraconazole, a common anti-fungal agent, has anticancer activity. The purpose of this study was to evaluate the efficacy of the chemotherapy with itraconazole on unresectable, metastatic, and recurrent gastric cancer. **Methods:** All patients were referred to our clinic with a clinical diagnosis of unresectable gastric cancer. The regimen consisted of 160 mg/m2 nab-paclitaxel IV on day 1, 100 mg/m2 oxaliplatin IV on day 1, 60 mg/m2 S-1 orally on days 1-7, and 400mg itraconazole orally on days 1-3, repeated every 3 weeks. Conversion surgery was allowed. The primary endpoint was overall survival (OS). **Results:** Between 2015 and 2018, 23 patients were enrolled. Their median age was 68 years (range 40-80 years); stomach/gastroesophageal junction: 21/2; Stage IIIA/IIIB/IV: 2/1/20. Among 10 patients who had liver metastases, 2 had simultaneous lung metastases. Nine patients had peritoneal dissemination. Five patients with stage IV had recurrent disease after primary surgery followed by adjuvant S-1. The other 18 patients had no history of surgery or chemotherapy. Response rate was 70% (CR/PR: 2/14). Among 12 patients (67%) who had conversion surgery, R0 resection was conducted in 8 and no residual disease was observed in 2. Among enrolled 23 patients, median OS was 22 months (95%CI: >12 months) and 1-year OS rate was 81.8% (95%CI: 46.7%-95.5%). Grade 3/4 neutropenia in 5 (22%), no grade 3/4 thrombocytopenia, grade 2 peripheral sensory neuropathy in 6 (26%). **Conclusions:** The addition of itraconazole to chemotherapy showed promising efficacy with high conversion surgery rate and with acceptable toxicities. Clinical trial information: UMINFO0021340.

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**Perioperative chemotherapy alone versus preoperative chemoradiotherapy for locally advanced distal esophageal and gastroesophageal junction cancer: A 10-year review of the British Columbia (BC) Cancer Registry. First Author: Shirin Lucy Liu, BC Cancer, Vancouver, BC, Canada

**Background:** The optimal treatment strategy for resectable cancer of the distal esophagus (ESOPH) and gastroesophageal junction (GEJ) remains controversial. This study evaluates patterns of practice in BC, rates of complete surgical resection, and survival outcomes of patients treated with perioperative chemotherapy alone (CA), per MAGIC or FLOT4 protocol, versus preoperative chemoradiotherapy (CRT), per CROSS protocol. **Methods:** We undertook a provincial analysis of initially resectable, locally advanced, cancer of the ESOPH and/or GEJ who underwent surgery in BC, from 2008 to 2018. Baseline patient, tumor, treatment, and clinical outcome data were collected from the BC Cancer Registry. Kaplan-Meier survival and multivariate regression analyses were conducted. **Results:** Among 575 patients, 468 underwent surgery and were included (Table). More surgeries were aborted intraoperatively in the CA cohort compared to CRT (12% vs 2%, p <0.001). There was no difference in age, sex, or ECOG performance status among the cohorts, and 83% were adenocarcinoma. While 82% of ESOPH involving GEJ (N=251, 54%) is treated with CRT, only 53% of GEJ alone (N=217, 46%) is treated with CRT (p<0.001). CRT is associated with a higher rate of complete or partial pathologic response compared to CA (59% vs 39%, p=0.002). R0 resection rate was 90% and 94% in the CA and CRT cohort, respectively (p=0.383). There is no statistically significant difference in overall survival, with medians of 29.6 and 26.0 months for patients treated with CA and CRT, respectively (p=0.723). Cancer-specific survival is also not significantly different (p=0.565). In the CA cohort, 37% of patients complete all 8 cycles of FLOT and 52% of patients complete all 6 cycles of MAGIC (p=0.396).

**Conclusions:** Patients treated with CRT have higher rates of complete resection and pathologic response, but their survival advantage is not significantly different compared to those treated with CA.

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**Clinicopathological features of Epstein–Barr virus associated gastric carcinoma with submucosal invasion. First Author: Hiroki Osumi, Department of Gastroenterology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

**Background:** The incidence of lymph node metastasis (LNM) in pathological T1b (pT1b) gastric cancer (GC) is around 20% and the majority of them have no LNM. The Cancer Genome Atlas Research Network proposed the concept of molecular phenotype classifying GC into 4 phenotypes including Epstein–Barr virus (EBV)-positive gastric cancer (EBVG). EBV positive gastric cancer (EBVG) is associated with a low prevalence of LNM; however, EBV status is not considered in the present indication of endoscopic resection (ER). We aimed to clarify the implication of EBV status for ER of T1b GC. **Methods:** Consecutive cases of pT1b GCs treated with curative surgery between 2005 and 2014 were retrospectively analyzed. Tissue microarray was made and EBV-encoded RNA in situ hybridization was performed for evaluation of EBV status. Clinicopathological factors and LNM status were compared between EBVG and non-EBVG groups. **Results:** Among the 1221 pT1b GCs that underwent gastrectomy with regional lymph node dissection, 898 pT1bGCs were eligible in this study. EBVG accounted for 7.9% (71 of 98) cases. Compared to non-EBVG, EBVG was more frequent in males (p = 0.0055), the upper third region (p < 0.0001), showed elevated growth features (p = 0.0059), and was associated with a lower frequency of accompanying ulceration (p = 0.0022), greater depth of submucosal invasion (p = 0.017), and lower frequency of lymphatic invasion (p < 0.0001). Frequency of LNM was significantly lower in EBVG than in non-EBVG (4.2% vs. 21.9%, p < 0.0001). In EBVG, tumors without lymphovascular invasion showed significantly lower frequency of LNM than those with lymphovascular invasion (0 of 50, vs 3 of 21, 14.3%; p = 0.023). Histologically, 84.5% (60 of 71) of EBVG included carcinomas with lymphoid stroma and/or lacriform components. **Conclusions:** pT1b EBVG is a convincing candidate for ER, regardless of risk factors other than lymphovascular invasion.
Camrelizumab combined with capecitabine and oxaliplatin followed by camrelizumab and apatinib as first-line therapy for advanced or metastatic gastric or gastroesophageal junction cancer: Updated results from a multicenter, open label phase II trial. First Author: Lin Shen, Beijing Cancer Hospital, Beijing, China

Background: Capecitabine plus oxaliplatin (CAPOX) is one of the standard first-line treatments for advanced or metastatic gastric cancer. Camrelizumab (SHR-1210, an anti–PD-1 antibody) shows promising anti-tumor activity in patients (pts) with advanced or metastatic gastric or gastroesophageal junction (G/GEJ) cancer. Camrelizumab combined with CAPOX for untreated G/GEJ cancer was assessed as a part of an ongoing multicenter, open-label phase 2 trial (cohort 1), and encouraging preliminary results were reported. Here, we present the updated safety and efficacy data.

Methods: In this cohort, systemic treatment naïve pts with HER2 advanced or metastatic G/GEJ adenocarcinoma were given camrelizumab 200 mg on Day 1, capcitabine 1000 mg/m² on Days 1-14, and oxaliplatin 130 mg/m² on Day 1 of each 21-day-cycle for 4 to 6 cycles followed by camrelizumab 200 mg every 3 weeks plus apatinib 375 mg qd until disease progression or intolerable toxicity. The primary endpoint was objective response rate.

Results: At data cutoff (Jan 20, 2019), 4 of the 48 enrolled pts were evaluable. Partial response was observed in 28 pts (65%), and 19 (44%) were confirmed. Stable disease in 14 pts and progressive disease in 10 pts were reported. Median estimates for duration of response and progression-free survival were not reached. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 9 pts (21%), included neutropenia, diarrhea, rash and elevated creatinine, grade 2 anorexia, and grade 3 leucopenia and grade 3 anemia. No treatment-related deaths were reported.

Conclusion: The updated results confirmed that camrelizumab plus CAPOX followed by camrelizumab plus apatinib was well tolerated with notable antitumor activity as first-line therapy in advanced or metastatic G/GEJ cancer pts. Expansion of this cohort in a phase 3 study are under way. Clinical trial information: NCT03472365.
Prognostic value of serum soluble programmed death-ligand 1 (sPDL1) and dynamics during chemotherapy in advanced gastric cancer patients. First Author: Wooschan Park, Seoul National University Hospital, Seoul, South Korea

Background: The soluble form Programmed Death-Ligand 1 (sPDL1) is suggested to have immunosuppressive activity and under investigation as a candidate biomarker for immuno-oncology drug development. In this study, we measured the serum sPDL1 at pre-and post-chemotherapy and evaluated its prognostic implication and dynamics during chemotherapy in advanced gastric cancer (GC). Methods: We prospectively enrolled 68 GC patients who were candidates for palliative standard first-line chemotherapy, and blood was serially collected at pre-and post-one cycle of chemotherapy, at best response and disease progression. sPDL1 was measured using an enzyme-linked immunosorbent assay. Response to chemotherapy, overall survival (OS), progression-free survival (PFS) and other prognostic factors including neutrophil-lymphocyte ratio (NLR) were obtained. The cut-off values of sPDL1 levels and changes for survivals were found using C-statistics. Results: The median baseline sPDL1 was 0.8ng/mL (range, 0.06 - 6.06ng/mL). The median OS and PFS were 14.9 months (95% CI: 7.3 - 22.4) and 8.0 months (95% CI: 5.9 - 10.6), respectively. sPDL1 and NLR showed a positive correlation. Patients with low levels of sPDL1 at diagnosis (< 1.92ng/mL) showed a better OS and PFS than the patients with a high sPDL1 (OS: 18.3 vs. 95 months, P = 0.057; PFS: 8.6 vs. 6.0 months, P = 0.04). The baseline sPDL1 before treatment were higher in the PD group than in the SD and PR groups (mean: 2.91, 1.17, 1.19, P = 0.019). Patients whose sPDL1 increased after first cycle of chemotherapy showed the tendency of worse PFS and OS with disease progression. sPDL1 increased compared with baseline (mean: 1.3, 1.45, P = 0.029). Conclusions: sPDL1 at pre-chemotherapy confers the prognostic value for PFS and OS in GC patients under palliative first-line chemotherapy. The dynamics of sPDL1 correlated with disease course.

Association of frequent amplification of chromosome 11q13 in esophageal squamous cell carcinoma with clinical benefit to immune checkpoint blockade. First Author: Feng Wang, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Esophageal squamous cell carcinoma (ESCC) is the predominant histological subtype of esophageal cancer in South America and East Asian countries and remains an unmet medical need worldwide. Previous studies have shown the efficacy of programmed cell death 1 (PD-1) targeted therapy in a subset of patients with metastatic ESCC. However, robust predictive biomarkers to PD-1 antibody-based immunotherapy remain undefined. Methods: Patients included in this analysis were part of multi-center, phase Ib/I trial (NCT02915432) evaluating the safety and activity of toripalimab, a humanized PD-1 antibody in solid tumors. To identify molecular determinants of response, we performed whole-exome sequencing (WES), messenger RNA sequencing and immunohistochemistry on patients’ samples and evaluated genomic and transcriptional biomarkers, PD-L1 expression and tumor mutational burden (TMB) for correlation in this analysis were part of multi-center, phase Ib/II trial (NCT02915432). Results: The soluble form Programmed Death-Ligand 1(sPDL1) is suggested to have immunosuppressive activity and under investigation as candidate biomarker to PD-1 based immunotherapy. Further, in subgroup with female primary tumor site, peritoneal metastases, ascites, lymphadenopathy in peritoneal cavity, number of organs involved > 2, sPDL1 was statistically significantly better than FOLFOX in PFS. Intravenously docetaxel plus S1 still saw response after IPF. Conclusions: both either POI or IPF improved survival compared to FOLFOX, especially in patients with female primary tumor metastasis. Only POF, not IPF, improved response rate compared to FOLFOX. Clinical trial information: NCT02845908.

Trifluoridipiracil (FTD/TPI) in patients (pts) aged >65 years with metastatic gastric/gastric/esophageal cancer (mGC/mGES). Subgroup analysis from TAGS. First Author: Kohei Shiitara, National Cancer Center Hospital East, Chiba, Japan

Background: 60% of newly diagnosed GC pts are >65 y of age, a proportion that is increasing. The global phase 3 study TAGS (NCT25000443) demonstrated the efficacy and safety of FTD/TPI in previously treated pts with mGC/mGES. Here we report results in the pt subgroup aged >65 y in TAGS. Methods: Pts with mGC/mGES treated with ≥2 prior chemotherapy regimens were randomized (2:1) to receive FTD/TPI (35 mg/m² BID on days 1—8 of each 28-day cycle) or placebo, plus best supportive care. A preplanned efficacy analysis was performed in pts aged ≥65 y. Results: Of 507 randomised pts, 272 (46%) were aged ≥65 y (range 65—89). Of these, 131 (48%) were ≥75 y. Following treatment, median (95% CI) overall survival was 10.3 months (8.2—12.6) in the ≥65 y subgroup vs 13.1 months (10.9—15.1) in the overall population (HR 1.195; P = 0.024). In the ≥65 y subgroup, median (95% CI) disease-free survival, progression-free survival and overall survival were 4.0 months (2.9—5.0) vs 5.6 months (4.1—7.1), 6.5 months (4.0—9.0) vs 10.6 months (8.2—13.0), and 10.3 months (8.2—12.6) vs 13.1 months (10.9—15.1), respectively. Conclusions: FTD/TPI had an efficacy benefit in pts aged ≥65 y, and the FTD/TPI safety profile was similar in this subgroup vs the overall population (table). Treatment-related deaths (one in each treatment group) did not occur in pts aged ≥65 y. No drug-related deaths associated with cardiotoxicity were reported in pts aged ≥65 y. Although dose modifications were made more often in this subgroup, there was no increase in discontinuations vs the overall population. Conclusions: FTD/TPI was safe and effective in pts aged ≥65 y, who had a higher incidence of moderate renal impairment vs the overall population. Clinical trial information: NCT25000443.
4038 Poster Session (Board #143), Mon, 8:00 AM-11:00 AM
Trifluridine/tipiracil (FTD/TPI) in patients (pts) with metastatic gastroesophageal junction cancer (mGEJC): Subgroup analysis from TAGS. First Author: Wasan Manohar, Christie NHS Foundation Trust, Toronto, ON, Canada
Background: The incidence of GEJC is increasing in North America and Europe, especially among white men. Many pts present with metastatic disease or relapse locally or systemically after resection of early-stage disease. The global phase 3 study TAGS (NCT02500043) demonstrated the efficacy and safety of FTD/TPI in previously treated pts with metastatic gastric cancer (mGC/mGEJC). Here we report results in the mGEJC subgroup. Methods: Patients with mGEJC treated with ≥2 prior chemotherapy regimens were randomized (2:1) to receive FTD/TPI (35 mg/m² BID on days 1–5 and 8–12 of each 28-day cycle) or placebo, plus best supportive care. A preplanned efficacy and safety analysis was performed in pts with mGEJC. Results: Of 507 randomized pts, 145 (29%) had GEJC (97%) and 362 (71%) had GEJC (9%) as the sole primary disease site (FTD/TPI, 98/337; placebo, 47/170). Of pts with mGEJC, 85% were male and 83% were white (overall population, 73% and 70%). Baseline characteristics were generally balanced for pts with mGEJC across treatment groups, except for fewer pts having prior gastrectomy (40% vs 55%) and more pts having received ≥3 prior regimens (74% vs 66%) in the FTD/TPI group than in the placebo group. FTD/TPI had an efficacy benefit in pts with mGEJC, and the FTD/TPI safety profile was similar in this subgroup and the overall population (table). Conclusions: FTD/TPI showed a manageable safety profile and efficacy benefit in pts with mGEJC in the TAGS trial, despite heavier pretreatment of the FTD/TPI than the placebo group. Clinical trial information: NCT02500043.

4039 Poster Session (Board #144), Mon, 8:00 AM-11:00 AM
Pooled safety analysis from phase 3 studies of trifluridine/tipiracil (FTD/TPI) in patients (pts) with metastatic gastric/gastroesophageal junction cancer (mGC/mGEJC) and metastatic colorectal cancer (mCRC). First Author: Eric Van Cutsem, University Hospitals Gasthuisberg, Leuven and KU Leuven, Leuven, Belgium
Background: FTD/TPI was approved in 2015 for pretreated pts with mCRC based on the phase 3 RECOURSE trial. FTD/TPI recently demonstrating significantly improved overall survival vs placebo in pretreated pts with mGC/mGEJC in the phase 3 TAGS trial. Methods: We pooled the pooled overall survival (OS) results from TRAVERSE in all pts who received ≥1 dose of FTD/TPI (safety population). Pts were required to have ECOG PS 0/1 and to have received ≥2 previous chemotherapy lines. Results: FTD/TPI and placebo were administered to 335 and 168 pts, respectively, in TAGS, and 533 and 265 pts in RECOURSE. Baseline characteristics were balanced across treatment groups and reflected the disease populations. In the pooled population, 66% of pts were men and 75% had received ≥3 prior systemic treatments. The safety profile of FTD/TPI was comparable between studies (table). In TAGS and RECOURSE, the most common any-cause grade (gr) ≥3 AEs in FTD/TPI-treated pts were neutropenia (34%; 35%), anemia (19%; 17%), and leukopenia (9%; 13%). Gr ≥3 febrile neutropenia occurred in 2% and 4% of pts and gr ≥3 GI AEs in 21% and 12%. Gr ≥3 cardiac AEs were reported in 1% of FTD/TPI-treated pts (both studies), in contrast to results obtained with other third-line agents. Similar proportions of FTD/TPI-treated pts in both studies had AEs leading to dose delay, dose reduction, or treatment discontinuation. Dosing delay was used more often than dose reduction to manage AEs. TRAEs leading to death occurred in one FTD/TPI-treated pt (<1%) in each trial. Conclusions: In a pooled analysis, FTD/TPI was well tolerated with a consistent safety profile in pts with mGC/mGEJC or mCRC. The most frequent AEs were hematologic and GI, which were managed with dose delays/ dose reductions. Clinical trial information: NCT02500043, NCT01607957.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Efficacy and safety of sintilimab in combination with XELOX in first-line gastric or gastroesophageal junction carcinoma (GC/GEJC). First Author: Noriyuki Nomura, Tokyo Medical and Dental University, Tokyo, Japan

**Background:** Immune checkpoint inhibitors have shown clinical benefit in advanced GC/GEJC. This phase 1b study evaluates the efficacy and safety of sintilimab, an anti-programmed cell death-1 antibody (PD-1 Ab) in combination with XELOX for GC/GEJC in first-line setting. **Methods:** This phase 1b study enrolled treatment-naive, unselected locally advanced or metastatic GC/GEJC patients without HER2 amplification in cohort F. Patients received sintilimab 200 mg IV q3w until disease progression, unacceptable toxicity or death, in combination with XELOX (oxaliplatin 130 mg/m² IV D1 and capecitabine 1000 mg/m² PO BID D1-14) for up to 6 cycles. The primary objective was to evaluate the efficacy of the combination per RECIST v1.1 and safety and tolerability. **Results:** Totally 20 patients were enrolled in cohort F. As data cutoff (15 Jan 2019), median follow up was 5.8 months (range, 2.4 to 12.5). The median dose of sintilimab was 6.5 (range, 4 to 12). The objective response rate (ORR) was 85.0% (95% CI, 62.1 to 96.8) and disease control rate (DCR) was 100.0% (95% CI, 83.2 to 100). Among 17 patient with BOR of PR, two patients achieved a complete response (CR) of the target lesion. The median duration of response was 12.5 months and 8 (70.0%) patients. The incidence of treatment emergent adverse events (TEAEs) was 85.0%. Treatment-related AEs (TRAEs) occurred in 14 (70.0%) patients. The incidence of Grade 3 TRAEs was 14 (7.0%) events in 6 (30.0%) patients. No TRAEs that resulted in death. As data cutoff, 12 patients were still in treatment and were under survival follow up. The biomarker analysis including PD-L1 expression in tumor specimen was ongoing. **Conclusions:** Sintilimab combined with XELOX shows promising anti-tumor efficacy and a tolerable safety profile. The further randomized, phase 3 study of Sintilimab in combination with XELOX in this setting is ongoing (NCT02937116). Clinical trial information: NCT02937116.

Recurrent risk evaluation in stage IB gastric cancer with TP53 codon 72 polymorphism. First Author: Satoshi Nishizuka, Iwate Medical University, Iwate, Japan

**Background:** Post-operative adjuvant chemotherapy is not currently indicated for Stage IB gastric cancer. However, about 10% of these patients experience recurrence and metastasis. Our previous study on a panel of gastric cancer cell lines indicated that TP53 codon 72 polymorphisms may affect the degree of biological malignancy. Hence, we hypothesized that the TP53 codon 72 polymorphisms may have been associated with post-operative survival without adjuvant chemotherapy. In this study, we investigated the risk of recurrence after treatment of Stage IB gastric cancer patients carrying the TP53 codon 72 polymorphism and attempted to identify a subpopulation that should receive post-operative adjuvant chemotherapy. **Methods:** Among 658 gastric cancer patients who received gastrectomy with curative-intent, 130 Stage IB patients were enrolled in the present study. The TP53 codon 72 polymorphisms of formalin-fixed paraffin-embedded cancer tissue sections were assessed by direct sequencing using originally designed primers. Overall survival rate (OS) and relapse-free survival rate (RFS) were analyzed based on the status of TP53 codon 72 polymorphism 'Arg/Arg', 'Arg/Pro' and 'Pro/Pro'. The hazard ratio for each subgroup was compared by TP53 codon 72 polymorphism. All interaction values were calculated using the likelihood test. **Results:** Of the 125 patients for whom polymorphism analysis results were available, the 5- and 10-year OS was 84.5% and 63.9%, respectively. The 5- and 10-year RFS was 82.2% and 64.3%, respectively. When the study cohort was divided into two groups according to polymorphism status (i.e., Arg/Arg and Arg/Pro vs. Pro/Pro), both the OS (hazard ratio [HR], 1.968; 95% confidence interval [CI], 0.770-7.430, p = 0.045) and RFS (HR, 1.976; 95% CI, 0.778-7.515, p = 0.033) of the Pro/ Pro group across the entire observation period were significantly lower than those for the Arg/Arg and Arg/Pro group. The majority of recurrences in Pro/Pro group across the entire observation period were significantly lower than those for the Arg/Arg and Arg/Pro group. The hazard ratio for the Arg/Arg and Arg/Pro group. The majority of recurrences in Pro/Pro group across the entire observation period were significantly lower than those for the Arg/Arg and Arg/Pro group. 

Poster Session (Board #144), Mon, 8:00 AM-11:00 AM

Analysis of symptoms and functional HRQoL scales in TAGS, a phase III trial of trifluridine/tipiracil (FTD/TPI) in metastatic gastric cancer (mGC). First Author: Feng Zhang, National Cancer Center Hospital, Tokyo, Japan

**Background:** The phase 3, randomized, double-blind, placebo-controlled study (TAGS) evaluated the efficacy and safety of FTD/TPI (35 mg/m² given orally twice a day on days 1–5 and 8–12 of a 28-day cycle) in mGC patients who had previously received ≥2 prior regimens for advanced disease and demonstrated a clinically relevant and statistically significant benefit in OS and PFS with a predictable and manageable safety profile. HRQoL data and analysis between QoL and time to ECOG status deterioration (2 or more) are reported here. **Methods:** HRQoL was evaluated using EORTC QLQ-C30 and the gastro-specific module (QLQ-ST022) questionnaires at baseline and at every 4 weeks thereafter until treatment discontinuation. Prespecified key HRQoL changes from baseline and time to deterioration. Changes ≥ 10 points were deemed clinically relevant. A time-dependent Cox-regression analysis was performed to evaluate the association of 10-point Global Health Status deterioration with worsening ECOG status. **Results:** Of 507 patients randomized, 332/337 (98.5%) of FTD/TPI and 164/170 (96.5%) of placebo had baseline QoL data. Overall compliance was 84% for both questionnaires. Depression and disease were generally balanced between the two groups; QoL scores were also similar between groups. HRQoL was largely maintained during treatment in both arms for most items; mean changes from baseline remained under the 10-point threshold. Clinically relevant changes from baseline were observed only for pain relief at cycle 2 (favouring FTD/TPI); and improved role function at cycle 3 (favouring placebo). The HRQoL analysis including death or progression as an event, FTD/TPI was associated with a positive trend suggesting a reduced risk of QoL deterioration across all scales compared to placebo (HRs ranged from 0.57 to 0.74). A 10-point Global Health Status deterioration was associated with a worsening ECOG status (HR, 95% CI, 1.51, 1.01 to 2.23). During treatment, HRQoL remained stable for most functional and symptom scales in both arms, suggesting that HRQoL is largely maintained with FTD/TPI. Treatment with FTD/ TPI was associated with a positive trend toward a lower risk of QoL deterioration compared to placebo across all scales. Changes in QoL were informative for patients’ expected ECOG status. Clinical trial information: NCT02500043.

Phase II feasibility trial of neoadjuvant chemoradiotherapy combined with atezolizumab in resectable esophageal adenocarcinoma: The PERFECT trial. First Author: Tom van den Ende, Amsterdam UMC, University of Amsterdam, Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam, Netherlands

**Background:** The CROSS study demonstrated the superiority of neoadjuvant chemoradiotherapy (nCRT) over surgery alone (van Hagen et al. NEJM. 2012). However, for resectable esophageal adenocarcinoma (EAC) by survival is only 43%. PD1/PDL1 checkpoint inhibitors have shown promising efficacy for several cancer types, including esophageal cancer. To further improve outcomes in EAC, we performed a phase II trial of nCRT combined with atezolizumab, a PD-L1 inhibitor. **Methods:** Pts with EAC received standard dose CROSS regimen (5 cycles of IV: carboplatin AUC2, paclitaxel 50 mg/m² and concurrent 23 fractions of 1.8 Gy on weekdays) with atezolizumab (5 cycles: 1200 mg IV, 3 weekly). Primary endpoint was the percentage of pts completing treatment with atezolizumab. Secondary endpoints included: toxicity, post-operative complications (Clavien-Dindo), Mandard score, R0 resection rate, PFS and OS. In total 40 pts will be enrolled. **Results:** Since July 2017, 39 pts have been enrolled (87% males, median age 63). Neoadjuvant treatment was completed by 31 pts and is ongoing in 8 pts. All cycles/fractions of nCRT were administered in 29/31 pts; 26 pts completed all cycles of atezolizumab, 24 pts finished complete neoadjuvant treatment. Reasons for missing any cycle of chemotherapy/atezolizumab included: toxicity (6 pts, in 3/ 6 pts immune-related adverse events (irAEs) and progression (1 pt). Grade 3-4 toxicity was observed in 15/31 pts (36/13 irAEs of any grade) which did not delay surgery. Thus far 23/31 pts were resected, 3 pts are planned for surgery, 3 pts had interval metastases preoperatively, 1 pt died during treatment (pulmonary embolism), and 1 pt declined surgery. Clavien-Dindo grade 3-4 complications were observed in 11/23 pts with no surgery related mortality. A pathological complete response (pCR), Mandard 1 was seen in 9/23 (39%) pts. All patients underwent an R0 resection. Updated results will be presented at the meeting. **Conclusions:** Based on data thus far, atezolizumab added to nCRT is feasible. A pCR was observed in 39% of patients, which is promising compared to 23% in the CROSS study. Treatment is associated with irAEs which are manageable. Biomarker research will be performed on blood (circulating tumor DNA), tissue (immune microenvironment) and feces (microbiome). Clinical trial information: NCT03087864.
Total neoadjuvant chemoradiotherapy (nCRT) for locally advanced gastric cancer (GC): The Memorial Sloan Kettering Cancer Center experience. First Author: Megan Greally, Memorial Sloan Kettering Cancer Center, New York, NY

Background: We reviewed pts with advanced/metastatic adenocarcinoma (ACC) or squamous cell carcinoma (SCC) of the esophagus that has progressed after first-line standard therapy (KEYNOTE-181). First Author: Antoine Adenis, Institut du Cancer de Montpellier, Montpellier, France

Methods: The subjects of this study were AGC patients that had received nivolumab monotherapy. Therefore, in this study, we retrospectively investigated the correlation between irAEs and efficacy in AGC patients treated with nivolumab. Methods: The EORTC QLQ-C30 and EORTC QLQ-ES18 were administered at baseline; week 2, 3, 4, 6, 9, 12, 18; every 9 weeks up to 1 year/end of treatment; and 30-day safety follow-up visit. Data from patients receiving ≥1 dose of study treatment and completing ≥1 HRQoL assessment were analyzed. The HRQoL population included 218 PD-L1 CPS ≥1 patients; irAE events were defined as those AEs having a potential immunological basis that required close follow-up, or immunosuppressive therapy and/or endocrine therapy. The median time to onset of irAEs was 30.5 days (range 3–407 days). Median follow-up period for survivors was 32 months (95% CI, 10.8 to 34.5). The median progression-free survival was 7.5 months (95% CI, 3.6 to 11.5) in the irAE group and 1.4 months (95% CI, 1.2 to 1.6) in the non-irAE group (HR = 0.11, p < 0.001). The median overall survival was 16.8 months (95% CI, 4.4 to not reached) in the irAE group and 3.2 months (95% CI, 2.2 to 4.1) in the non-irAE group (HR = 0.17, p < 0.001). Multivariate analysis demonstrated that high ALP level (HR = 2.88; 95% CI, 1.51 to 5.51) and absence of irAEs (HR = 3.06, 95% CI, 3.06 to 23.46 for yes vs. no) were associated with a poor prognosis. The most frequent irAEs were diarrhea/ colitis (n = 5). Grade 3 adverse events were observed in 6 patients; hyperglycemia (n = 2), diarrhea/colicis (n = 1), adrenal insufficiency (n = 1), increased aspartate aminotransferase increased (n = 1), peripheral motor neuropathy (n = 1). One of the 14 patients experienced the irAE after discontinuation of nivolumab due to progression of disease. There were no grade 4 or 5 adverse events related to nivolumab.

Conclusions: Development of irAEs was associated with clinical benefit for AGC patients receiving nivolumab monotherapy.
4050 Poster Session (Board #155), Mon, 8:00-11:00 AM
Perioperative (P) UGT1A1 genotype guided irinotecan (i) dosing ‘gFOLFIRINOX’ for gastroesophageal adenocarcinoma (GEA).
First Author: Daniel V. T. Cathcart; University of Chicago Medical Center and Biological Sciences, Chicago, IL
Background: Complete resection (RO) and pathologic response grade (PRG) correlate with long-term GEa outcome. FOLFIRINOX demonstrated efficacy in advanced GEA; gFOLFIRINOX improved tolerability. We evaluated RO, PRG and tolerability in this pilot study. Methods: Gastric body (GB) + esophagogastrectomy (EUG) GEa patients (pts) with cT3Nx or cT4+Nx were enrolled & treated with 4+4 + 4 postoperative weekly cycles of gFOLFIRINOX (5-FU 2400mg/m2 over 46 hrs; oxaplatin 85mg/m2; i) i: 180mg/m2 for UGT1A1 genotype 6/6, 135mg/m2 for 6/7, 90mg/m2 for 7/7) + (t)astuzumab (T) 6mg/kg then 4mg/kg for HER2+2. 1endpoint RO resection required 56 pts as baseline for 90% RO (rate intent to treat (ITT)) with 90% power + 0.05 alpha; i) 30/36 RO considered positive. Co-1endpoint was PR (Becker); 36 pts provided 85% power with 0.05 alpha for a complete (c)PR (G1a) rate of 16%. Zendpoints were safety/toxicity, PET response, & RO/PRG by tumor site, histologic subtype, HER2 status, & UGT1A1 genotype. We report efficacy and toxicity data from the neoadjuvant (Neo) portion of the study; postop data & survival outcomes will be presented at the meeting. Results: 4 sites enrolled 36 ITT pts between 2/2014-8/2018; 75% male, median age 66 (range 27-85). All pts completed all 4 cycles of Neo therapy. 10% had any dose reduction of iri (16%/0%/25% by 2/2014-8/2018; 75% male, median age 66 (range 27-85). All pts completed 4 cycles of Neo therapy: 10% had any dose reduction of iri (16%/0%/25% by

4051 Poster Session (Board #156), Mon, 8:00-11:00 AM
Best supportive care (BSC) with or without low-dose chemotherapy (chemo) in frail elderly patients with advanced gastroesophageal cancer (aGOAC). The uncontrolled randomisation of the GO2 phase III trial. First Author: Daniel Swinson, St James, Leeds, United Kingdom
Background: Before 2000, trials comparing BSC +/- chemo for aGOAC showed overall survival (OS) benefit, but in predominantly fit patients (pts). We have revisited this question in a modern context, using low-dose chemo in a frail population, with comprehensive baseline health and frailty assessment. Methods: In the GO2 trial, elderly and/or frail aGOAC pts with a “certain” indication for chemo were randomised between 3 chemo doses. In this GO2 substudy, pts with an “uncertain” indication for chemo were instead randomised to BSC: the lowest dose chemo. Pts were eligible if clinician and pt agreed the indication for chemo was uncertain. There was no PS threshold, but eGFR ≥30 and bilir < 2xULN were required. Baseline assessment included global QL, symptom & functional scales, frailty and comorbidity. Randomisation was 1:1 to BSC alone, or with oxaplatin 78 mg/m2 d1, capcitabine 375 mg/m2 bd d1-21 (modified if eGFR 30-50 ml/min or bilir 1.5-2.0 xULN), q21d. QL was reassessed after 19 and 8 wks. The primary endpoint analysis was OS, adjusted for baseline factors. The sample size for this exploratory substudy was not pre-set, but around 60 pts were anticipated. Results: 558 pts entered GO2 at 61 centres 2014-17, of whom only 45 pts (8%) at 21 centres entered this uncertain randomisation. This would provide 80% power at p = 0.05 (2-tailed) to detect an OS HR of 0.3. OS was shorter in pts with worse baseline PS (p < 0.01) or distant mets (p < 0.05). OS was not significantly improved with chemo; median OS was 11.3 vs. 13.8 wks, and 32% of patients could not continue treatment less with BSC-chemo than with BSC alone. Conclusions: In this frail, poor PS population, we observed a small survival benefit with chemo but this did not reach statistical significance. Clinicians should carefully consider BSC alone as a valid treatment option for aGOAC pts with poor PS and/or frailty. Clinical trial information: 44687907.

4052 Poster Session (Board #157), Mon, 8:00-11:00 AM
The quality of life in neoadjuvant versus adjuvant therapy of esophageal cancer (A) treatment trials (QUINTITT). First Author: Richard Malthaner; Health Sciences Centre, London, ON, Canada
Background: We compared the health-related quality-of-life (HRQOL) of standard neoadjuvant cisplatin and 5-FU chemotherapy plus radiotherapy (N) followed by surgical resection to adjuvant cisplatin, 5-FU, and epirubicin chemotherapy with concurrent extended volume radiotherapy (A) following surgical resection for resectable esophageal carcinoma. Methods: 96 patients with stage I to III resectable esophageal cancer were enrolled (N=71 A=25), prospective randomized trial (NCT00907543) from April 2009 to November 2016. Patients were randomized into 2 groups: N (47 cases) and A (49 cases). The primary end point was HRQOL using the FACT-E at one year. The secondary endpoints included other HRQOL measures, overall survival (OS), disease-free survival (DFS), and adverse events. Results: The median follow-up was 5.0 years (95% CI: 4.5 to 5.5). The majority of patients had adenocarcinomas of the distal esophagus/gastroesophageal junction (80.9% vs. 87.8%). The stage distribution was: 19% II; 22% III; 58% IV; T NxO-1 10%. Using an intention-to-treat analysis there was no significant difference in the FACT-E total scores at one year in the N and A groups (p = 0.638), with 35.5% vs. 41.2%, respectively showing an increase of ≥ 15 points (a priori minimal clinical difference) compared to pre-treatment (p = 0.638). The HRQOL was temporarily significantly inferior at 2 months in the N arm for FACT-E, EORTC QLQ25, and EQ-5D-3L in the dysphagia, reflux, pain, taste, and coughing domain (p < 0.05). There were no 30-day mortalities but 2.1% vs. 10.2% 90-day mortalities (p = 0.204). There were no significant differences in either 5-year OS (37.9% vs. 28.9% in the 0.321) or DFS (34.0% vs. 25.5%, p = 0.551. 48.9% of patients required chemotherapy to be modified or stopped in the N arm compared to 57.1% in the A arm (p = 0.421). 51.1% of patients were able to complete the entire 8-week course of chemotherapy without modification compared to only 14.3% in the A arm (p < 0.001). Chemotherapy related adverse events significantly more frequent in the neoadjuvant arm (p < 0.05). Surgery related adverse events were significantly more frequent in the neoadjuvant arm (p < 0.05).

Conclusions: Toxidrome intensity is challenging for patients with resectable esophageal cancer regardless if it is given before or after surgery. Less toxic protocols are needed. Clinical trial information: 00907543.
Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Concurrent chemoradiation (CRT) followed by esophagectomy is a standard of care for locally advanced esophageal (LA-EC) and GEJ adenocarcinoma. Approximately 50% of patients (pts) experience disease relapse within the 1st yr after treatment (tx) completion. No adjuvant tx has been shown to improve survival in these pts. Immune checkpoint inhibitors have activity in patients (pts) with LA-EC and GEJ adenocarcinoma. Approximately 50% of patients (pts) experience disease relapse within the 1st yr after treatment (tx) completion. No adjuvant tx has been shown to improve survival in these pts. Immune checkpoint inhibitors have activity in patients (pts) with LA-EC and GEJ adenocarcinoma.

Methods: We conducted a phase II trial evaluating safety and efficacy of durvalumab (durva), a monoclonal antibody against PD-L1, in pts with LA-EC and GEJ adenocarcinoma who have viable tumor in surgical specimen after neoadjuvant CRT and RP2D resection. Pts received durva 1500mg IV every 4 weeks for up to 1yr. Results: 24 pts were enrolled from 4/2016-1/2018 (median age: 60yrs (range, 43-70). 18 received carbo/paclitaxel and 6 received cis/flx-FU concurrently with radiation. Staging at diagnosis: T2N0 (n=3), 12.5%, T2N2 (n=2, 12.5%), T3N0 (n=6, 25%), T3N1 (n=5, 21%), T3N2 (n=4, 17%), T3N3 (n=1, 4%), T4N(n=1, 4%), 13 pts (79%) had positive lymph nodes. 12 pts (63%) were negative with surgery following CRT. 12 pts completed 1yr of tx, 12 came off tx before 1yr because of relapse(6), AE(s), and consent withdrawal (1). Median number of tx cycles was 12.5 (range, 2-13). Most common AEs were fatigue (n=8, 33.3%) and nausea (n=6, 25%). Spts (12.5%) developed grade 3 rAEs: pneumonitis (1), hepatitis (1), colitis (1). Median follow-up of 14.7-24.6mo. 17 are disease free (including 5 who came off tx before 1yr). 7pts (29%) have relapsed (3 alive, 4 died). 6/7 pts had distant relapse (lung, brain, bone, cervical LN) and 1 had locoregional relapse. 1-yr RFS and OS were 79.2% and 95.5%, respectively. 2-yr OS was 59.2%. RFS probability at 26 mo was 67.9%. Median progression-free survival (PFS) was 11.1 mo (range, 0.1-11.3mo). Of 19 pts (79%) had positive lymph nodes (LNs) and 1 had locoregional relapse. 1-yr RFS and OS were 79.2% and 95.5%, respectively. 2-yr OS was 59.2%. RFS probability at 26 mo was 67.9%. Median progression-free survival (PFS) was 11.1 mo (range, 0.1-11.3mo).

Conclusions: Early reduction in metabolic ITH is useful to predict response to palliative chemotherapy, PFS and OS in advanced GC patients.

Background: Phosphorylated FAK (pFAK) is a key target for novel therapeutics in cancer treatment. In our group, we have previously reported that the suppression of pFAK significantly reduces cell proliferation, migration and invasion in colorectal cancer cell lines. However, the role of pFAK in gastric cancer has not been reported yet. Here, we investigated the effect of targeting pFAK in gastric cancer cell lines.

Methods: We used four gastric cancer cell lines (SGC7901, MGC803, MKN28, and AGS) to examine the effect of targeting pFAK. The effects of pFAK inhibition on cell proliferation, migration, and invasion were evaluated using MTT assay, wound healing assay, and Transwell assay, respectively. The expression of pFAK was evaluated using Western blotting and IHC. The results were compared with those of non-phosphorylated FAK (a) and GAPDH (b).

Results: The MTT assay showed that the inhibition of pFAK significantly reduced cell proliferation in SGC7901, MGC803, and MKN28 cell lines (p < 0.05). The wound healing assay showed that the inhibition of pFAK significantly reduced cell migration in SGC7901, MGC803, and MKN28 cell lines (p < 0.05). The Transwell assay showed that the inhibition of pFAK significantly reduced cell invasion in SGC7901, MGC803, and MKN28 cell lines (p < 0.05). The Western blotting and IHC showed that the expression of pFAK was significantly reduced in SGC7901, MGC803, and MKN28 cell lines compared with non-phosphorylated FAK and GAPDH.

Conclusions: Our results suggest that targeting pFAK is a potential therapeutic approach for gastric cancer treatment. These findings support the development of novel therapeutic strategies targeting pFAK in gastric cancer.

Background: Metabolic intratumoral heterogeneity (ITH) gives important information on treatment response and prognosis. However, temporal changes in metabolic ITH and their predictive roles in advanced GC patients receiving palliative chemotherapy. Methods: Unselectably locally advanced or metastatic GC patients were prospectively enrolled before the first-line palliative chemotherapy and underwent FDG-PET/CT at baseline (T1) and at the first response evaluation follow-up (T2). SUVs (Standardized uptake values), volumetric parameters, and textural features including entropy, contrast and homogeneity were extracted from the primary gastric tumor at T1, T2, and D1 (T2-T1) was evaluated. Associations of these parameters with treatment response, progression-free survival (PFS), and overall survival (OS) were analyzed. Results: 87 patients were analyzed. Of 86 evaluable patients, 44 obtained partial response, 33 stable disease, and 8 progressed. The objective response rate was 51.8% (95% confidence interval [CI], 40.7% to 62.7%). The median DFS and OS were 7.3 months (95% CI, 5.4 to 8.2 months) and 11.5 months (95% CI, 10.1 to 14.3 months), respectively. From T1 to T2, metabolic ITH was significantly reduced (P < 0.01), and the degree of decrease was greater in responders than in non-responders (P < 0.01). By multiple Cox regression analyses adjusted for clinical variables, low entropy at T2 (P = 0.001), larger decreases in coefficient of variance (P = 0.003) and contrast at T2 (P = 0.017) were associated with better PFS. Low SUV at T2 (P = 0.001), larger decreases in coefficient of variance, low entropy at T2, and low contrast at T2 were associated with better OS.

Conclusions: Early reduction in metabolic ITH is useful to predict response to palliative chemotherapy, PFS, and OS in advanced GC patients.

Background: Fluzoparib (SHR3162) is an oral, selective PARP1 inhibitor. In our gastric cancer PDX model, fluzoparib + apatinib + paclitaxel demonstrated significant tumor growth inhibition as compared to apatinib alone, and fluzoparib + paclitaxel. In this phase I study, we hypothesized that the combination of fluzoparib + apatinib + paclitaxel should be safe and active in pts with advanced gastric and GEJ cancer. Methods: Dose-escalation phase (P1) explored 4 dose levels of fluzoparib with a 3+3 design to identify a recommended phase II dose (RP2D) for further study. Pts received fluzoparib (20, 30, 40, 60 mg twice daily) + apatinib (125mg/m2/day) + paclitaxel (60mg/m2, Day 1, 8, 15). Dose-expansion phase (P2) was to assess safety and efficacy. Pts received RP2D of fluzoparib + apatinib + paclitaxel until progression or intolerant toxicity. Treatment was repeated every 4 weeks. Pts had to have progressive disease after standard platinum-based regimen treatment. Adverse events (AE), PK, and response were assessed. Results: 39 pts (median age 58) were treated in P1 and P2, including fluzoparib 20mg (n=4), 30mg (n=27; 6 pts in P1, 21 pts in P2), 40mg (n=6), and 60mg (n=2). The median treatment duration for this study was 2.8 months. No DLTs were reported in 20mg cohort. One DLT occurred in 30mg cohort (grade 3 G3: hypophosphatemia), 1 DLTs (1 grade 4 G4: febrile neutropenia) occurred and 1 G4 neutropenia occurred and recovered in 3 days in 40mg cohort, 2 DLTs (1 G4 neutropenia, 1 G4 febrile neutropenia) in 60mg cohort. Therefore, 40 mg dose was deemed the MTD. There were no treatment-related deaths on study. The most common AEs were neutropenia, febrile neutropenia, and hypertension. 1 treatment-related discontinuation was observed. Of 36 evaluable pts, 12 (30.0%) had confirmed partial response and 13 had stable disease (36.1%). Median progression-free survival was 4.9 months. PK analysis will be presented. Conclusions: The RP2D of combination of fluzoparib + apatinib + paclitaxel is well tolerated and has activity in pts with advanced gastric and GEJ cancer who have failed to platinum-based regimens. Clinical trial information: NCT 03026881.
A digital pathology demonstration of an "immune hot" ICOS+/CD45RO+ immune phenotype and the impact on survival in patients with esophageal adenocarcinoma. First Author: Matthew Philip Humphries, Queens University Belfast, Belfast, United Kingdom

Background: Therapies targeting immune checkpoints are changing our understanding of the biology and treatment of cancer. Analysing the immune landscape in esophageal adenocarcinoma (EA) may help future prognostication and therapeutic decision-making. Methods: We assembled 310 EA cases in a tissue microarray format with associated clinicopathological information, including a discovery cohort of 156 EA from Northern Ireland and a 154 EA validation cohort from Aberdeen. We carried out validated immunohistochemistry (IHC), stained for range of adaptive immune (CD3, CD4, CD8, CD45RO and IFN) and immune checkpoint biomarkers (ICOS and IDO-1). Slides were digitised and assessed using QuPath image analysis software program to quantify their expression and correlate them with outcome. Results: In the discovery cohort we identified a group of patients highly expressing several immune biomarkers, conferring a significant positive survival advantage (p = 0.022). CD3, CD4, CD8, CD45RO, and ICOS were individually prognostic for better overall survival (Log rank p = 0.0003; p = 0.0292; p = 0.0015; p = 0.0008; p = 0.0026, respectively). Multivariate and correlation analysis identified a subgroup of CD45RO+/ICOS+ patients with significantly improved overall survival (p = 0.0002). The co-expression of CD45RO+/ICOS+ immunophenotype was investigated in the validation cohort and a confirmed survival advantage was seen (p = 0.042). Additionally, the Opal Multiplex IHC technology revealed the much higher frequency of single-cell, double labelling of CD45RO+/ICOS+ in immune hot cases. Conclusions: These data demonstrate the advantage of immune markers other than the traditional CD3/CD4/CD8 in EA prognosis. The fact that one of these biomarkers is an immune checkpoint inhibitor may have therapeutic implications.

Comprehensive molecular characterization of clinical response in ramucirumab-treated gastric cancer patients: Phase II trial with integrated genomic profiling. First Author: Seung Kim, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: The absence of tumor cells enables an enriched stromal environment to generate RNA signatures and through assembling genes involved in tumor stroma, four distinct stromal signatures that reflected biological processes such as signature vascular mature (VM), vascular immature/ inflammatory (VMI), vascular immature/non-inflammatory (VINI) and inflammatory alone (I) depending on nature of vasculature. We hypothesized that these stromal specific signatures may provide additional information to the pre-existing genomic profiling. Methods: We conducted a single-center phase II trial in which we treated 61 unselected patients with metastatic GC with ramucirumab plus paclitaxel as second line therapy and performed pre-planned integrated genomic profiling. Results: Sixty-two patients were enrolled in this study between May 2014 and June 2017. The cut-off date for treatment outcome analysis was January 2, 2019, at which time response evaluations were available for 57 patients with a median follow-up of 30.2 months. In an intent-to-treat analysis cohort, there was no CR and 22 patients achieved confirmed PRs resulting in an ORR of 35.5% (95% CI: 23.6 – 47.4). The response rate to ramucirumab was considerably enriched in VM/VMI group (29.2% (P = 0.0003) when compared to I (< 10%) or VINI group (< 10%). The strongest response defined by maximal response to ramucirumab was shown in GC patients with VM/VMI signatures. Of note, VM/VMI patients had prolonged duration of response to ramucirumab/paclitaxel demonstrating that these patients not only respond to ramucirumab but also had durable response. Conclusions: This is the first study to demonstrate a clinically robust correlation between tumor-based signature and response to anti-angiogenesis inhibitor. GC. Clinical trial registry: NCT02628991.

Landscape of innate and adaptive immunity targets in oesophagogastric adenocarcinoma (OGA). First Author: Elizabeth Catherine Smyth, Cambridge University Hospital NHS Foundation Trust, Cambridge, United Kingdom

Background: Anti-PD-1 therapy modestly improves survival in chemorefractory OGA. Combining PD-1 blockade with novel checkpoint inhibitors, T-cell co-stimulatory molecules, or myeloid suppressors could enhance PD-1 inhibition. Herein, we explore the landscape of known targetable immune markers in non-Asian OGA. Methods: OGA patient biopsies were prospectively collected and clinically annotated from 19 UK cancer centres (Oesophageal Cancer Clinical and Molecular Stratification – OCCAMS network). Genomic (WGS) and transcriptomic (bulk-RNA seq) data were generated using Illumina and processed using a validated in-house pipeline (Frankeli, Nat Genetics 2019). Gene expression was computed in transcripts per kilobase. Using unsupervised clustering patient clusters were selected according to the expression of gene targets for immune therapy - PD-L1, LAG3, TIM3, TIGIT, ICOS, CCR2, CCR5, CXCR4, and CSF1R. Immune cell infiltration was extrapolated using GSEA gene set enrichment analysis. Results: RNAseq data were available for 251 patients; 96% had operable tumours (Stage I: 6%; II: 63%; III: 22%; IV: 4%). In untreated patients (n = 156) 3 subgroups were identified: immune low (83, 53%) with low level expression of all 9 markers, immune high (14, 9%) with high expression of all or majority of markers and intermediate (59, 38%) with heterogenous marker expression. Clinicopathological variables (sex, age, smoking, tumour location (gastric/GE/esophagus) and tumour regression grade) were similarly distributed across subgroups. In a cohort of 114 patients with matched WGS and RNAseq data tumour mutation burden was not different between subgroups. In post-chemistry biospies (n = 95) a similar co-expression pattern was observed. Gene enrichment analysis supported infiltration by cells of innate and adaptive immune system in immune high patients. Neoantigen results, phenotypic immunohistochemistry and optimised survival outcomes according to lymphoid and myeloid target expression will be presented. Conclusions: High level co-expression of immune regulatory targets in OGA patients may limit the efficacy of anti-PD-1 monotherapy. Combination immune directed therapies may be required in this patient group.

Prospective validation of a serum miRNA panel for early detection of gastric cancer. First Author: Lihan Zhou, MIRXES PTE LTD, Singapore, Singapore

Background: High mortality from gastric cancer is related to the late manifestation of its symptoms. A blood-based non-invasive biomarker with the ability to detect all stages of gastric cancer could significantly improve patient outcomes. We aimed to develop a novel serum miRNA assay for diagnosis of gastric cancer. Methods: We conducted a multi-center study involving 892 gastric cancer and control subjects from Singapore and Korea to develop a multi-target miRNA assay. Using RT-qPCR, we quantified the expressions of 578 serum miRNAs and constructed a 12-miR biomarker panel through multi-variant data analysis. The results were generated with the use of a logistic-regression algorithm, with the value of 40 or more considered to be positive. We subsequently validated this multi-miR assay in a large prospective cohort involving 4566 subjects and compared its performance with traditional markers such as H.Pylori and Pepsinogen. All participants underwent gastroscopy independent of the assay results. Results: Of the 4566 subjects that underwent gastroscopy and histopathological examination in the prospective cohort, 125 were diagnosed with gastric cancer. The 12-miR assay achieved an Area-Under-Curve (AUC) of 0.84, significantly outperforming (p-value < 0.01) that of H.Pylori (AUC of 0.64) and Pepsinogen (AUC of 0.62). The sensitivity of the miRNA assay in detecting early (stage 0-2) and late (stage 3-4) stage gastric cancer was 82.6% (95% CI, 68.6% to 92.2%) and 88.4% (95% CI, 78.4% to 94.9%) respectively at a specificity of 70.0% (95% CI, 67.8% to 71.9%). In comparison, H.Pylori showed a sensitivity of 80.4% at a specificity of 44.3% whereas the Pepsinogen showed sensitivity of 95.2% at a specificity of 95.3%. Using the miRNA assay as a pre-screening tool could potentially reduce number of endoscopy needed by 62% in detecting one case of gastric cancer. Conclusions: Our serum miRNA panel is a useful, non-invasive screening test for gastric cancer. It is cost-effective and can reduce unnecessary diagnostic endoscopy.
4066 Poster Session (Board #171), Mon, 8:00 AM-11:00 AM
Neoadjuvant epirubicin, oxaliplatin, capetebiube, and radiation therapy (NEOX-RT) followed by surgery for locally advanced gastric cancer (LAGC): A phase II multicenter trial. First Author: Antonino De Paoli, Radiation Oncology Dept - IRCCS CRO Aviano-National Cancer Institute, Aviano, Italy

Background: This study evaluates the feasibility, safety and efficacy of a trimodality treatment, with surgery postponed after neoadjuvant chemotherapy (CT) and chemoradiotherapy (CRT), in LAGC. Methods: Patients (pts) with cT3-4 and/or N+ LAGC were eligible. Staging included endoscopic ultrasound, PET-CT and laparoscopy. Three cycles of EOX (Epirubicin 50mg/m2,q21 days, Oxaliplatin 130mg/m2,q21 days, and Capetebiube 50mg/m2,bid by continuous oral administration (c.a.), followed by IMRT with 45Gy/25 frs, concurrent Capetebiube 625mg/m2 bid c.a. and weekly Oxaliplatin 30mg/m2 for 5 wks, was planned. Early PET-CT was performed after the 2nd EOX cycle to assess response or disease progression. Restaging was repeated after CT and CRT. Surgery was planned 4-6 wks after CRT, 22 wks from the start of NEOX-RT. Pathologic complete response (pCR) was the primary endpoint. Results: From November 2008 to March 2016, 51 pts (5 G-E Junction, 17 Cardia, 15 Corpus, 14 Antrum) entered the study. The NEOX-RT program was completed in 46 pts (90%) who proceeded to surgery and are assessable. Grade 3-4 toxicity (NCI-CTC criteria v.3) occurred in 13/51 pts (25%) during EOX, including 1 toxic death, and 9.5% CT cycles required dose modification, resulting in a CT compliance of 90%. No pts had progression during CT.
Persistent G2-G3 toxicity occurred in 32/46 pts (69%) during CRT. However, 41/46 pts (89%) received the planned 45Gy with Capetebiube at dose >75% and 15 cycles of weekly Oxaliplatin in 51 patients (99%). pCR after resection (R0) was 89%; 4 pts (8.7%) had peritoneal carcinomatosis at surgery done after a median of 23 wks. pCR was reported in 9/46 pts (19.6%). Major postop complications occurred in 9 pts (11%). At median 1-up of 62 mos (23-109), 5-yr OS and DFS in all and pCR pts were 58%, 100% and 51%, 75%, respectively. Conclusions: This trimodality program was feasible and safe. Most pts completed the planned treatment. The pCR rate of 19.6% was remarkable and met the hypothesis of pCR = 20%. A high R0 rate was also reported and delayed surgery didn’t increase complications. The notable survival rates are available to be compared with ongoing phase III trials. Clinical trial information: 2008-002715-40.

4068 Poster Session (Board #173), Mon, 8:00 AM-11:00 AM
Prognostic significance of sarcopenia in metastatic esophageal squamous cell carcinoma. First Author: Kirsty Taylor, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Sarcopenia is defined as low skeletal muscle mass and represents a quantifiable marker of frailty. Disease related symptoms of anorexia, nausea and dysphagia, in addition to reduced physical activity contribute to muscle wasting in metastatic esophageal squamous cell cancer (MESCC) patients. This study set out to evaluate the prognostic utility of sarcopenia and its association with nutritional indices. Methods: MESCC patients (pts) with available abdominal CT imaging, attending Princess Margaret Cancer Centre between 2011 and 2016, were identified from the institutional database. Skeletal muscle index (SMI), normalized by height, was calculated at the third lumbar (L3) vertebra using SliceOMatic software. SMI cutoffs for sarcopenia were 34.4cm2/m2 in females and 45.4cm2/m2 in males based on previously established consensus. Nutritional risk index (NRI) was calculated using weight and albumin with malnutrition defined as < 97.5%. Results: Of the 58 pts analyzed, 26 presented with de novo MESCC, median age was 64 (range 48-85), 30 pts were ECOG PS ≤1 and 45% received systemic therapy, 93% of pts experienced weight loss >5% in the 3 months preceding diagnosis and median BMI was 20.4 (range 16.3-34.9). Twenty-four (41%) pts were sarcopenic (SP) with differences in BMI and NRI (p < 0.05) compared to non-sarcopenic (NSP) pts. Median BMI in SP pts was 18.9 (16.3-25.6), 46% had a BMI < 18.5 and none were obese (BMI ≥ 30). By NRI, 58% of SP pts were malnourished. Males comprised 71% of SP pts (p = 0.03) but no difference from NSP MESCC pts was identified with age, race, ECOG PS or smoking status with univariate analysis. Median overall survival (OS) was 6 months; 4.2 in SP pts and 6.2 in NSP pts. Significant difference was identified with NRI (p = 0.009) but not sarcopenia (p = 0.247) or BMI (p = 0.393). With a multi-variate Cox model for NRI and sarcopenia, including age, sex, race, and ECOG PS, only ECOG PS was a significant predictor of mortality, HR for 2.3 vs 0.1 of 5.4 (2.5-11.9) p < 0.001. Conclusions: Sarcopenia at diagnosis was not associated with OS. NRI was superior to BMI alone with respect to discriminating pt outcomes, however ECOG PS was the only measure significantly associated with survival.

4067 Poster Session (Board #172), Mon, 8:00 AM-11:00 AM
The impact of postoperative complications on survival outcomes in patients with cT3/4a gastric cancer. First Author: Masanori Tokunaga, National Cancer Center Hospital East, Kashiwa, Japan

Background: Recently, the negative impact of postoperative complications on long-term survival outcomes has been reported in patients with gastric cancer. However, most are single center, retrospective studies with different definitions of postoperative complications. The objective of this study was to evaluate the impact of postoperative complications on long-term outcomes using the data of a multicenter randomized controlled trial (JCOG1001). Methods: This study included 1,191 out of all 1,204 patients enrolled in JCOG1001 which was aimed to confirm the superiority of burseryctomy for patients with cT3/4a locally advanced gastric cancer. Complications were graded by Clavien-Dindo classification. The relationships between the grade (≥ grade II or ≥ grade III) or type (all or intra-abdominal infectious (pancreatic fistula, anastomotic leakage, and intra-abdominal abscess)) of complications and survival outcomes were evaluated. Results: The incidences of ≥ grade II and ≥ grade III all complications were 23.0% and 9.7%, and those of ≥ grade II and ≥ grade III intra-abdominal infectious complications were 13.4% and 6.9%, respectively. The hazard ratios for overall survival (OS) of patients with ≥ grade II and ≥ grade III all complications and those of patients with ≥ grade II and ≥ grade III intra-abdominal infectious complications were shown in Table. With whichever definition we adopted, postoperative complications were significantly associated with OS in both univariable and multivariable analysis. Conclusions: Postoperative complication was identified as an independent prognostic factor in patients with cT3/4a gastric cancer. Hazard ratios for overall survival by univariable and multivariable Cox proportional hazard model. Clinical trial information: UMIN000003688.

4069 Poster Session (Board #174), Mon, 8:00 AM-11:00 AM
Impact of adjuvant therapy in patients with a microscopically positive margin after resection for gastrointestinal cancer. First Author: Lucy Xiaolu Ma, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: A microscopically positive (R1) resection margin following resection for gastrointestinal (GE) cancer has been documented to be a poor prognostic factor. The optimal strategy and impact of different modalities of adjuvant treatment for an R1 resection margin remain unclear. Methods: A retrospective analysis was performed for patients (pts) with GE cancer treated at the Princess Margaret Cancer Centre from 2006 to 2016. Electronic medical records of all pts with an R1 resection margin were reviewed. Kaplan-Meier and Cox proportional hazards methods were used to analyze recurrence free survival (RFS) and overall survival (OS) with stage and neoadjuvant treatment as covariates in the multivariate analysis. Results: We identified 78 GE cancer pts with an R1 resection. 11% had neoadjuvant chemotherapy, 14% chemoradiation (CRT), 75% surgery alone. 28% had involvement of the proximal margin, 13% distal, 56% radial, 3% had multiple positive margins. By the American Joint Committee on Cancer 7th edition classification, 88% had a pT3-4 tumour, 66% pN2-3 nodal involvement, 64% grade 3, 68% with lymphovascular invasion, 3% were pathological stage I, 21% stage II and 74% stage III. Adjuvant therapy was given in 46% of R1 pts (24% CRT, 18% chemotherapy alone, 3% radiation alone, 1% reoperation). Median RFS for all pts was 12.6 months (95% CI 10.3-17.2). Site of first recurrence was 71% distant, 16% locoregional, 13% mixed. Median OS was 29 months (95% CI 22.9-50) for all pts. The 5 year survival rate was 23% (95% CI 12%-43%). There was no significant difference in RFS (log-rank test p = 0.63, adjusted p = 0.14) or OS (log-rank test p = 0.68, adjusted p = 0.65) regardless of adjuvant therapy. Conclusions: Most pts with positive margins after resection for GE cancer had advanced pathological stage and prognosis was poor. Our study did not find improved RFS or OS with adjuvant treatment and only one pt had resection. The main failure pattern was distant recurrence, suggesting that pts being considered for adjuvant RT should be carefully selected. Further studies are required to determine factors to select pts with good prognosis despite a positive margin, or those who may benefit from adjuvant treatment.
4047 Poster Session (Board #175), Mon, 8:00 AM-11:00 AM

A landscape of circulating tumor DNA in esophageal adenocarcinoma and squamous cell carcinoma. First Author: Kabir Mody, Mayo Clinic, Jacksonville, FL.

Background: Esophageal cancer (EC) is a lethal malignancy with limited treatment options. Genomic analyses have led to the elucidation of numerous dysregulated genes in esophageal adenocarcinoma (AC) and squamous cell carcinoma (SCC), and the potential for advancement of targeted therapies in this disease. Data regarding circulating tumor DNA (ctDNA) plasma analysis in EC in real-world clinical practice is limited. Methods: We performed ctDNA next-generation sequencing (NGS) analysis in patients (pts) with EC (February 2015 - February 2018). ctDNA analysis was performed using Guardant 360 (Guardant Health, CA) which detects single nucleotide variants and insertion/deletion mutations, and specific amplifications and fusions, in up to 73 different genes. The mutant allele fraction (MAF) for detected alterations was calculated relative to wild type in ctDNA. Therapeutically relevant was defined as alterations within OncoKB levels 1-3B and R1. Results: Among 450 pts, 487 total samples were analyzed (77% AC, 31% SCC). ctDNA NGS revealed at least one genomic alteration (excluding variants of uncertain significance and synonymous mutations) in 81% of pts (90% AC, 88% SCC). Median number of alterations per AC patient was 4 (range, 1-9) and a monoclonal (range, 0.02%–83.7%); SCC was 5 (range, 1-26), with a median MAF of 0.99% (range, 0.01%–85.2%). The total number of unique alterations was 1,162. The most commonly altered genes in AC: TP53 (70%), KRAS (20%), ERBB2 (18%), EGFR (16%), PIK3CA (16%); in SCC: TP53 (88%), PIK3CA (24%), CNOT1 (23%), KRAS (21%), EGFR (19%). Therapeutically relevant mutations were described. Conclusions: ctDNA plasma profiling of pts with EC is a feasible alternative and non-invasive method to gather comprehensive genomic data. Further large comparison studies to assess landscape of genomic alterations observed through ctDNA versus tissue-based assays, in addition to studies of targeted therapy outcomes based on ctDNA-detected alterations, are needed.

4070 Poster Session (Board #176), Mon, 8:00 AM-11:00 AM

Ramucirumab (RAM) for sorafenib intolerant patients with hepatocellular carcinoma (HCC) and elevated baseline VEGF levels: PFS results from two randomized phase 3 studies (REACH, REACH2). First Author: Josep M Llovet, Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Oral multikinase inhibitors that have shown improvements in overall survival (OS) in HCC are associated with clinically important toxicities that commonly require dose adjustment or discontinuation (DC) due to intolerability. REACH and REACH-2 studied RAM in patients (pts) with HCC who progressed on sorafenib (SOR) and/or sorafenib-intolerant (sorafenib, SOR) and REACH-2 only enrolled pts with baseline AFP >400 ng/mL. In REACH-2 RAM treatment (trt) improved OS compared to placebo (P), and Grade 3/4 immune-related AEs (irAEs) were immature at data cutoff. Grade 4 irAEs were consistent with other grade 3 irAEs (most frequently hypertension) and considered not treatment related to FOLFOX4. Grade 3 immune-related AEs occurred only in 15.3% of pts. The preliminary safety of avelumab + axitinib in HCC is manageable and consistent with the known safety profiles of avelumab and axitinib when administered as monotherapy. This study demonstrates antitumor activity of the combination in HCC. Preliminary follow-up is ongoing. Clinical trial information: NCT03289533.

4071 Poster Session (Board #177), Mon, 8:00 AM-11:00 AM

First-line avelumab + axitinib in patients with advanced hepatocellular carcinoma: Results from a phase 1b trial (VEGF Liver 100). First Author: Masatsugu Kudo, Kindai University, Faculty of Medicine, Osaka, Japan.

Background: Combining an immune checkpoint inhibitor with a targeted anti-angiogenic agent may leverage complementary mechanisms of action for treatment of advanced/metastatic (a/m) hepatocellular carcinoma (HCC). Avelumab is a human anti-PA-L1 IgG1 antibody with clinical activity in various tumor types; axitinib is a tyrosine kinase inhibitor selective for VEGF receptors 1/2. VEGF Liver 100 (NCT02895533) is a phase 1b study evaluating safety and efficacy of avelumab + axitinib in treatment-naive patients (pts) with HCC; interim results are reported here. Methods: Eligible pts had confirmed a/m HCC, measurable lesion, a fresh or archival tumor specimen, ECOG PS ≤1, and Child-Pugh class A. Pts received avelumab 10 mg/kg IV Q2W + axitinib 5 mg orally BD until progression, unacceptable toxicity, or withdrawal. Endpoints included safety and objective response (RECIST v1.1; modified (m) RECIST for HCC). Results: Interim assessment was performed after a minimum follow up of 6 months based on the released study data set (clinical cut-off date: Aug 1, 2018). As of the cut-off date, 22 pts (median age: 68.5 y) were treated with avelumab (median: 20.0 wk) and axitinib (median: 19.9 wk). The most common grade 3 treatment-related adverse events (TRAEs) (≥10% of patients) were hypertension (50.0%) and hand-foot syndrome (22.7%); no grade 4 TRAEs were reported. Immune-related AEs (irAEs) (≥10% of pts) were hypothyroidism (31.8%) and hyperthyroidism (13.6%). No grade ≥3 irAEs were reported; no pts discontinued treatment due to TRAEs or irAEs. Based on Waterfall plot calculations, tumor shrinkage was observed in 15 (68.2%) and 16 (72.7%) pts by RECIST and mRECIST, respectively. ORR was 13.6% (95% CI, 2.9%-34.9%) and 31.8% (95% CI, 13.9%-54.9%) by RECIST and mRECIST, respectively. OS data were immature at data cutoff. Conclusions: The preliminary safety of avelumab + axitinib in HCC is manageable and consistent with the known safety profiles of avelumab and axitinib when administered as monotherapy. This study demonstrates antitumor activity of the combination in HCC. Preliminary follow-up is ongoing. Clinical trial information: NCT03092895.
Multicentric prospective study of validation of angiogenesis-related gene polymorphisms in hepatocellular carcinoma patients treated with sorafenib: Interim analysis of INN53 ATE study. First Author: Andrea Casadei Gardini, IRST-IRCCS, Meldola, Italy

**Background:** In the ePHAS study we analyzed three eNOSpolymorphisms and at univariate analysis, patients with eNOS-786-TT genotype had significantly shorter median Progression Free Survival (PFS) and Overall Survival (OS) compared to those with other genotypes. On the basis of these preliminary results, our aim is to validate in a prospective study this data in patients with HCC treated with sorafenib. **Methods:** This is a prospective Italian multicenter study, that includes 141 HCC patients receiving sorafenib. We analyzed eNOS-786and tt genotype analyzed by Real Time PCR in relation to the primary end point (OS). Event-time distributions were estimated using the Kaplan-Meier method and survival curves were compared using the log-rank test. **Results:** 141 HCC patients (122 males and 19 females), prospectively treated with sorafenib from May 2015 to September 2018 were included. Median age was 69 years (range 28-88 years). 120 patients had Child-Pugh A and 21 had Child-Pugh B7. 43 had BCLC-B and 98 patients had BCLC-C. Atunivariate analysis, we confirmed that eNOS-786 TT genotype were significantly associated with a lower median OS than the other genotypes (9.5 vs 15.7 months; HR 3.69, 95% CI 1.02-2.83; p=0.0424). Following adjustment for clinical covariates (age, gender, eNOS TT genotype, BCLC stage, serum albumin level, MELD score), multivariate analysis confirmed eNOS-786 and BCLC stage as the independent- prognostic factors predicting OS (TT vs CT+CC; HR: 2.39, 95% CI 1.14-5.03 p=0.0211; C vs B:2.23, 95% CI 1.44-7.47; p=0.0339). **Conclusions:** In this prospective study we confirmed the prognostic role of eNOS-786 in advanced HCC patients treated with sorafenib. Clinical trial information: NCT02786342.

Randomized clinical trial of transcatheter arterial chemoembolization plus radiofrequency ablation versus transcatheter arterial chemoembolization for hepatocellular carcinoma with intermediate stage (BCLC stage B) hepatocellular carcinoma beyond Milan criteria. First Author: Xin Yin, Liver Cancer Institute & Zhong Shan Hospital, Fudan University, Shanghai, China

**Background:** To determine treatment efficacy and safety of transarterial chemoembolization (TACE) combined with radiofrequency ablation (RFA) (hereafter, TACE+RFA) in patients with intermediate stage (BCLC stage B) hepatocellular carcinoma (HCC) beyond Milan criteria. **Methods:** In this randomized clinical trial, 110 patients with intermediate stage HCC beyond Milan criteria (single tumor with diameter 5-7cm, median: 3-5 multiple nodules with diameter less than 5cm) were included and randomly assigned to TACE+RFA group (n=55) and TACE group (n=55) at liver cancer institute, Zhongshan hospital. The primary endpoint was overall survival (OS). The secondary end point was progression-free survival (PFS), time to progress (TTP) and best objective response (BOR). **Results:** The median OS in TACE+RFA and TACE group were 29 and 18 months, respectively. The median TTP and BOR were 15.7 months and 69.1 % in TACE+RFA group and 12.4 months and 40.0 % in TACE group (P=0.004). The 1-, 3-, and 4-year overall survivals for TACE+RFA group and TACE group were 97.2%, 67.9% and 59.4% versus 84.0%, 46.7% and 37.3 %, respectively (P = 0.008). The corresponding PFS were 47.3%, 27.2% and 21.7% versus 35.6%,15.3% and 11.4 %, respectively (P = 0.04). The incidence of major complications in TACE+RFA group were comparable to those in TACE group (P=0.14). **Conclusions:** TACE+RFA was superior to TACE in improving tumor response and overall survival for patients with intermediate stage (BCLC stage B) hepatocellular carcinoma beyond Milan criteria. Clinical trial information: NCT03636620.

IGF-Child-Pugh score as a predictor of treatment outcome in advanced hepatocellular carcinoma patients treated with sorafenib. First Author: Yeshia I. Abugabal, University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Our recent published studies concluded that Lower levels of Insulin like growth factors-I (IGF-I) is correlated with shorter overall survival (OS) in HCC, and IGF-CP scores assigned based on serum bilirubin, serum albumin level, prothrombin time, and plasma IGF-1 provides better prognostic stratification. Sorafenib is the first frontline drug approved for the treatment of CP class A patients with advanced HCC. CP class A is the standard criterion for active therapy and trials entry in HCC. In this study we aimed at evaluating the predictive ability of IGF-CP to sub-stratifly OS and better predict sorafenib outcomes. **Methods:** Total of 101 patients were prospectively enrolled from MD Anderson Cancer Center (MDACC). Blood sample were collected and tested for IGF-I and IGF-CP was calculated into class A, B and C. Median OS and progression free survival (PFS) were analyzed, and log rank test was used to compare PFS and OS between subgroups of IGF-CP score of patients. **Results:** Among CP class, patients who were reclassified as IGF-CP (B) (Old A/new B) had significantly shorter OS in months (m) was 7.6m (95% CI= 5.23-26.51m ) and PFS of 2.99m (95% CI=2.53-5.26m) with (P<0.001) in both, as compared to patients’ who classified as class A by both scoring systems (AA), who had OS of 15.43m (95% CI=12.3-31.18m) and PFS of 4.97m (95% CI=3.26-7.2m), (P<0.001) in both. **Conclusions:** IGF-CP score sub-stratified CP A class, and provided better prognostic stratification and accuracy than CP score in predicting sorafenib survival outcomes in HCC. This approach may lead to a paradigm shift in predicting efficacy and toxicity of systemic HCC therapies and in stratifying patients for active therapy and selection in HCC clinical trials.
Background: Antitumor activity with pembrolizumab, an anti–PD-1 antibody, has been observed in patients (pts) with advanced/metastatic biliary tract cancers (BTC), who have limited treatment options. We present follow-up data from pts with advanced BTC treated with pembrolizumab in the KN158 (NCT02628067; phase 2) and KN028 (NCT02054806; phase 1) studies. 

Methods: Eligible pts ≤ 18 y in the KN158/KN028 BTC cohorts had histologically/cytologically proven incurable advanced BTC that progressed after/failed any number of prior standard treatment regimens, measurable disease per RECIST v1.1, ECOG PS of 0/1, and no prior immunotherapy. PD-L1–positivity (membranous PD-L1 expression in ≥ 1% of tumor and associated inflammatory cells or positive staining in stroma) was required for eligibility in KN028, but not KN158. Pts received pembrolizumab 200 mg Q3W (KN158) or 10 mg/kg Q2W (KN028) for up to 2 y. Radiographic imaging occurred Q2W for 12 mo (KN158) or Q8W for 6 mo (KN028) and Q12W thereafter. Primary efficacy endpoint in both studies was ORR by RECIST 1.1. Response assessed by independent central review is occurring alteration pair (odds ratio = 8.5; q-value = 1.08 x 10^-13, Fisher’s exact test). 42.9% of patients had at least one alteration for which a targeted agent has either been approved or is under investigation. 91 (8.2%) patients had FIGHT-202 rearrangements, involving 64 unique partner genes, 37 (84.1%) of which were observed only once. The most prevalent rearrangement partner, BICCL1, occurred in only 28 (30.7%) FIGHT-202 rearrangement positive patients. FIGHT-202 activating point mutations were found in 13 (1.2%) patients. Of 1,091 evaluable patients for microsatellite instability (MSI) or tumor mutational burden (TMB), only 10 (0.9%) were MSI-H and 131 (1.2%) had high TMB (≥ 20 mutations/Mb). Non-KRAS, non-IDH1/H2-High TMB patients had FIGHT-202, IDH1 or IDH2 activating alterations. Conclusions: The high frequency (42.9%) of patients with actionable alterations and myriad FIGHT-202 rearrangement partners strongly support the use of fusion partner-agnostic CGP in advanced CCA.
4083 Poster Session (Board #188), Mon, 8:00 AM-11:00 AM Final analysis of phase II trial of regorafenib (REG) in refractory advanced biliary cancers (BC). First Author: Dae Won Kim, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL.

**Background:** While gemcitabine plus cisplatin has demonstrated significant antitumor activity as 1st line therapy of BC, there is no effective treatment after failure of gemcitabine-based therapy. REG is an oral multi-kinase inhibitor that targets angiogenesis, oncogenesis and cancer proliferation/metastasis. We evaluated the efficacy of REG in BC. **Methods:** Patients (pts) with histologically proven BC who progressed on at least one line of systemic therapy received REG 160 mg daily 21 days on/7 days off, in 28 day cycles. The primary endpoint was 6-month (mo) overall survival (OS) and the secondary endpoints were median OS, progression free survival (PFS) and response rate (RR). Pre and post-treatment plasma were collected for cytokine evaluation. **Results:** A total of 39 pts received at least 1 dose of REG; 32 pts were evaluable for efficacy. Median age was 62 (range: 27-88) years and the primary sites of tumor were intrahepatic cholangiocarcinoma (68.8%), extrahepatic (18.8%), and gallbladder (12.5%). Pts were considered evaluable for efficacy if patients received more than 1 cycle of REG. For 32 evaluable pts, 6 mo OS was 52% with median PFS of 2.8 mo (95% CI: 1.1-4.5) and median OS of 7.9 mo (95% CI: 0.18-17). Median PFS and OS of the pts (n=20) failed 1 line of therapy were 3.7 mo (95% CI: 3.2-4.1) and 13.8 mo (95% CI: 1.8-25.8), respectively. Median PFS and OS of the pts (n=12) failed 2 lines were 1.8 mo (95% CI: 1.63-1.97) and 4.5 mo (95% CI: 2.6-6.3), respectively. RR was 9.4% (2 PR and 1 unconfirmed PR) and DCR was 22.5%. Total 7 pts (grade 3/4) adverse events were observed, and the most common AE were fatigue (56.4%) and hypertension (53.8%). Dose modification was required in 49% of the pts. Among the 23 cytokines analyzed, elevated baseline VEGF-A was associated with good prognosis (HR 0.62, p=0.01). Elevated baseline TIMP-1 (HR 1.79, p=0.04) and IL-6 (HR 1.30, p=0.04) were found elevated with poor prognosis. TMB increased BMP-9, GP130, VEGF-R2 and VEGF-R3 and increased IL-6, PIGF, TIMP-1, VCAM-1 and VEGF-A significantly. **Conclusions:** The primary endpoint was met in this study. VEGF-A may be further evaluated as a predictive biomarker for REG in BC. Further randomized trials are warranted to confirm the efficacy and the correlative data. Clinical trial information: NCT02115542.

4085 Poster Session (Board #190), Mon, 8:00 AM-11:00 AM Frequency of BRCA mutation in biliary tract cancer and its correlation with tumor mutational burden. First Author: Gilbert Spizzo, Experimental Oncology, Tyrolean Cancer Research Institute, Innsbruck, Austria

**Background:** Biliary tract cancers constitute ~3% of cancers worldwide with incidence increasing, especially for intrahepatic cholangiocarcinoma (IHC). The prognosis of these tumors remains dismal and novel treatment strategies are needed to improve overall survival. **Methods:** BRCA mutations occur in biliary tract cancers but their frequency in distinct sites of biliary tract cancer is unknown. Moreover, no data are available correlating BRCA mutation with immunogenic markers such as TMB, MSI, or PD-L1 expression. **Results:** TMB was increased in 61% of pts, MSI was evaluated by NGS of known MSI loci (MiSeq on 47 genes, NextSeq on 592 genes) and PD-L1 IHC (SP142). TMB elevations were observed in 242s Gastrointestinal (Noncolorectal) Cancer (EHC) (n = 189), gallbladder (GBC) (n = 353) tumors. The most common mutations identified were BRCA (55.6%), TP53 (55.6%), CDKN2A (26.1%), KMT2D (20%, 13%) and CDKN2A (13%). Overall, 20% of pts harbored FGFR fusions, 12% of BRCA, and 7% of PTEN. TMB and MSI were correlated with poor prognosis. Moreover, elevated TMB was seen in IHC and EHC, but not in GBC. No correlation was found between number of FGFR fusions and number of BRCA mutations. **Conclusions:** These data provide rationale for trials testing PARP inhibitors in combination to confirm the efficacy and the correlative data. Clinical trial information: NCT02456714.

4086 Poster Session (Board #191), Mon, 8:00 AM-11:00 AM Efficacy and safety of FOLFIRINOX in advanced biliary tract cancer after failure of gemcitabine plus cisplatin: A phase II trial. First Author: Ali Belkouz, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands

**Background:** Currently there is no established standard treatment after failure of gemcitabine plus cisplatin in advanced biliary tract cancer (BTC). Based on the efficacy of FOLFIRINOX in advanced pancreatic cancer, which has histological and prognostic similarities with BTC, a Phase 2 study was conducted to determine whether FOLFIRINOX is effective and safe in BTC. **Methods:** Patients with BTC and an ECOG PS of 0/1 who had disease progression or unacceptable adverse events (AEs) after at least 3 cycles of GemCis were included. Patients received oxaliplatin 85 ml/m², irinotecan 180 mg/m², leucovorin 400 mg/m², fluorouracil bolus at 400 mg/m², followed by fluorouracil continuous infusion of 2400 mg/m² over 46-hour every 2 weeks. This phase 2 study was conducted according to the two-stage Simon's Design. Stage 2 was activated if at least 1 objective response rate (ORR) or 2 stable diseases were observed among 10 patients in stage 1 and a maximum of 3 patients had severe AEs within the first 6 weeks of treatment. If more than 4 patients required a dose reduction in stage 1, stage 2 was initiated with a standard dose reduction (fluorouracil bolus was omitted and irinotecan reduced to 140 mg/m²). Primary outcome was ORR per RECIST 1.1 and secondary outcomes were overall (OS), progression free survival (PFS), and safety profile. **Results:** Forty patients were screened and 30 patients were included between May 2016 and July 2018. Median age was 60 years and 63% of patients were males. In stage 1, 5 patients required a dose reduction within the first 6 weeks due to AEs, leading to initiation of stage 2 with modified FOLFIRINOX after inclusion of 10 patients. The partial response rate was 10% (3/30), disease control rate 67%, and median OS and PFS of 10.7 and 6.2 months, respectively. Most common grade 3/4 adverse events include neutropenia (50%), anemia (17%), diarrhea (13%), thrombocytopenia (10%), and deviated liver function tests (10%). **Conclusions:** This is the first Phase 2 study with modified FOLFIRINOX in BTC showing promising disease control rate, OS, and safety profile, with an acceptable adverse events profile. Timedirected and biomarker-driven FOLFIRINOX is currently tested as a first-line treatment for patients with BTC in the ongoing randomized phase 2/3 ARMABICLIA trial (NCT02591030). Clinical trial information: NCT02456714.
Background: The management of CCA has evolved as targeted and immune checkpoint inhibitor (ICI) therapies have emerged. We used comprehensive genomic profiling (CGP) to characterize the genomic alterations (GA) that have potential to personalize therapy for CCA. Methods: 3634 CCA underwent MSKCP CGP on 0.8-1.1 M of the coding genome to identify GAs in exons and select introns in up to 404 genes, TMB, microsatellite status (MSI) and % monoallelic genome (gLOH). PD-L1 expression was determined by IHC (Dako 22C3). Results: 52% of CCA were female with a median age of 62 years (range 16 - 89). The most common biopsy sites were liver (74%), lymph node (4%), bile duct (3.3%), and lung (2%). MSI-high was rare (1%), and 118 and 47 cases had TMB > 10 and > 20 mut/mb respectively. Of the latter, 51% (24/47) were MSI-H, PD-L1 amplification (AMP) was present in 0.27%. Of 490 CCA tested, 43 (9%) were positive for PD-L1 expression. 11% of cases had gLOH. Of 450 CCA tested, 43 (9%) were positive for PD-L1 expression. 11% of cases had gLOH.

Nab-paclitaxel plus S-1 as first line treatment for advanced or metastatic cholangiocarcinoma (CCA) that warrants further investigation for sensitivity to PARP inhibitors and ICPI respectively. Two Stage design.

Conclusions: The development of PPE or grade ≥3 HTN with C was associated with prolonged OS and PFS in pts with previously treated aHCC although some imbalances in baseline characteristics between comparator groups were present. Clinical trial information: NCT01908426.

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Novel staging system using carbohydrate antigen (CA) 19-9 in extrarepative cholangiocarcinoma (ECCA) and its implications on overall survival (OS).

**Methods:** Patients with ECCA were included if they reported to the National Cancer Database (2004-2015). The patients were classified based on their CA19-9 levels and a new staging system was proposed. The current knowledge, we considered 37 U/ml as our cut-off. Kaplan Meier method was used to compare OS between the groups. The net reclassification improvement (NRI) model was used to assess the predictive improvement in the proposed survival model.

**Results:** A total of 2100 patients met the inclusion criteria: 601 (32%) and 1436 (68%) had normal and elevated CA19-9 levels, respectively. Rates of chemoradiation (p=0.16) and radiation therapy (p=0.07) were similar between groups, but patients with elevated CA19-9 were less likely to undergo resection. Resected patients with CA19-9 elevation had higher 30-day mortality (p=0.02) and lower OS (p<0.01). Patients with elevated CA 19-9 levels had decreased stage-specific survival in all stages (p<0.01). On adjusted analysis, CA19-9 elevation was independently predicted poor OS (HR= 1.67 [1.42-1.97]) with impact re-susvival in all stages (p<0.0001). Timing for maximum tumor regression could be divided to 4 categories by the response at 100 days after enrollment: category A (<30% in size), B (<30% to C, 0% to +20%), and D (> +20%). CA19-9 arm obtained more category A & B (61 [67%] vs. 33 [36%], P< 0.0001). Each category predicted best response and overall survival (p < 0.0001). Timing for maximum tumor shrinkage could be divided to 4 categories by the response at 100 days after enrollment: category A (<30% in size), B (<30% to C, 0% to +20%), and D (> +20%). CA19-9 arm obtained more category A & B (61 [67%] vs. 33 [36%], P< 0.0001). Each category predicted best response and overall survival (p < 0.0001).

**Conclusions:** Elevated CA19-9 was found to be an independent risk factor for mortality and its inclusion in the newly proposed staging system markedly improved OS discrimination.

**New proposed staging system.**

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<tr>
<th>New Stage</th>
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Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: H3B-6527 overexpression is hypothesized to hyperactivate FGFR4 and its downstream signaling pathway leading to enhanced tumor growth in HCC/ICC. Targeting FGFR4 may have therapeutic benefit in HCC/ICC with altered FGFR19 signaling. A phase 1 study (NCT02834780) was initiated to assess H3B-6527, an investigational highly selective covalent FGFR4 inhibitor. Methods: Adult pts with advanced HCC or ICC, ECOG PS 0-1, well compensated liver function, and who progressed after at least one prior therapy, were administered H3B-6527 orally QD (once daily) on a 21-day cycle following a 3+3 design. Patients in the dose escalation phase were treated regardless of FGFR19 status. Adverse events (AEs), pharmacokinetics (PK), and pharmacodynamics (PD) were assessed. Response was determined by RECIST 1.1 or modified RECIST every 6 weeks. Results: As of 06-Jan-2019, 37 pts have been treated with H3B-6527 at doses of 300 to 1400 mg QD (23 pts in escalation; 14 in expansion). In dose escalation, a total of 17 patients with HCC, Child-Pugh A received prior systemic therapy including 100% with prior TKI and 35% with prior IO. 12% had hepatitis B virus and 47% had hepatitis C virus. H3B-6527 plasma levels increased with dose from 300 to 1000 mg QD and plateaued. H3B-6527 was rapidly absorbed with a tmax of ~2-3 h and showed a terminal half-life of ~4-5 h, following administration of 1000 mg (fasted). No dose-limiting toxicities or toxicities ≥ Grade 3 were observed among dose-escalated AEs (TRAE) have been observed on the once daily fasted schedule; 2 of 17 pts with HCC achieved PRs and an additional 4 pts with stable disease were on treatment for ≥ 5 months. Conclusions: H3B-6527 is well tolerated and demonstrates early signs of clinical activity. Dose expansion on QD schedule and exploration of BID dosing is underway. H3B-6527 is well tolerated and demonstrates early signs of resistance and to identify other potential targetable alterations. The assay was enhanced to include all protein-coding exons and relevant introns of FGFR2. In 5/8 pts, genomic profiling of an initial tumor biopsy was performed. Results: 8 pts with FGFR2-altered CCA (7 gene fusions, 1 amplification) were treated with FGFR-targeted therapies. 7/8 pts exhibited stable disease or partial response. 19 total acquired mut in FGFR2. First Author: Teresa Macarulla Mercade, Hebron Institute of Oncology, New York, NY.

<table>
<thead>
<tr>
<th>Pt Baseline FGFR Alteration</th>
<th>FGFR2 Acquired Resistance Mutations</th>
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<tbody>
<tr>
<td>FGFR2-KIAA1217</td>
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Background: Non-invasive detection of acquired resistance to FGFR inhibition in patients with cholangiocarcinoma harboring FGFR2 alterations. First Author: Annie Varace, Memorial Sloan Kettering Cancer Center, New York, NY.

Background: FGFR2 alterations are present in 14% of cholangiocarcinomas (CCA) and are promising targets of investigational FGFR-directed therapies. Cell-free DNA profiling has emerged as a non-invasive approach to monitor disease and longitudinally characterize tumor evolution. We describe the use of circulating tumor DNA (ctDNA) among patients (pts) with FGFR2-altered CCA receiving FGFR-targeted therapy in the identification of acquired FGFR2 mutations (mut) at resistance.

Methods: Serial blood samples were collected from 8 pts with FGFR2-altered CCA and next generation sequencing. Plasma ctDNA collected at baseline and resistance to FGFR-targeted therapy were sequenced using a custom ultra-deep coverage ctDNA panel, MSK-ACCESS, incorporating dual index primers and unique molecular barcodes to enable background error suppression and high-sensitivity mut detection. The assay was enhanced to include all protein-coding exons and relevant introns of FGFR2. In 5/8 pts, genomic profiling of an initial tumor biopsy was performed. Results: 8 pts with FGFR2-altered CCA (7 gene fusions, 1 amplification) were treated with FGFR-targeted therapies. 7/8 pts exhibited stable disease or partial response. 19 total acquired mut in FGFR2. First Author: Teresa Macarulla Mercade, Hebron Institute of Oncology, New York, NY.
Clinical and prognostic significance of serum levels of fatty acid binding proteins in hepatocellular carcinoma (HCC). First Author: Yehia I. Abugabal, University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Limited data are available about the prognostic effect of fatty acid binding proteins (FABPs) in viral and non-viral-related hepatocellular carcinoma (HCC). Previous studies suggested that selected FABPs could be a potential target markers for HCC chemotherapy response and may correlated with presence of cirrhosis and poor outcome. We aimed to test the association between plasma levels of Liver (L)-FABP, Heart (H)-FABP, and Adipose (A) FABP and HCC. **Methods:** we enrolled 767 HCC patients from MD Anderson Cancer Center. Under IRB approval, baseline patients' characteristics were retrieved from medical records and blood samples were collected and tested form plasma levels of L-, H-, and A-FABPs. Descriptive statistics were performed and the median values of FABPs among 200 normal controls (NC) were used as cutoff values of FABPs. Overall survival (OS) was estimated by Kaplan Meier curve and log rank test. **Results:** FABPs were highly expressed in HCC cases than controls. Mean values (±SE) of AFABP, HIFABP, and LFABP were significantly higher in cases in 25% (6.7, 10.8±5), and 47.8 (1.9) than controls [19.1 (1.8), 7.7 (2), 22. 9 (3)]. P < .001. FABPs were significantly associated with comorbidities of Child-Pugh Score (CTP), advanced stage in Barcelona clinic liver cancer stage (BCLC), higher AFP levels, vascular invasion and thrombosis, and tumor nodularity. Median OS (months) (95%CI) were significantly short in patients with higher level of AFABP, HFABP, and LFABP [9.3 (6.8-1.9), 9.4 (6.8-11.9), and 11.1 (8.9-13.3)] as compared to patients with low levels [11.4 (13.8-18.9), 16.4 (14.2-18.6), and 17.9 (14.9-20.9) respectively (P < .01). The significance was observed in non-viral related HCC for LFABP and HFABP, but not AFABBP. **Conclusions:** To the best of our knowledge, we describe the largest study correlating FABPs levels with clinical and prognostic characteristics of HCC. Higher levels were associated with poor survival. These findings suggest that LFABP and HFABP may be used as potential prognostic biomarkers for non-viral-related HCC.

4100 Poster Session (Board #205), Mon, 8:00 AM-11:00 AM
**Predictors of poor outcome for transarterial chemoembolization (TACE) in hepatocellular carcinoma (HCC).** First Author: Petra Prins, Medstar George-town University Hospital, Washington, DC

**Background:** The use of TACE in select patients with BCLC stage B HCC has been shown to improve survival. Despite this, it remains unclear which patients will benefit from repeated TACE versus switching to systemic therapy upon disease progression. The purpose of this study is to identify prognostic factors that predict poor outcomes in patients who receive TACE. **Methods:** In this single-institutional retrospective analysis, patients with unresectable HCC were treated with TACE between 2007-2016. Relevant factors such as staging by BCLC stage B, Child-Pugh score, vascular invasion (VI), tumor thrombus (TT), AFP levels, and number of TACE treatments within six months from the initiation of TACE were analyzed using either Pearson’s chi-square test or the student’s t-test. The Kaplan-Meier method was used for survival analysis. **Results:** Patients (n = 176) underwent TACE; 45% had stage I-II disease, 42% were BCLC stage B prior to TACE, 71% were Child-Pugh A, 21% had extrahepatic spread, 34.7% had VI, and 26% had TT. The median number of TACE treatments was 2 (range, 1-6). The median overall survival (mOS) was 43 months (95% CI 31.3-54.2) and mOS from start of TACE was 34m (95% CI 26.2-41.8). Elevated AFP (>400) correlated with decreased mOS (25m vs. 35m, p=0.041). Similarly, the presence of TT correlated with poor outcomes (25m vs. 37m, p=0.015). The mOS was also negatively impacted by having 3 or more TACE treatments within a 6 m period (25m vs. 38m, p=0.09). AFP >400, TT, and interval between TACE were independent factors in this multivariate analysis, resulting in a shorter mOS of approx. 2 years compared to 3 years in patients without these negative prognostic factors. There was a strong association with both elevated AFP and TT (Chi square p=0.009). **Conclusions:** Elevated AFP (>400), the presence of TT, and a need for 3 or more TACE treatments within 6 months appear to be independent predictors for shorter mOS in patients receiving TACE. Patients with these poor prognostic factors tend to have more aggressive HCC, and earlier initiation of systemic therapy might provide benefit to these patients. A larger study is needed for confirmation of these findings.

4101 Poster Session (Board #206), Mon, 8:00 AM-11:00 AM
**An open label, single-arm, two-stage, multicenter, phase II study to evaluate the efficacy and safety of TLC388 as second-line treatment in subjects with poorly differentiated neuroendocrine carcinomas (TCOGT1214).** First Author: Ming-Huang Chen, Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan

**Background:** Therapeutic options for metastatic poorly differentiated neuroendocrine carcinoma (NEC) after prior platinum-based chemotherapy are unknown. Carcinoembryonic antigen, like agonist and inotocin, are approved chemotherapies in small cell lung cancer (SCLC). NEC is considered to have similar biological behavior to SCLC. The aim of this study was to analyze the efficacy of TLC388 (Liptotecan) Hydrochloride, which is a novel camptothecin analog, in pretreated metastatic NEC patients. **Methods:** This single-arm, 2-stage, phase 2 clinical trial was conducted at 4 community and academic centers in Taiwan. Patients aged 20 years or older enrolled between July 2015 to May 2018 had confirmed metastatic NEC with prior systemic therapy with etoposide plus cisplatin. Patients received intravenous 40 mg/m² of TLC388 on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxic effects. **Results:** twenty-three patients with a median age of 61 (range, 44-73) years, including 18 men (78%), were enrolled. Patients received a median of 2 (range, 0-6) treatment cycles. Among 20 evaluable patients, three patients showed a stable disease and no patient a complete or partial remission, resulting in a disease control rate of 15%. Median PFS was 1.8 (95% CI, 0.4-15) months and median OS was 4.3 (95% CI, 1.7-15) months. The most common treatment-related hematologic adverse events at grade 3 or higher were leukopenia (22.7%), anemia (31.8%), and thrombocytopenia (18.2%), respectively. **Conclusions:** TLC388 shows modest antitumor activity in metastatic NEC. Clinical trial information: NCT02457273.

4102 Poster Session (Board #207), Mon, 8:00 AM-11:00 AM
**A phase I study of oncolytic immunotherapy of metastatic neuroendocrine tumors using intralesional rose bengal disodium: Cohort 1 results.** First Author: Timothy Jay Price, Queen Elizabeth Hospital, University of Adelaide, Adelaide, Australia

**Background:** Metastatic neuroendocrine neoplasms (mNEs) originating in the gastrointestinal tract are frequently slow growing yet both symptom and disease control remain important. Treatment options include resection, chemotherapy, systemic somatostatin analogues (SSA) or peptide receptor radionuclide therapy (PRRT), but additional options are needed and one such option is hepatic intralesional (IL) rose bengal disodium (PV-10), an oncolytic immunotherapy under development for solid tumours. **Methods:** This phase 1 study is evaluating the safety, tolerability and reduction of biochemical markers and symptoms resulting from percutaneous administration of PV-10 in 12 subjects with progressive mNEN with hepatic lesions not amenable to resection or other potentially curative therapy. Target lesion(s) must be 1.0 - 6 cm in diameter with evidence of both local and systemic disease control. Enrolment to Cohort 2 is underway. Clinical trial information: NCT02693067.
A phase II, open label, multicenter trial of avelumab in patients with advanced, metastatic high-grade neuroendocrine carcinomas NEC G3 (WHO 2010) progressing after first-line chemotherapy (AVENEC). First Author: Christian Fottner, I. Medical Department, Mainz University Medical Center, Mainz, Germany

Background: High grade Neuroendocrine Neoplasias (NEN) are rare tumors with a poor prognosis and no established second line therapy when progressive after first line platinum-based chemotherapy resulting in a median overall survival (OS) of 5 months. This study aims to evaluate the efficacy and safety of the anti-programmed death ligand 1 (PD-L1) antibody Avelumab in patients (pts) with NEN G3 progressing after first-line chemotherapy. Methods: In a multicenter, national, single-arm, open-label, phase II trial the efficacy and safety of Avelumab was evaluated in patients with metastatic progressive Neuroendocrine Carcinomas (NEC G3) according to WHO 2010, excluding Merkel cell carcinoma and small cell lung cancer. Results: From December 2017 - July 2018 a total of 29 pts (20 male, 69%), were enrolled (16 NEC G3 and 11 moderately differentiated NETG3). Mean age was 59.2 ± 10.2 years (range 33-75), median follow up 16.5 weeks (3-48). Median Ki67 was 60% (range 20-95%). Site of origin included pancreas (12), genito-urinary tract (4), stomach, esophagus (3), colon-rectum (3), lung (2), ear-nose-throat (1). In an interim analysis the DCR (stable disease or partial remission according to irRECIST) after 8 weeks was 32% (4 SD, 2 PR). In responders, mean duration of disease control was 20 ± 13.8 weeks, with 4 pts, showing stable disease or partial remission ≥6 months. Median OS was 4.2 months (range 1- >12). Treatment-related adverse events were observed in 10/29 pts (34.4%), and were mainly mild to moderate (CTCAE-grade 1 [52%], 2 [44%] and 3 [4%]) and included fatigue (n=6; 20.7%), diarrhea (n=4; 13.7%), fever/chills after infusion (n=4; 13.7%), loss of appetite and nausea (n=4; 13.7%), skin rash (n=1; 3%), deterioration of preexisting psoriasis (n=1; 3%) and abdominal pain (n=1; 3%). Conclusions: Immuno-therapy with avelumab in pretreated high grade NEN shows relevant activity in a subset of patients with excellent tolerability. Clinical trial information: NCT03352934.

The SUNEVO (GETNE-1408) trial to evaluate the activity and safety of the combination of sunitinib with evofosfamide (TM-302) in patients with G1/2 metastatic pancreatic neuroendocrine tumours (pNETS) naive for systemic treatment: A phase II study of the Spanish Task Force Group for Neuroendocrine and Endocrine Tumors (GETNE). First Author: Enrique Grande, MD Anderson Cancer Center Madrid, Madrid, Spain

Background: Angiogenesis plays an important role in tumorigenesis and progression of pNETs. Evofosfamide (EVO) is a DNA alkylator prodrug that selectively activates under hypoxia. Sunitinib as monotherapy shows a wide spectrum of activity in terms of tumor shrinkage as only two patients achieved stable disease or partial remission. Evofosfamide in combination with sunitinib-induced hypoxia might increase the cytotoxic activity of EVO in patients with metastatic pNETS and naive for systemic treatment other than somatostatin analogues (SSA). Methods: This is a phase-II, single-arm, and multicenter trial of EVO (340mg/m2 on days 8, 15 and 22 every 4 weeks) and sunitinib (37.5mg/day continuously). Primary endpoint was Objective Response Rate (ORR) by RECIST v1.1 assessed every 8 weeks. A Simon two-stage optimal design was used, considering a minimum of 3 responses in the first 18 pts in order to start with the second stage (power = 0.80, alpha = 0.05).

Results: Between May/2015 and May/2018, 17 pts were included (median age was 62.4 y.o). Prior SSA was reported in 7 pts (41.2%). Dose reductions were reported in 20% (sunitinib) and 100% of pts (EVO). Conclusions: Combination of sunitinib and EVO failed to demonstrate activity in terms of tumor shrinkage as only two patients achieved response, therefore, second stage was not proceeded. While cross trial comparisons are difficult, response rate of 12% with the combination was disappointing. Concerns over toxicity arose; translational analysis are ongoing. Clinical trial information: NCT02402062.

Oxaliplatin and 5-fluorouracil (FOLFOX) in advanced well-differentiated digestive neuroendocrine tumors: A multicenter national retrospective study from the French Group of Neuroendocrine Tumors (GFTN). First Author: Paul Giroix, CHD Vendée La Roche Sur Yon, La Roche Sur Yon, France

Background: Oxaliplatin-based regimens have shown promising antitumor activity in digestive neuroendocrine tumors (NETs), however the available data are limited. Our aim was to assess the tumor response and survival in a large series of patients treated with oxaliplatin and 5-fluorouracil (FOLFOX) for advanced digestive NETs.Oxaliplatin-based regimens have shown promising antitumor activity in digestive neuroendocrine tumors (NETs), however the available data are limited. Our aim was to assess the tumor response and survival in a large series of patients treated with oxaliplatin and 5-fluorouracil (FOLFOX) for advanced digestive NETs. Methods: All patients with advanced well-differentiated digestive NETs treated with ≥ 3 cycles of FOLFOX between 2004 and 2018 in 12 centers of the French GTE, were retrospectively included. Best response according to the RECIST 1.1 criteria, progression-free survival (PFS) and overall survival (OS) were evaluated. The prognostic factors for PFS were investigated by multivariate analysis using a Cox proportional hazard model including variables with a p value < 0.20 in univariate analysis. Results: One hundred and fourteen patients were included. Primary tumor location was pancreas (n = 88), small intestine (n = 37), stomach (n = 7) and unknown without lung tumor at CT scan (n = 13). Partial response rate was of 31% for pancreatic NETs, 13% for small intestine NETs, 14% for gastric NETs, 25% for rectal NETs and 38% for unknown primary NETs. Median PFS were 24, 16, 9, 9, 14, 4 and 6 months, and median OS were 30, 28, 31, 25 and 15 months. Significant poor prognostic factors for PFS after FOLFOX in digestive NETs were: progressive disease (HR = 2.5, p = 0.018), hepatic involvement > 50% (HR = 1.8, p = 0.009), prior targeted therapy (HR = 1.5, p = 0.015), age > 65 y.o. and rectal primary tumor (HR = 4.2, p = 0.001). The 9, 11, 13 and 15 month OS for pancreatic NETs, the 9, 11, 12 and 14 month OS for small intestine NETs, the 9, 11, 12 and 14 month OS for gastric NETs, and the 11, 12, 13 and 15 month OS for unknown NETs, the 9, 11, 12, 13 and 15 month OS for rectal NETs, the 9, 11, 12, 13 and 15 month OS for unknown primary NETs, the 9, 11, 12, 13 and 15 month OS for unknown without lung tumor NETs were: 70%, 60%, 50%, 40% and 30% respectively. Conclusions: FOLFOX has a promising clinical activity for gastro-enteropancreatic NETs, especially in insulinomas.

The final results of the TALENT trial (GETNE1509): a prospective multicohort phase II study of lenvatinib in patients (pts) with G1/G2 advanced pancreatic (panNETs) and gastrointestinal (gNETs) neuroendocrine tumours (NETs). First Author: Jaume Capdevila, Medical Oncology Department, Vall d’Hebron University Hospital; Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: Approved systemic therapies for advanced NETs have showed limited tumor shrinkage and no data of activity after progression to prior targeted agents (TA) is available. Lenvatinib, a potent VEGFR1-3 & FGFR1-4 inhibitor may increase efficacy and revert primary and acquired resistance to TA. We report the final results of the TALENT trial. Methods: Two independent cohorts were included: panNETs and gNETs. All pts had baseline documented progression disease (PD) by RECIST. For panNETs, PD to TA was mandatory, regardless of prior therapy with somatostatin analogs (SSAs) or chemotherapy (CHT); and for gNETs, PD on SSAs. Pts were treated with lenvatinib at 24 mg qd until PD or intolerable toxicity. The primary endpoint was overall response rate (ORR) by central radiology review. Progression-free (PFS) and overall survival (OS) were assessed by investigator. With 55 pts per arm, our study was powered to identify an ORR ≥25% (90% power, 5% α-error). Results: We recruited 111 pts: 55 panNETs and 56 gNETs (78% from small intestine). Prior therapies were CHT 32%, SSAs 87%, everolimus 70% and sunitinib 30% for panNETs. ORR was 29%, 42.3% for panNETs and 16.3% for gNETs. With a median follow-up of 19 m, PFS and OS for panNETs were 15.5 m (95% CI 11.3-not reached (NR)) and 29.2 m (95% CI 23.2-NR); and 15.4 m (95% CI 11.5-19.4) and NR for gNETs, respectively. Pts who obtained a response by RECIST had a significantly better PFS than others (HR = 2.5, p = 0.018), hepatic involvement > 50% (HR = 1.8, p = 0.009), prior targeted therapy (HR = 1.5, p = 0.015), age > 65 y.o. and rectal primary tumor (HR = 4.2, p = 0.001). The 9, 11, 13 and 15 month OS for pancreatic NETs, the 9, 11, 12, 13 and 15 month OS for small intestine NETs, the 9, 11, 12, 13 and 15 month OS for gastric NETs, and the 9, 11, 12, 13 and 15 month OS for unknown NETs, the 9, 11, 12, 13 and 15 month OS for unknown primary NETs, the 9, 11, 12, 13 and 15 month OS for unknown without lung tumor NETs were: 70%, 60%, 50%, 40% and 30% respectively. Conclusions: FOLFOX has a promising clinical activity for gastro-enteropancreatic NETs, especially in insulinomas.
### Molecular characterization of the tumour microenvironment in neuroendocrine malignancy

**First Author:** David James Pinato, Imperial College London, London, United Kingdom

**Background:** A comprehensive characterization of the tumour microenvironment is lacking in neuroendocrine tumors (NETs), where immunotherapy is undergoing efficacy testing. We investigated drivers of cancer-related immunosuppression across NETs of various sites and grade using multi-parameter immunohistochemistry and targeted transcriptomics. **Methods:** Tissue microarrays (n = 102) were stained for PD-L1 & 2, Indoleamine-2,3-dioxygenase-1 (IDO-1) and evaluated in relationship to functional characteristics of tumor-infiltrating T-lymphocytes (TILs) and biomarkers of hypoxia/angiogenesis including VEGF-A, HIF-1α and Carbonic Anhydrase IX. PD-L1 expression was tested in circulating tumour cell (CTCs, n = 12) to evaluate its relationship with metastatic dissemination. **Results:** PD-L1 expression was highest in lung NETs (n = 30, p = 0.007), whereas PD-L2 was highest in PNETs (n = 53, p < 0.001) with no correlation with grade, stage or biomarkers of hypoxia. Incubation of GQP-1 and BON-1 NET cells in 1% O2 did not induce PD-L1 expression confirming transcriptional independence from hypoxia. PD-L1+ NETs (n = 26, 25%) had frequent IDO-1 co-expression (p = 0.03), greater CD4+FOXP3+ and CD8+PD1+ TILs (p < 0.001) and necrosis (p = 0.02). CD4+FOXP3+ PD-L1+IDO-1+ co-expressing tumours in 75% of evaluated patients (n = 12). **Conclusions:** PD-L1 expression correlates with T-cell exhaustion independent of tumour hypoxia and is enhanced in a subpopulation of CTCs, suggesting its relevance to the progression of NETs. These findings support a potential therapeutic role for PD-L1/IDO-1 inhibitors in a subset of NETs.

### Background

- **TILs (p = 0.001)**, necrosis (p < 0.001), and necrosis (p = 0.006). Survival was predicted by tumour grade (p < 0.001) and necrosis (p < 0.001) but not PD-L1, PD-L2 or IDO-1. High-grade NETs had lower CD4+ FOXP3+ and CD8+PD1+ TILs density (p < 0.001) and Nanostaging immune-profiling revealed enrichment of mismatching-related transcripts in cases with poorer prognosis. We identified PD-L1+ CTC subpopulations in 75% of evaluated patients (n = 12).

### Impact of gender on multikinase inhibitors (MKIs) toxicity in patients (pts) with metastatic androgenetic or androgen-refractory prostate cancer (MPCAR) and evalution of tyrosine kinase inhibitors (TKIs)

**First Author:** Jorge Hernando-Cubero, Vall Hebron University Hospital, Vall Hebron Institute of Oncology (VHIO), Barcelona, Spain

**Background:** Retrospective data in some cancer types suggested a possible different toxicity profile with chemotherapy and targeted therapies according to gender. However, data from prospective studies are still very limited, especially in infrequent tumors such as NETs. **Methods:** Pts with advanced pancreatic and gastrointestinal NETs treated with pazopanib or lenvatinib in the multicenter open-label phase II studies PAZONET and TALENT respectively, were included in the analysis. Both studies were performed by Spanish Task Force Group for Neuroendocrine Tumors (GETNE). All grade 3-4 toxicities were analyzed separately. Additionally, all grade 3-4 toxicities were analyzed separately.

### Results:

- **Liver toxicity:** 51 pts (47.7% female) with 121 adverse events (AEs) (20% G3-4) divided in 121 categories were included. In female patients, liver toxicity, headache, pyrexia, nausea/vomiting, hair/skin disorders and dizziness were significantly more common (table). The only toxicity with higher incidence in men was dysphonia (OR 0.42, 95% CI 0.2-0.9, p = 0.02). There were no gender differences in grade 3-4 toxicities. **Conclusions:** We observed significant differences in toxicity AEs by gender in two prospective phase II studies with MKIs in NETs patients. Potential different approach to manage toxicity may be adopted based on gender.

### Toxicity (all grades)**

<table>
<thead>
<tr>
<th>Toxicity (all grades)</th>
<th>Women (%)</th>
<th>Men (%)</th>
<th>Difference (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver toxicity</td>
<td>64.9</td>
<td>41.9</td>
<td>22.3</td>
<td>2.97 (1.54-5.73)</td>
<td>0.001</td>
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<tr>
<td>Headache</td>
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<td>14.9</td>
<td>2.5 (1.16-5.4)</td>
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<td>Pyrexia</td>
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<td>8.1</td>
<td>13.5</td>
<td>3.44 (1.26-9.36)</td>
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<tr>
<td>Nausea/Vomiting</td>
<td>70.3</td>
<td>58.1</td>
<td>12.2</td>
<td>2.08 (1.07-4.05)</td>
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<tr>
<td>Hair disorders</td>
<td>23.8</td>
<td>10.8</td>
<td>12.2</td>
<td>2.72 (1.09-6.75)</td>
<td>0.02</td>
</tr>
<tr>
<td>Skin disorders</td>
<td>56.8</td>
<td>44.6</td>
<td>12.2</td>
<td>1.9 (1.007-3.61)</td>
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<tr>
<td>Dizziness</td>
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<td>10.8</td>
<td>2.68 (1.02-7.02)</td>
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<tr>
<td>Dysphonia</td>
<td>17.6</td>
<td>36.5</td>
<td>18.9</td>
<td>0.42 (0.2-0.9)</td>
<td>0.02</td>
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</tbody>
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### Blood-borne next-generation sequencing analysis of neuroendocrine tumors

**First Author:** Walid Labib Shaib, Winship Cancer Institute, Emory University, Atlanta, GA

**Background:** Neuroendocrine tumors (NET) comprise around 2% of all malignant tumors of the gastrointestinal system. The genomic landscape of NET has not been well studied. The aim of this study was to confirm the feasibility of next generation sequencing (NGS) using ctDNA in NET and characterize common alterations in the genomic profile. **Methods:** Molecular analysis was performed in 114 plasma samples from 114 patients with NET using clinical-grade NGS of ctDNA (QuartetGEM™) across multiple institutions were evaluated. The tests detects single nucleotide variants in 54-73 genes, copy number amplifications, fusions, and indels in selected genes. **Results:** A total of 114 NET patients were evaluated, of which 64 (56.1%) were female. Mean age was 59.7 years with a range between 23-89 years. ctDNA NGS testing was performed on 114 plasma samples; 1 patient had testing performed twice. Genomic alterations were defined in 94% (n = 94/114, 82.5%) samples with a total of 289 alterations identified after excluding variants of uncertain significance (VUS) and somatic mutations. Alterations were identified in at least one sample from 83 patients; TP53 associated genes were most commonly altered (n = 83/289, 28.7%), followed by KRAS (n = 22, 7.6%), P13CA (n = 15, 5.2%), CCNE1 (n = 15, 5.2%), BRAF (n = 13, 4.5%), MYC (n = 12, 4.1%), ERBB2 (n = 11, 3.8%), APC (n = 10, 3.5%), EGFR (n = 10, 3.5%), MET (n = 10, 3.5%), PNET (n = 9, 3.1%), RB1 (n = 9, 3.1%), CDK6 (n = 7, 2.4%), AR (n = 5, 1.7%), ARID1A (n = 5, 1.7%), FGFR1 (n = 5, 1.7%), and PDGFRA (n = 5, 1.7%). Other genomic alterations of low frequency, but clinical relevance included: CDK4 (n = 4, 1.3%), NF1 (n = 4, 1.3%), RAF1 (n = 4, 1.3%), GNAS (n = 3, 1.0%), KIT (n = 3, 1.3%), BRA2A (n = 2, 0.7%), CCND2 (n = 2, 0.7%), CTNNB1 (n = 2, 0.7%), IAK2 (n = 2, 0.7%), NRAS (n = 2, 0.7%), SMAD4 (n = 2, 0.7%), and TERT (n = 2, 0.7%). Alterations in AKT1, ALK, ATM, BRCA1, CCND1, CDKN2A, FGFR2, MTR, RHOM, and STK11 were all reported once (n = 1, 0.3%). **Conclusions:** Evaluation of ctDNA is feasible among individuals with NET. Liquid biopsies are not invasive and can provide personalized options for targeted therapies in NET patients.

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4111 Poster Session (Board #216), Mon, 8:00 AM-11:00 AM

Analysis of patient diaries in the NETTER-1 Study of 177Lu-DOTATATE versus high-dose octreotide in progressive midgut neuroendocrine tumors. First Author: Jonathan R. Stroobos, Moffitt Cancer Center, Tampa, FL

Background: The primary statistical analysis for the NETTER-1 trial showed a clinically and statistically significant PFS benefit with 177Lu-DOTATATE vs. high-dose octreotide. 177Lu-DOTATATE treatment was also correlated with a significant delay in time to deterioration in HRQoL. In addition to HRQoL questionnaires, patients were asked to record presence or absence of a range of symptoms in a daily diary. Methods: A Mixed Model Repeated Measures (MMRM) was used to analyze the change, compared to baseline, of the occurrence of abdominal pain, diarrhea and cutaneous flushing as these symptoms were regarded as the most relevant to judge the overall disease status. For each visit (week = 0, 4, 8, etc.) the number of days with symptoms during the previous period was calculated. At baseline, the number of days with symptoms was counted over the previous 6 weeks, whereas the time frame between visits lasted 4 weeks. Results: The estimated number of days with symptoms declined significantly more in the 177Lu-dotate arm compared to the octetocide arm. The difference in change and the confidence intervals for the symptoms abdominal pain, diarrhea and flushing of skin are, respectively: -3.11 [-4.88; -1.34], -3.11 [-5.04; -1.19] and -0.08 [-0.26; 0.10]. Conclusions: Analysis of symptom diaries confirms that 177Lu-Dotate can palliate clinically relevant symptoms when compared to high-dose octreotide.

4112 Poster Session (Board #217), Mon, 8:00 AM-11:00 AM

Efficacy and safety of pembrolizumab in patients with advanced adrenocortical carcinoma. First Author: Nitya Prabhakar Raj, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Adrenocortical carcinomas (ACC) are rare and aggressive. Treatment options are limited and marked by poor efficacy and substantial toxicity. In this phase II single-center study, the efficacy and safety of pembrolizumab was assessed in patients (pts) with advanced ACC. Methods: Enrolled pts were aged ≥18 y with advanced ACC, ECOG ≤ 1, available tumor samples for biomarker analysis. Pts received pembrolizumab 200 mg IV Q3W for 2 y or until disease progression, intolerability, patient/physician decision to stop treatment. Imaging was performed every 9 wks. Tumor PD-L1 positivity (modified proportion score ≥ 1% or presence of stromal interface) was evaluated. Primary endpoint was ORR (by RECIST v1.1). Secondary endpoints included DOR, PFS, OS, safety. Somatic and germline next-generation sequencing was performed. Results: 39 pts were treated. Median age 62 (range, 19-87), 28% ECOG 0, 72% received ≥ 1 therapy. In available samples to date, 7/31 (23%) PD-L1+. At time of analysis, median follow-up among survivors was 17.8 mo (range, 5.4-34.7). ORR was 23.1% (95% CI, 11.1-39.3); 0 CR, 9PR. Seven pts (17.9%) had SD as best response. Among the 9 PRs, median time to PR was 4 mo (range, 1.7-10.5) and median DOR was not reached (95% CI, 4.1-not reached). Three pts achieving PR completed 2 y of treatment with ongoing response noted. Tumor PD-L1 status is currently available in 6 pts with PR, 2/6 (33%) PD-L1+. Median PFS was 2.1 mo (95% CI, 2.0-10.7). Median OS was 24.9 mo (95% CI, 4.2-60.0). Two pts (22%) had OS>2y. Median PFS was 4.4 mo (95% CI, 36-69%). In the 34 tested tumors, germline testing identified 2 PR pts with Lynch syndrome; the remaining 7 PRs were MSS. Median tumor mutation burden for all PRs was 4.1 mutations/megabase (range, 0-31.5). There was no significant relationship between somatic alterations and response to treatment. Grade 3/4 AEs included 2/3 (6.7%) pneumonitis. All evaluable patients except one had stable disease at 3 mo. Response Discussion: Pembrolizumab demonstrated antitumor activity and was well tolerated in advanced ACC. Durable responses were noted. Complete evaluation of tumor PD-L1 and microsatellite status will be reported at the meeting. Clinical trial information: NCT02673333.

4113 Poster Session (Board #218), Mon, 8:00 AM-11:00 AM

Surgery and peptide receptor radionuclide therapy: An effective multimodal approach for metastatic neuroendocrine tumors. First Author: Andrea Frilling, Imperial College London, London, United Kingdom

Background: Neuroendocrine neoplasia (NE) of the pancreas (PanNEN) or small bowel (SBNEN) frequently present with metastases at initial diagnosis, undermining the efficacy of surgical treatment. Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues,90Y-DOTATOC and 177Lu-DOTATATE, has been shown to achieve prolonged progression-free survival (PFS) and overall survival (OS) in a substantial number of non-surgical patients with advanced NE. Our aim was to prospectively determine the efficacy of a combination of radical loco-regional surgery and 177Lu PRRT in patients with metastasised NE. Methods: A set of inclusion criteria was defined (e.g. PanNEN or SBNEN, G1/G2 NEN, initial tumour diagnosis, treatment naive patient, stage IV NEN, positivity on 68Ga-DOTA-TATE or DOTATOC PET/CT, eligibility for surgery and PRRT). Patients underwent PRRT within 3 months following surgery. Follow-up included biochemistry and imaging. Outcome measures included 1-, 3-, and 5-year OS and PFS from initial diagnosis. Results: Forty-one patients met eligibility criteria and were included. There were 26 males (63.4%) and median age at surgery was 58.8 years (range 32.1-78.3). All patients with SBNEN underwent right hemiectomy, terminal ileal resection and mesenteric lymphadenectomy. In PanNEN patients either Whipple procedure or distal pancreatectomy and peripancreatic lymphadenectomy were performed. The median number of PRRT cycles was 4 (range 2-6). Post-treatment mortality was 0%. Surgical morbidity was 12% (all grade 1 according Clavien-Dindo) and transient grade 1 toxicity occurred post PRRT in 40%. There was no grade 3 toxicity. Median follow-up was 5.48 years (range 0.53 – 11.98). Median PFS and OS were 3.33 years and 9.07 years, respectively. Progression-free survival (with 95% CI) was at 1-, 3-, and 5-years 80% (68.7-92.6), 60.9% (45.9-75.9) and 43.3% (27.4-59.3), respectively. Overall survival (with 95% CI) at 1-, 3-, and 5-years is 80% (68.7-92.6), 60.9% (45.9-75.9) and 43.3% (27.4-59.3), respectively. Conclusions: Radical loco-regional surgery for primary tumours combined with PRRT provides a novel, highly efficacious approach in metastatised NEN.

4114 Poster Session (Board #219), Mon, 8:00 AM-11:00 AM

Clinical efficacy and toxicity data on phase I study of fosbretabulin in combination with everolimus in neuroendocrine tumors. First Author: Arman Chaun, University of Kentucky, Division of Medical Oncology, Lexington, KY

Background: Fosbretabulin, a synthetic, water-soluble, phosphorylated prodrug of the natural product combretastatin A4 (CA4P), initially isolated from the bark of the South African bush willow, Combretum caffrum, is the lead compound in a class of agents termed vascular disrupting agents (VDAs). Everolimus, an mTOR inhibitor, is FDA approved for the management of well-differentiated NETs. A Phase I trial combining fosbretabulin and everolimus to determine the recommended Phase II trial dose (RP2D), safety data and early clinical efficacy in metastatic GEPNET patients was conducted. Methods: An investigator-initiated, single center, open-label, phase I study involving GEPNETs incorporated partial order continual reassessment method (PO-CRM) to define the dose escalation. The primary objective was to establish the maximum tolerated dose (MTD) of the combination of everolimus and fosbretabulin in NETs that have progressed after at least one prior regimen for metastatic disease. Secondary objective included identifying the safety profile of the combination using NCI CTCAE4 reporting criteria. Patients received daily oral everolimus (2.5 mg, 5 mg, 7.5 mg, and 10 mg). Fosbretabulin was administered IV 60 mg/m2 either q3 weekly or q weekly based on PO-CRM. Patients were treated for 12 weeks with all combinations. RECIST 1.1 was used to evaluate radiological responses at 3 months. Results: Of the 17 patients enrolled, 16 completed the 12-week trial. One patient was not evaluable due to noncompliance. A DLTs were observed at day 21. The highest dose of 10 mg daily oral everolimus in combination with weekly 60mg/m2 IV fosbretabulin is the RP2D. No grade 4 or 5 toxicities were noted. Grade 3 toxicities were seen in 5 patients; abdominal pain and hyperglycemia (not related to study drug), fatigue (possibly related), decreased lymphocyte count and anemia (related). 2 patients had diarrhea (> 3 days duration) and 1 patient had transient pain due to pneumonitis. All evaluable patients except one had stable disease at 3 months. One patient showed SD but not target lesion demonstrated PD. One patient had > 30% decrease in tumor size but overall sum of lesions showed SD. A detailed table with all grade toxicities and waterfall plot of RR will be presented at the meeting. Conclusions: Ten mg PO daily everolimus plus 60 mg/m2 fosbretabulin IV weekly is the RP2D. Early clinical data suggests clinical activity and stable disease in all but one patient at 3 months. Clinical trial information: NCT03014292.
**Antitumor efficacy of concurrent everolimus with hepatic transarterial bland embolization (evero-embo) in patients with metastatic well differentiated neuroendocrine tumor (NET).** First Author: Lowell Brian Anthony, University of Kentucky, Lexington, KY

**Background:** Hepatic transarterial embolization (HAE) is an effective loco-regional therapy for neuroendocrine tumor (NET) management. Systemic targeted therapies, such as everolimus and sunitinib, are typically held 2-4 weeks prior to and after procedures. The safety of concurrent use of everolimus with HAE has been previously reported. Association of HAE and everolimus for NET has been evaluated. The current study evaluated the efficacy of concurrent everolimus and evero-embo to the historical efficacy of bland HAE. This study aimed to examine the clinical debulking activity of evero-embo and to compare the median hepatic PFS of evero-embo to the historical median hepatic PFS of ~9 months. In this study, the clinical efficacy of evero-embo was examined. Methods: A review of clinical and radiographic data was conducted for all sequential patients who underwent evero-embo between September 2016 and April 2018 at the University of Kentucky Markey Cancer Center. An independent radiologist performed RECIST measurements. Patients were required to have had systemic everolimus for ≥1 month prior to embolization in order to be included in this study and to have undergone bland embolization immediately post procedure. Additional follow up is necessary to compare the median hepatic PFS of evero-embo to the historical drug-eluting bead HAE PFS.

**Results:** A total of 51 HAEs with concurrent systemic everolimus were performed in 34 NET patients. Twenty one of 24 patients were noted to have had a partial response. Rest had stable disease. Hepatic progression was not observed in 22/24 patients. Eight patients had 1 or 2 vomiting episodes across all 51 PFS. Approximately-four patients experienced post procedure (median of 17 months). None of these 21 patients had hepatic progression. Conclusions: Evero-embo results in a partial response rate of 62% and may have significant antitumor activity when compared to bland hepatic artery embolization in NET patients. With a median follow-up of 17 months, there was no hepatic progression noted in any patient. Additional follow up is necessary to compare the median hepatic PFS of evero-embo to the historical drug-eluting bead HAE PFS.

**Efficacy and safety of lanreotide 120 mg in the treatment of clinical symptoms associated with inoperable malignant intestinal obstruction (IMO).** First Author: Lionel Duck, Clinique St-Pierre, Ottignies, Belgium

**Background:** Intestinal obstruction is a severe complication in patients (pts) with digestive or gynecological cancers. For inoperable pts, there is a need to relieve symptoms and limit nasogastric tube (NGT) use. Previous studies have suggested the efficacy of somatostatin analogues in relieving obstruction-related symptoms such as nausea, vomiting and pain. Methods: This was a single arm, prospective study (NCT02275338). Pts with IMO received one deep subcutaneous injection of LAN 120mg at day 0 (D0). Evaluations were performed on D7, 14 and 28. The primary endpoint was the proportion of responders before or at D7. Response was defined as ≥2 vomiting episodes/day (for pts without NGT at baseline) or no vomiting recurrence (after NGT removal), during at least 3 consecutive days at any time point between the D0 and D7. In line with the literature, a proportion of 30% responders was used as reference for defining statistical significance. Responders at D28 were offered a second LAN 120 mg injection. Results: 52 pts with advanced GI or ovarian malignancies were included in 15 Belgian sites. 17 pts without NGT and 35 with NGT. 21 pts received a second dose of LAN. Median age was 68.0 (59.5; 76.0) years. On D7 the proportion of responders in the ITT population was 24/52 (46.2%), significantly greater than the reference proportion of 30% (one-sided binomial test: p = 0.006). Pts without NGT responded better (15/ 17, 88.2%) than pts with NGT (9/35, 25.7%). Pts without ascites responded better (57.7% vs 34.6%). Pts with NGT showed a steady trend for clinical improvement leading to sustainable responses of 45.7% on D14. Median time to response was 9 days for the overall population; 3 days for patients without NGT vs 14 days for patients with NGT (p < 0.001). The most frequently reported AEs were GI disorders (in 34 pts). The most common events were diarrhoea and abdominal pain. Conclusions: Our study is the first using long acting LAN 120mg in patients with IMO and suggests an effect in controlling clinical symptoms in pts with and without NGT at baseline. LAN 120 mg safety profile was similar to that reported for the other indications. Clinical trial information: NCT02275338.
**4119** Poster Session (Board #224), Mon, 8:00 AM-11:00 AM
Molecular profile of ampulla of vater carcinoma (AVC): A rare tumor type with meaningful molecular alterations. First Author: João Pinto, Oncology Division, Hospital Beatriz Angeles, Loures, Portugal

**Background:** AVC is a rare type of cancer with dismal prognosis and limited therapeutic options due to the lack of specific clinical trials. Two histologic subtypes predominate, namely pancreatobiliary and intestinal. A variety of molecular alterations have been described in AVC, but their clinical and therapeutic implications have not been studied in detail. **Methods:** Retrospective cohort study of patients (pts) diagnosed with AVC treated in our institution from 2010 to 2018. We routinely performed Next Generation Sequencing in all AVC tumors. Our main objectives were to describe the molecular profile of AVC and correlate with clinical outcomes. **Results:** Out of 26 pts with AVC, 13 pts were male (50%), median age 65 (range 43-83), 7 pts (27%) had stage IV disease at diagnosis. Histologic type was pancreatobiliary in 18 pts (69%), intestinal in 7 pts (27%) and mixed in one case (4%). We identified KRAS mutations (mut) in 10 pts (7 pancreatobiliary, 2 intestinal, 1 mixed), TP53 mut in 6 pts (4/1/1), PIK3CA mut in 3 pts (3/0/0), ERBB2 mut in 3 pts (2/1/0), CTNNB1 mut in 3 pts (2/1/0). In pancreatobiliary we found single cases with RNF43, BRCA1 and CHEK2 mut; while in intestinal we found single cases with NRAS and BRAF mut. One tumor of intestinal subtype had microsatellite instability (MSI). Three pts were included in phase I clinical trials, 2 of them with trials based on tumor profile (ERBB2 mut with pan-HER inhibitor and MSI with immunotherapy). Median overall survival (OS) was 21 months for pts with stage I, II and III disease (95% CI 12.37-not reached) and 13.2 months for stage IV disease at diagnosis (95% CI 5.73-not reached). In cox models, median OS was not dependent on KRAS or TP53 mutation status, or histological subtypes. **Conclusions:** AVC is a rare type of cancer with two differentiated histological subtypes harboring unique molecular alterations that can be matched to investigation trials. A broader knowledge of the biology of these tumors is needed to improve patient outcomes.

**4121** Poster Session (Board #226), Mon, 8:00 AM-11:00 AM
H3B-6527 clinical biomarker assay development and characterization of HCC tumor samples. First Author: Pavan Kumar, H3 Biomedicine, Inc., Cambridge, MA

**Background:** FGF4R/FGF19 signaling axis is a novel therapeutic target in HCC. Multiple covalent FGF4R inhibitors, including H3B-6527, are under clinical development. Preclinical efficacy studies in mice (including PDX) have shown that FGF19 expression (FGF19*) is a predictive biomarker for FGF4R inhibitor response. The mechanisms driving FGF19 expression in HCC is largely unknown however, in some cases, focal amplification of ch11q13.3 containing FGF19 gene is thought to drive the FGF19 expression. Consistent with the preclinical observations, clinical studies have also shown that FGF19* is a predictive biomarker for FGF4R inhibitor response. However, these trials have also reported a large number of FGF19* patients failing to respond to FGF4R inhibitors necessitating refinement of patient selection strategies. In an attempt to obtain deeper insights into the role of FGF19* as a predictive biomarker and potentially uncover additional biomarkers that will enable improvement in patient selection strategies, we have characterized a set of 258 HCC patient samples **Methods:** Samples were acquired from biobanks and utilized to qualify clinical assays including FGF19 copy number (FISH), mRNA expression (qRT-PCR), FGF19 protein (IHC), and a focused NGS panel for assessing both mutations and copy number. A multiplexed protein and mRNA platform enabled assessment of p-ERK and Ki67 (protein) and Cyp7A1 (mRNA) amongst other exploratory PD biomarkers from two PFP slides. **Results:** FGF19 positivity rates for IHC and qRT-PCR were 18% (41/225) and 42% (87/209), respectively. The overall correlation was 60%, with 63% (22/35) IHC positive cases also being positive by qRT-PCR. For IHC+qRT-PCR (+) cases, RNA quality may correlate with clinical outcomes. **Conclusions:** This study represents one of the largest ever conducted to assess the expression of FGF19* in HCC samples. The datasets will be distributed to interested investigators for further research.
Neoadjuvant FOLFIRINOX versus adjuvant gemcitabine in pancreatic cancer.

First Author: Adam R Wolfe, Ohio State, Columbus, OH

Background: In the metastatic or adjuvant setting for pancreatic cancer, the combination chemotherapy of fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) has longer overall survival (OS) compared to gemcitabine therapy. We conducted an institutional study to compare the efficacy of neoadjuvant modified FOLFIRINOX (neo-mFOLFIRINOX) to adjuvant gemcitabine (adj-gem) for pancreatic cancer patients who completed resection. Methods: The study retrospectively enrolled patients from 2006 to 2013 from Ohio State University. While patients were resected, neo-mFOLFIRINOX or gemcitabine were considered to be resectable upfront. Patients who received neo-mFOLFIRINOX were either staged as borderline resectable (BR) or unresectable (UR) by the institutional tumor board group. 111 patients received adj-gem (average cycles, 5.5) and 52 patients received neo-mFOLFIRINOX (average cycles, 3.5). The survival rates were determined by the Kaplan-Meier method and analyzed using Cox regression and log-rank test. Results: At a median follow up of 21.3 months, the median OS was 35.4 months in the neo-mFOLFIRINOX group and 21.8 months in the adj-gem group (hazard ratio, 0.56, 95% confidence interval (CI), 0.37-0.84 p = 0.005). The OS rate at 3 years was 46% in the neo-mFOLFIRINOX group and 24% in the adjuvant gemcitabine group (p = 0.001). The median disease free survival (DFS) was 18.6 months in the neo-mFOLFIRINOX group and 12.0 months in the adj-gem group (hazard ratio, 0.63, 95% CI, 0.43-0.93 p = 0.022). The DFS rate at 3 years was 17% in the neo-mFOLFIRINOX group and 11% in the adj-gem group (p = 0.02). On surgical pathological specimen review, the neo-mFOLFIRINOX group had statistically (p < 0.05) lower tumor grade, lower rates of perineural invasion and lymphovascular invasion, lower pathological T stage, lower pathological N stage, and lower number of nodes positive compared to the adj-gem group. Frequencies of obtaining R0 resections were higher in the neo-mFOLFIRINOX group versus the adjacent gemcitabine group (40.4, p = 0.2). The average age and performance status were similar between the two groups. Conclusions: At our institution, BR and UR pancreatic cancer patients who received neo-mFOLFIRINOX and completed resection had longer OS, DFS, and more favorable pathological indicators compared to those patients treated with upfront surgery and adjuvant gemcitabine. Randomized clinical trials comparing neoadjuvant versus adjuvant FOLFIRINOX are needed to validate these findings.

PanC0: An open-label, single-arm pilot study of phosphorus-32 (P-32; Oncosil) microparticles in patients with unresectable locally advanced adenocarcinoma (LAPC) in combination with FOLFIRINOX or gemcitabine + nab-paclitaxel (GPN) chemotherapies. First Author: Paul J. Ross, Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom

Background: LAPC is associated with a poor prognosis. Current standard treatment is limited to chemotherapy or chemo-radiotherapy. P-32 Microparticles is a brachytherapy device that implants a predetermined dose of P-32 into pancreatic tumours via endoscopic ultrasound (EUS) guidance. This report the initial results of a pilot study in combination with chemotherapy. Methods: Eligible patients were permitted to receive either GNP or FOL-FIRINOX. P-32 was implanted at week 4 or 5. The dose of P-32 was calculated from tumour volume to deliver an absorbed dose of 100 Gy. Diffusion-weighted MRI and EUS were used to calculate the tumour volume. P-32 was injected via a 22G needle inserted into the tumour mass. Response was assessed according to RECIST 1.1 with CT scans every 12 weeks. AEs were reported as per CTCAE v4.0 criteria.

Results: 42 patients were enrolled (Intent-to-Treat population (ITT)) of which 42 were implanted with the device (Per Protocol population (PP)). 10 received FOLFIRINOX and 40 GNP. Median age was 65, 28 were male and all had a PS 0/1. 1070 adverse events (ITT) were reported; 153 (80% of patients) were ≥ Grade 3. The most common AEs of ≥ Grade 3 were haematological (39, 46%) and gastrointestinal disorders (30, 34%). No serious device- or radiation-related toxicities have been reported. PP Local Disease Control Rate at Week 16 was 96%; 95% CI: 77-97% and at Week 24 was 71%; 95% CI: 55-84%. Overall Response Rate (ORR) was 31%; 95% CI: 18-47%. Median change in tumour volume from Baseline to Week 16 and to Week 24 was -38% (range +89% to -90%) and -27.5% (range +139% to -79%). Ten (24%) patients underwent surgical resection following repeat staging. Eight patients had R0 margin. Conclusions: The use of EUS-guided implantation of P-32 is feasible, with an acceptable safety profile in combination with first-line chemotherapy for LAPC patients. Encouraging OR and DCR are observed. Further follow-up to inform results of local progression free survival and progression free survival is warranted. Acknowledgements: The study was supported by Specialised Therapeutics Australia Pty Ltd. Clinical trial information: NCT03003078.

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4127 Poster Session (Board #232), Mon, 8:00 AM-11:00 AM
Final results of JASPAC05: Phase II trial of neoadjuvant S-1 and concurrent radiotherapy followed by surgery in borderline resectable pancreatic cancer. First Author: Shinichiro Saka, Department of Hepato-Biliary-Pancreatic Surgery, National Cancer Center Hospital East, Kashiwa, Japan

Background: Borderline resectable pancreatic cancer (BRPC) is frequently associated with positive surgical margins and a poor prognosis when treated with upfront surgery. This study was designed to assess whether neoadjuvant chemoradiotherapy (CRT) with S-1 increases the R0 resection rate. Methods: This was a multicenter, single-arm, phase II study. Patients with BRPC received S-1 (40 mg/m² bid) and concurrent radiotherapy (50.4 Gy in 28 fractions) before surgery if they fulfilled any of the following: (1) bilateral impingement of the superior mesenteric vein or portal vein; and (2) tumor contact ≥ 180° with the superior mesenteric artery, common hepatic artery, or celiac axis. The primary endpoint was the R0 resection rate in BRPC confirmed by central review. Secondary endpoints were overall survival (OS), progression-free survival (PFS), response rate (RECISTv1.1), pathological response rate, surgical morbidity (Clavien–Dindo classification), and toxicity (CTCAEv4.0). At least 40 patients were required, with one-sided α = 0.05 and β = 0.05, with an expected and threshold value for the primary endpoint of 30% and 10%. Results: Fifty-two patients were eligible, of whom 41 had BRPC by central review. Surgery was completed in 50 (96%) patients and was well tolerated. The rate of grade 3/4 toxicity with CRT was 43%. The R0 resection rate was 52% (95% CI, 37.6%–66.0%) in 52 eligible patients and 63% (95% CI, 46.9%–77.9%) in 41 patients with BRPC. The radiological response rate was 5.8%, while a decrease of ≥ 50% of the diameter was observed in 32% of patients. The median PFS was 2 months in arm A and 2 months in arm B. The median OS was 3 months in arm A and 2 months in arm B. The median OS was 3 months in arm A and 2 months in arm B. A phase III/IV adverse events were observed in 75% of operated patients. Among the 52 eligible patients, the 2-year OS rate, median OS, and median PFS were 51%, 25.8 mo, and 6.7 mo. Of the 41 patients with BRPC, the 2-year OS rate, median OS, and median PFS were 58%, 30.8 mo, and 10.4 mo. Conclusion: S-1 and concurrent radiotherapy might be feasible and effective at increasing the R0 resection rate with encouraging survival rates in BRPC. A phase III/III trial evaluating this treatment is ongoing. Clinical trial information: NCT02459652.

4128 Poster Session (Board #233), Mon, 8:00 AM-11:00 AM
NEONAX trial: Neoadjuvant plus adjuvant nab-paclitaxel plus gemcitabine for resectable pancreatic cancer, a phase II study of the AO1 pancreatic cancer group (AOC-PACG) in national clinical analysis. First Author: Waldemar Uhl, Ruhr-University Bochum, St. Josep Hospital, Bochum, Germany

Background: Survival in pancreatic cancer (PDAC) is still poor even after curatively intended resection. Perioperative treatment approaches improve outcome in various tumor entities. Data on perioperative treatment in resectable PDAC is limited and debate whether neoadjuvant chemotherapy might improve subsequent surgery by adding perioperative morbidity or mortality. Methods: NEONAX is a randomized phase II study (planned 166 patients) of perioperative gemcitabine/nab-paclitaxel (Arm A: 2 pre- and 4 post-operative cycles, Arm B: 6 cycles adjuvant) for patients with primarily resectable PDAC. Primary objective is DFS at 18 months after randomization. Secondary objectives are 3-year OS-rate and DFS-rate, progression during neoadjuvant therapy, R0/R1 resection rate and QoL. Results: NEONAX was initiated in March 2015 in 26 centers for PDAC surgery in Germany. The data report the safety interim analysis (IA) of the first 48 patients. 25 patients were randomized to Arm A and 23 to Arm B. Patients’ median age was 65.3 years (56.3% males, 43.8% females, 85.4% ECOG 0). Out of 25 patients in Arm A 20 patients (80%) underwent surgery, compared to 21 of 23 patients (91.3%) in Arm B with upfront surgery. Reasons for no resection were intraoperatively determined small liver metastases (2 cases, Arm A), withdrawal of informed consent (2 cases in each arm) and 1 patient with uncontrolled cholestasis (arm A). Postoperative complications occurred in 45% of arm A and 42.8% of arm B. (pancreatic fistula: 15% in arm A and 9.5% in arm B, infections: 10% in arm A and 9.5% in arm B) All resected patients were alive 60 days after surgery. At least 1 adverse event (AE) occurred in 91% (CSCAE = grade ≥ 3, 40% of the patients) and 39.1% of adjuvant treatment arm. Most common AEs were neutropenia (16.7%), fatigue (10.4%) and infections (10.4%). Conclusions: There was an increase in NCI-CSCAE ≥ grade 3 events in the perioperative arm, but this was manageable and did not result in increased peri- or postoperative morbidity. 8% of patients in the perioperative arm did not get resected due metastases detectable during surgery, but not on preoperative imaging immediately prior to surgery. Therefore, it cannot be determined whether these metastases were preexistent or developed during neoadjuvant treatment. In conclusion, the first interim analysis of the NEONAX trial shows that this protocol can be safely applied to patients with resectable PDAC in a perioperative setting. Clinical trial information: NCT02047513.

4129 Poster Session (Board #234), Mon, 8:00 AM-11:00 AM
Metformin use and pancreatic cancer survival in U.S. veterans with diabetes mellitus: were there racial differences? First Author: Adetunji T. Toriola, Washington University School of Medicine in St. Louis, St. Louis, MO

Background: Experimental and observational studies suggest that metformin holds promise in improving survival among pancreatic cancer patients. However, findings from prior observational studies have been questioned because most did not control for immortal time bias, which can overestimate the survival benefit of a drug. In addition, previous studies did not present data on African American patients. Thus, it is unknown if any survival advantage from metformin extends to African Americans. To address these limitations, we analyzed data from the U.S. Veterans Health Administration (VHA). Methods: A population-based retrospective cohort study of 3,811 (N = 773 are African Americans) pancreatic cancer patients with pre-existing diabetes mellitus diagnosed within the VHA between October 1, 1998 and December 30, 2010, and followed until December 2014. We calculated hazard ratios (HR) and 95% confidence intervals (CI) using both the time-varying Cox proportional hazards regression model, which controls for immortal time bias, and conventional Cox model. Analyses were adjusted for confounders. We also stratified analyses by race. Further, we performed analyses among patients who were metformin naïve (N = 1158) at the time of pancreatic cancer diagnosis (most representative of patients enrolled in clinical trials). Results: Median survival was 4.5 months among metformin users versus 3.7 months among non-users. Metformin use was not associated with pancreatic cancer survival in analysis using the time-varying Cox model. Analyses using conventional Cox model, metformin use was associated with an artificial survival benefit: HR = 0.89 (95% CI 0.83-0.98, P-value = 0.01). Among patients who were metformin naïve at the time of pancreatic cancer diagnosis, metformin use was associated with improved survival in analyses using the time-varying Cox model: HR = 0.77 (95% CI 0.61-0.98, P-value = 0.03). The HRs were 0.78 (95% CI 0.61-0.99, P-value = 0.04) among non-Hispanic Whites and 1.20 (95% CI 0.75-1.93, P-value = 0.45) among African American patients. Conclusions: We observed no associations between metformin use and pancreatic cancer survival. Nevertheless, among metformin naïve (non-Hispanic White patients) among patients who were metformin naïve at the time of pancreatic cancer diagnosis, which requires conformation in other studies.

4130 Poster Session (Board #235), Mon, 8:00 AM-11:00 AM
Relacorilant (RELA) with nab-paclitaxel (NP): Safety and activity in patients with pancreatic ductal adenocarcinoma (PDAC) and ovari an cancer (OvCa). First Author: Pamela N. Munster, University of California San Francisco, San Francisco, CA

Background: Glucocorticoid receptor (GR) pathway activation has been linked with chemotherapy resistance (CTR). RELA (formerly CORT125134, Corcept Therapeutics), a potent selective GR modulator, in combination with paclitaxel reduced CTR and enhanced activity toward tumor growth in preclinical models of multiple tumor types. Methods: Subjects (pts) with advanced cancer were treated with paclitaxel (NP) and RELA. With the probability of survival after 3 cycles of cytotoxic therapy, ECOG status 0–1, and adequate marrow function were planned. Clinical trial information: NCT02762981. Relacorilant (RELA) with nab-paclitaxel (NP): Safety and activity in patients with pancreatic ductal adenocarcinoma (PDAC) and ovarian cancer (OvCa). First Author: Pamela N. Munster, University of California San Francisco, San Francisco, CA

Background: Glucocorticoid receptor (GR) pathway activation has been linked with chemotherapy resistance (CTR). RELA (formerly CORT125134, Corcept Therapeutics), a potent selective GR modulator, in combination with paclitaxel reduced CTR and enhanced activity toward tumor growth in preclinical models of multiple tumor types. Methods: Subjects (pts) with advanced cancer were treated with paclitaxel (NP) and RELA. With the probability of survival after 3 cycles of cytotoxic therapy, ECOG status 0–1, and adequate marrow function were planned. Clinical trial information: NCT02762981.

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Elevated pretreatment serum IL-8 and PD-L1 and overall survival in a phase III randomized advanced pancreatic cancer clinical trial. First Author: Ashok Macdonald, Penn State College of Medicine, Hershey, PA

Background: We previously reported the prognostic and predictive utility of pretreatment serum PD-L1 in the CTCG MA.31 serum bank (SABCS 2018, abstr PD3-10). IL-8 (CXCL8) is a pro-inflammatory cytokine that binds to CXCR1 and CXCR2 and promotes tumor immune escape and progression. High serum IL-8 levels are associated with poor prognosis in many cancers, and have recently been reported to predict for reduced OS to nivolumab in lung cancer and melanoma (ASCO 2018, abstr #3025). In this study, we retrospectively evaluated combined pretreatment serum IL-8 and PD-L1 on overall survival (OS) from a phase III randomized pancreatic cancer trial of first-line therapy (octreotide + 5-FU vs. 5-FU) that had reported no significant OS difference between treatment arms. Methods: This study had 147 patients with serum available for this retrospective biomarker analysis from an advanced pancreatic cancer phase III clinical trial. The ELLA immunoassay platform (ProteinSimple, San Jose, CA) was utilized to quantitate serum levels of IL-8 and PD-L1. Kaplan-Meier life table analysis was used to correlate serum biomarkers with overall survival (OS). Results: In univariate analysis, pretreatment serum IL-8 was a significant continuous variable (HR = 1.004; p = 0.012) and trended significant at the median cutpoint (HR = 1.379; p = 0.098) for OS, however serum PD-L1 was not significant at any cutpoint. When serum PD-L1 and IL-8 levels were analyzed as combined biomarkers (median cutpoints), the serum IL-8 high/ PD-L1 high cohort had significantly shorter OS compared to the IL-8 low / PD-L1 low cohort (HR = 1.816; p = 0.017). Conclusions: In this phase III randomized clinical trial in advanced pancreatic cancer, pretreatment serum IL-8 was a significant biomarker for OS, but serum PD-L1 was not. Higher combined pretreatment serum levels of PD-L1 and IL-8 (both biomarkers high) were more prognostic for reduced OS in this phase III pancreatic cancer trial. Further study of circulating IL-8 and PD-L1 is warranted in pancreatic cancer for evaluation of targeted and investigational therapies, including the immune checkpoint inhibitors and anti-IL8 therapy.

Association of BRCA-mutant pancreatic cancer with high tumor mutational burden (TMB) and higher PD-L1 expression. First Author: Andrea A. Scott, Department of Internal Medicine V (Hematology and Oncology), Innsbruck, Austria

Background: In the U. S. 56, 000 Americans are expected to be diagnosed with pancreatic cancer in 2019. Prognosis in pancreatic cancer is poor. Therefore, new treatment strategies are urgently needed to improve survival. BRCA1 and BRCA2 mutations have been described to be the most common genetic mutations involved in familial pancreatic cancer. The optimal treatment regimen to use in BRCA-mutant pancreatic cancer has still to be established. Moreover, no data are available on association of BRCA mutation with immune-associated markers such as tumor mutational burden (TMB), microsatellite instability (MSI) or PD-L1 expression. Methods: Tumor samples of 2824 patients with pancreatic ductal adenocarcinoma were analyzed for BRCA mutation by NGS and for other genes (MiSeq on 47 genes, NextSeq on 592 genes). From all 461 patients, the OS was not different between 1L non-platinum vs. 1L platinum groups (19 M vs 19.3 M), regardless of their HRD status. (Table) The OS was superior for gHRD vs. non-gHRD (28.7 M vs 18.2 M), regardless of 1L treatment choice. However, similar significant OS superiority was neither observed in sHRD vs. non-sHRD, nor in VUS sHRD vs. non-VUS sHRD. In a subgroup analysis of 1L platinum treated patients, the OS was superior in gHRD vs. non-gHRD (HR = 17.9; p = 0.004) but there was no OS difference between sHRD and non-sHRD. Conclusions: In advanced PDAC patients, only gHRD predicted better overall survival for first-line platinum chemotherapy. These findings emphasize the importance of germline mutation testing of HRD in pancreatic cancer. Biomarker validation and functional definition of HRD such as loss of heterozygosity analysis is underway.
Clinical and immune responses using anti-C3D-x anti-EGFR bispecific antibody armed T cells (BATs) for locally advanced or metastatic pancreatic cancer. First Author: Lawrence G. Lum, University of Virginia, Charlottesville, VA

Background: Conventional chemotherapy (chemo) for locally advanced pancreatic cancer (LAPC) and metastatic pancreatic cancer (MPC) has dismal responses and poor survival rates. Arming activated T cells (ATC) with anti-C3D-x anti-EGFR bispecific antibody (BATs) makes every ATC into an EGFR-specific cytotoxic T cell that secretes cytokines, proliferates, and kills tumor.

Methods: We report on 5 phase I (P1) and 15 phase II (P2) patients. In our phase I study, BATs were used to treat LAPC. In a phase I trial (NCT0140874) at Karmanos Cancer Institute (NCT0140874) in a dose escalation involving 3 weekly infusions of 1, 2, and 4 x 10^10 BATs/infusion, followed by a booster infusion at 3 months (mos) for a total of up to 8 x 10^10 BATs. No dose limiting toxicities were observed in the outpatient infusions. Fifteen patients treated on a phase II (NCT02620865) at KCI and (NCT03269526) at University of Virginia received biweekly infusions of 10^10 BATs/infusion over 4 weeks for a total of 8 x 10^10 EGFR BATs. Results: Four patients had stable disease (SD) for 6.1, 6.5, 5.3, and 36 mos. Two patients had complete responses (CR) when chemo was restarted after BATs. The median overall survival (OS) for 17 evaluable patients (3 of 4 infusions in the P1 and all infusions in the P2) was 31 mos, and the median OS for all 20 patients (3 in the P2 who did not complete 8 infusions) is 14.5 mos (95% CI, 7.5-45.2 mos). Patient IT20104 had an apparent “pseudoprogression” after 3 BATs infusions, but achieved a CR after restarting capcitabine and is alive off therapy at 54 mos (24 mos after stopping capcitabine). In the P1 patients, specific cytotoxicity to MiaPaCa-2 by peripheral blood mononuclear cells (PBMC) increased from 21% to 31% 2 weeks after the 3rd infusion, and IFN-γ EliSpots increased from < 20 to 1000 IFN-γ EliSpots/10^5 PBMC (p < 0.03). Patient IT2121 (SD for 36 mos) increased IFN-γ EliSpots from 2900 to 23,000 IFN-γ EliSpots/10^5 PBMC after 8 infusions. Innate cytotoxic responses in the P1 patients significantly increased after infusions (p < 0.04). Levels of IP-10 increased significantly (p < 0.04), and levels of IL-8 decreased but not significantly (p < 0.07). Conclusions: Infusions of BATs are safe and induce endogenous adaptive anti-tumor responses. Targeting PDAC-Tregs in P2 patients may show improved OS, as there is emerging evidence that BATs infusions can induce anti-tumor activity and immune-sensitize tumors to subsequent chemo. Clinical trial information: NCT014084, NCT03269526, NCT02620865.

Improved overall survival (OS) for advanced pancreatic cancer (PDAC) patients (pts) enrolled in the Kidney Tumor (KYT) program whose tumors harbored highly actionable molecular alterations and who received molecularly-matched therapies (tx). First Author: Michael J. Pishvaian, Georgetown University, Washington, DC

Background: Initial results from the KYT program demonstrated that 27% of PDACs harbor highly actionable molecular alterations (herein labelled “actionable biomarkers”), defined as biomarkers that predict for a high response rate to appropriately targeted tx, in any cancer type. Within this cohort, the median progression-free survival on molecularly-matched tx was 2 months longer than unmatched tx. Here, we present OS data emphasizing the 125 pts with “actionable biomarkers” who did or did not receive molecularly-matched tx. Methods: PanCAN and Perthera have coordinated tumor molecular profiling through commercial labs (NGS/HC panels) for PDAC pts since 2014. Results are reviewed by a molecular tumor board, and tx options are prioritized based on the actionable biomarkers, in the context of the pt’s tx history. Pts are followed longitudinally to track physician tx choices and survival outcomes. Cox regression was used to assess differences in OS (measured from date of diagnosis until death). Results: Of 1053 pts who received a Perthera Report, 25% had “actionable biomarkers”. OS analyses across 454 pts with adequate tx history are shown in the Table below. Notably, pts with “actionable biomarkers” who received a molecularly-matched tx had a significantly increased OS compared to those with “nonactionable biomarkers” who did not receive molecularly-matched tx. Subgroup analyses related to tx history and specific molecular pathways that warrant further investigation will be discussed. Conclusions: When the ~25% of PDAC pts whose tumors harbored “actionable biomarkers” received molecularly-matched tx, they had a better OS. These findings support the need for more pts with PDAC, and just as importantly, to maximize access to molecularly-matched tx for appropriate pts, to achieve the best pt outcomes.

Clinical outcomes after curative therapy of resectable pancreatic ductal adenocarcinoma (PDAC) remain suboptimal. For early control of systemic disease with aggressive perioperative chemotherapy (CTX), we conducted a prospective trial in the National Clinical Trials Network (NCTN) setting. Methods: S1505 was a randomized phase III trial comparing pre-operative CTX (pre-op) to diagnostic biopsy (Dx) to pre-op CTX to either mFOLFIRINOX versus gemcitabine/nab-paclitaxel. Patients with locally resectable PDAC were randomized to 12 weeks post-op) CTX with either mFOLFIRINOX (5-fluorouracil, irinotecan, oxaliplatin – without bolus 5-FU and leucovorin; Arm 1), or gemcitabine/nab-paclitaxel (Arm 2). Eligibility required adult patients with ECOG PS 0 or 1, confirmed tissue diagnosis of PDA, and resectable disease: no involvement of the celiac, common hepatic, or superior mesenteric arteries (and, if present, variants); < 180° interface between tumor and vessel wall, of the portal or superior mesenteric veins; patent portal vein/splenic vein confluence; no metastases. Primary outcome is 2-year overall survival (OS), using a “pick the winner” design; for 100 eligible patients, accrual up to 150 patients was planned, to account for cases deemed ineligible at central radiology review. Results: From 2015 to 2018, 147 patients were enrolled; accrual up to Arm 1; 73 to Arm 2. At central radiology review, 42/147 (29%) were ineligible; of these, 15 (36%) had venous involvement ≥180°, 22 (52%) had arterial involvement, 28 (67%) had distant disease. One patient had distal cholangiocarcinoma (ineligible); one withdrew consent after randomization. Eligible patients (n = 103) had median age 64 years; males 58%; whites 89%; PS 0 64%. Of 103, 99 (96%) started and 86 (83%) completed preop CTX. There was one death due to sepsis and 61 additional patients experienced grade 3/4 toxicities. To date, 76 of 99 (77%) patients went to surgery and 72 (73%) underwent resection. Conclusions: This is the first-ever NCTN study to eval preop CTX for resectable PDA. Accrual was brisk, establishing feasibility. Ineligible cases after central radiology review highlight quality control and physician education imperatives for neoadjuvant PDA trials. Preop CTX safety and resection rates are encouraging. Follow up for OS is ongoing. Clinical trial information: NCT02562716.

Methylated circulating tumor DNA (Meth-DNA) as an independent prognostic factor in metastatic pancreatic adenocarcinoma (mPAC) patients. First Author: Paul B. Fishman, University of Virginia, Charlottesville, VA

Background: Circulating tumor DNA has emerged as a prognostic biomarker in oncology. Many different genes can be mutated within a tumor, complicating procedures, even with highly sensitive next-generation sequencing (NGS). DNA methylation in promoter of specific genes is an early key epigenetic change during oncogenesis. Specific methylated genes could be a potential relevant cancer biomarker that may substitute for NGS panels. The aim of this study was to assess the prognostic value of Meth-DNA in mPAC.

Methods: Prognostic value of Meth-DNA was assessed in a prospective cohort (PLAPAN) of mPAC (training cohort), correlated with NGS, then in two prospective independent validation cohorts from two randomized phase II trials (PRODIGE 35 and 37). Plasma samples were collected before chemotherapy on EDTA-coated tubes. Meth-DNA was quantified using two specific markers of pancreatic DNA methylation by digital droplet PCR and correlated with prospectively registered patient (pts) characteristics and oncologic outcomes (progression free survival (PFS) and overall survival (OS)). Results: 330 patients (pts) were enrolled. 60% (n = 58) of the 96 pts on the P1 cohort had at least one Meth-DNA marker. The correlation with NGS assessment was R = 0.93 (Pearson; p < 0.001). 59.5% (n = 100/168) and 59% (n = 39/66) of pts had detectable Meth-DNA in the 2 validation cohorts. In the training cohort, Meth-DNA was correlated with poor OS (HR = 1.82; 95% CI 1.07-2.42; p = 0.026). In validation cohorts, Meth-DNA was a prognostic factor of PFS (HR = 1.78; 95% CI 1.07-2.99; p = 0.001) and OS (HR = 0.71 [0.55-0.91]) in PRODIGE 35, as in PRODIGE 37: PFS HR = 1.79 (95% CI 1.07-2.99; p = 0.026) and OS HR = 2.08 (95% CI 1.18-3.68; p = 0.01), respectively. In multivariate analysis adjusted on gender, age, CA19-9 > 40U/mL, treatment arm, number of metastatic sites and presence of albumin < 3.5 g/dL, Meth-DNA was independent prognostic factor of OS in both trials: HR = 1.81 (95% CI 1.10-2.98; p = 0.02) and HR = 3.62 (95% CI 1.32-9.93; p = 0.01). Conclusions: This study demonstrates that Meth-DNA is a strong independent prognostic factor in mPAC. These results argue for patient’s stratification on cDNA status for further randomized trials. Clinical trial information: NCT02827201 and NCT02352337.
BIONADEGE: Genomic profiling of small bowel adenocarcinoma from the NADEGE prospective cohort. First Author: Thomas Aparicio, Department of Gastroenterology, Saint Louis Hospital, Paris, France

Background: Small bowel adenocarcinoma (SBA) is a rare tumour. Large genomic analyses with prognostic assessments are lacking. Methods: BIONADEGE is an ancillary study of the NADEGE cohort that enrolled 347 patients (pts) with SBA from 2009 to 2012. Next generation sequencing investigates the presence of 740 hot spot somatic mutations in 46 genes involved in carcinogenesis. The MSI (MicroSatellite Instable) status was assessed using 5 microsatellites. The MMR (Mismatch Repair) status was assessed by immunohistochemistry and sequencing of 11 MMR genes in tumors from 347 (20.0%) pts. The proportion of each MMR protein was calculated from densitometry of immunohistochemistry staining. Results: A total of 196 tumor samples were collected and 125 pts had conclusive results for mutation analysis. The clinical and tumours characteristics were comparable in the NADEGE and BIONADEGE cohort except for metastatic stage at diagnosis underrepresented in the BIONADEGE cohort (17.7%) due to missing tumour sample. A predisposing disease was reported in 25 (20.0%) cases (among them 14 Lynch syndromes and 7 Crohn diseases). The number of mutation observed was 0 in 9.6% pts, only 1 in 32.0%, 2 in 26.4% and ≥3 in 32.0%. The most frequent genomic alteration were KRAS (44.0%), TP53 (38.4%), PIK3CA (20.0%), APC (18.4%), SMAD4 (14.4%) and ERBB2 (7.2%). Altogether, a genomic alteration was observed in 90.3% of tumours. KRAS mutation were more frequent in synchronous metastatic tumour than in localized tumour (72.7% vs 38.2%, p = 0.003). There was no significant difference of mutation rate according to primary location for the most frequently altered gene. With caution to small sample, IDH1 mutation is more frequent and APC alteration never observed in Crohn disease. The rate of dMMR was 38.6% in localized tumour and 0% in synchronous metastatic tumour. After a median follow-up of 55 months (95%CI [44-63]), M0 stage, pNO, pT1-2 were associated with better survival in univariate analysis. No significant prognostic value of genomic alteration was associated with OS. dMMR status was associate with a better prognosis for OS in pts with MMR status determined by immunohistochemistry (HR = 0.55 [0.29-1.01], p = 0.055). Conclusions: A high frequency of targetable alteration is observed in SBA. There is several specificities according to predisposing disease. No association between genomic alteration and prognostic was observed except a trend for a better prognosis associate with dMMR.

TENERGY: Multicenter phase II study of atezolizumab monotherapy following definitive chemoradiotherapy with 5-FU plus cisplatin in patients with locally advanced esophageal squamous cell carcinoma. First Author: Hideaki Bando, Aichi Cancer Center Hospital, Nagoya, Japan

Background: The standard treatment for patients with unresectable locally advanced esophageal squamous cell carcinoma (ESCC) is definitive chemoradiotherapy (CRT) using 5-FU plus cisplatin. However, complete response (CR) rates are only 11% to 25%, and median overall survival (OS) is 9 to 10 months. The improved therapeutic efficacy of combining immunotherapy with radiation has been gaining interest. Our basic research suggested that sequential treatment with anti-PD-L1 agents soon after completion of CRT is the best combination. Twelve months of anti-PD-L1 antibody following platinum-based CRT significantly improved progression-free survival (PFS) and OS in patients with locally advanced non-small cell lung cancer (Antonia SJ, et al. N Engl J Med. 2018). Based on this background information, we have planned a phase II clinical trial to evaluate the safety and efficacy of atezolizumab monotherapy following definitive CRT in patients with locally advanced ESCC. Methods: The main inclusion criteria are unresectable locally advanced ESCC without distant metastasis, completion of treatment with 60 Gy of radiation plus two combined cycles of chemotherapy (cisplatin 70 mg/m² on day 1 and 5-FU 700 mg/m² on days 1–4, every 28 days), and adequate organ function. Within 4 weeks after CRT, patients will be registered in the study and started on 1200 mg of atezolizumab every three weeks until 12 months or disease progression. The primary endpoint is the OR rate by the investigator’s assessment. Overall response rate (ORR), disease control rate, OS, treatment-related adverse events, and OS rate by central assessment are secondary endpoints. A total of 50 patients will be enrolled, including 40 with locally advanced ESCC and 10 with postoperative loco regionally recurrent ESCC. As an exploratory biomarker study, biopsies from the primary site and blood collections will be performed at 3 time points before CRT, after CRT, at 7 days, and four weeks after the start of atezolizumab. We will analyze the phenotype of immune-competent cells, neoantigens, tumor mutation burden, PD-L1 status, and Human Leucocyte Antigen haplotyping. Clinical trial information: UMIN000034373.
Modified FOLFOX versus modified FOLFOX plus nimotuzumab and ipilimumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction: Moonlight, a randomized phase 2 trial of the German Gastric Group of the AIO. First Author: Salah-Eddin Al-Batran, Institute of Clinical Research (IKF) at Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt, Germany

Background: The majority of patients (pts) with gastroesophageal cancer present with inoperable or metastatic disease and there is a strong need for efficient and tolerable first-line (1L) treatment. Oxaliplatin-based regimens like FOLFOX have become one standard of care. However, median survival is still below 12 months. Results from trials using nimotuzumab plus ipilimumab treatment of subjects with advanced/metastatic GC and GEJ cancers demonstrated clinical activity, in pts whose tumors did or did not express PD-L1; in addition, nimotuzumab alone and in combination with ipilimumab demonstrated clinical benefits in various other tumor types. Based on this clinical experience, the AIO-STO-0417 trial (Moonlight) has been designed to evaluate the combination of chemotherapy with two checkpoint inhibitors in first-line therapy of pts with gastroesophageal adenocarcinoma. Methods: This is a prospective, multicenter, randomized, investigator-initiated phase II trial. Pts with HER-2-negative, inoperable advanced or metastatic gastric or gastroesophageal junction cancer will be randomized 1:1 to 1L treatment with FOLFOX (Oxaliplatin 85 mg/m²; Leucovorin 400 mg/m²; 5FU 400 mg/m² on d1 of each treatment cycle and 5FU 1200 mg/m² continuous infusion over 24 hrs d1 and d2) every 2 weeks plus Nivolumab 240 mg every 2 weeks and Ipilimumab 1mg/kg every 6 weeks (Arm A) or FOLFOX alone (Arm B). Primary endpoint of the trial is progression-free survival based on the ITT population. Main secondary endpoints are overall survival, objective response rate, Safety and Quality of life (EORTC QLQ-C30). 118 pts (59 per arm) will be enrolled to provide 80% power for detecting an average HR of 0.68 using the log rank test at a one-sided type I error of 10%. At the date of submission, (Feb 2019), 28 of planned 118 pts are randomized. Clinical trial information: NCT03647969.

Phase II study of a telomerase-specific oncolytic adenovirus (OBP-301, Telomelyn) in combination with pembrolizumab in gastric and gastroesophageal junction adenocarcinoma. First Author: Uzma Khan, Weill Cornell Medical College, New York, NY

Background: Although checkpoint inhibitors (CPIs) can produce durable responses in gastric cancer patients (pts) in the 3rd line setting, the response rate is only 10-15%. Therefore, there is a huge unmet need to enhance the response rate of CPIs to provide benefit to wide range of pts. A novel concept in immuno-oncology is the use of cancer specific oncolytic viral therapy. In addition to the specific killing of the tumor by the virus, these agents can induce an immunogenic cell death in the tumor to augment the immune activation driven by PD-1 inhibition. OBP-301 is an oncolytic adenovirus genetically modified to be able to selectively replicate in cancer cells by introducing human telomerase reverse transcriptase (hTERT) promoter. Results of a phase I study of OBP-301 in solid tumor pts demonstrated the safety and efficacy of intra-tumoral injection of OBP-301. A pre-clinical study of the combination of OBP-301 with anti-PD-1 antibody has also shown significant synergistic activity as well. Based on these encouraging pre-clinical and clinical data, we designed a phase II clinical trial to examine the safety and efficacy of combination of pembrolizumab and OBP-301 in the treatment of PD-L1 positive metastatic gastric/GEJ adenocarcinoma. Methods: This is a multicenter, non-randomized phase II trial of OBP-301 with pembrolizumab in metastatic gastric/GEJ adenocarcinoma that has progressed on at least 2 lines of prior therapy. Eligibility criteria include PD-L1 positive tumors as defined by a combined positive score (CPS) >50 and good organ function. The primary endpoints are to examine objective response rate and safety of OBP-301 with pembrolizumab. The secondary endpoints are to examine disease control rate, duration of response, overall survival and progression-free survival. Correlative studies are planned to identify biomarkers for responses to the combination of pembrolizumab and OBP-301. All eligible pts will receive 1x1011 Viral Particles/mL of OBP-301 administered every 2 weeks for total of 4 injections, injected directly into tumor via upper endoscopy. Every pt will also receive pembrolizumab 200 mg IV every 3 weeks for 2 years or until progression. Pts will be enrolled in a Simon two stage design, with 18 pts in the first stage. If 3 or more pts respond to the combination therapy, the study will move forward to stage 2, with 19 more pts enrolled. The study is currently enrolling pts.

Phase II clinical trial of anti-programmed death-1 antibody (nivolumab) combined with nimotuzumab as second-line treatment of advanced esophageal squamous cell carcinoma. First Author: Feng Wang, Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Background: Approximately 40% of patients (pts) with esophageal cancer are diagnosed with advanced unresectable or metastatic disease; the 5-year survival rate for advanced disease is 5%. No standard therapy is available in China. A phase II clinical trial using gemcitabine plus cisplatin (GC) for advanced esophageal squamous cell carcinoma (ESCC) patients progressed after first-line chemotherapy. Inhibition of programmed cell death protein-1 (PD-1) has demonstrated promising antitumor activity and manageable safety in pts with advanced unresectable or metastatic ESCC. SHR-1210, a humanized IgG4 monoclonal antibody, has high affinity and specificity for PD-1 molecule. SHR-1210 was generally well tolerated and had preliminary antitumor effects in pts with solid tumors, including ESCC. Nimotuzumab, a humanized anti-epidermal growth factor receptor monoclonal antibody h-r3, has been shown to be effective and safe in the treatment of head and neck cancer,non-small cell lung cancer (NSCLC) and esophageal Cancer in several phase II studies. The purpose of this study is to observe and evaluate the efficacy and safety of anti-PD-1 antibody SHR-1210 combined with nimotuzumab as second-line therapy in patients with advanced ESCC.

Methods: Patients, age 18-75, with measurable tumor lesion, failed in or progression after 1st line chemotherapy, were enrolled in this study. Patients received SHR-1210 200 mg every 2 weeks (Q2W) combined nimotuzumab 200 mg weekly until disease progression, death or unacceptable toxicity. Assessments included response by RECIST v1.1 every 6 wks and safety (physical examination, vital signs, ECOG PS, laboratory tests). The primary endpoint is the objective response rate (ORR), and the secondary endpoints include the diseases control rate (DCR), duration of response (DR), progression-free survival (PFS), and overall survival(OS). Additionally, we try to identify biomarker to predict efficacy of SHR-1210 and Nimotuzumab with target capture sequencing and gene expression profile as exploratory endpoints. Clinical trial information: NCT03766178.
TPS4148 Poster Session (Board #249b), Mon, 8:00 AM-11:00 AM
RAP: A phase II trial with ramucirumab, avelumab, and paclitaxel as second line treatment in gastro-esophageal adenocarcinoma of the arbe\nschaft (AIO). First Author: Ruma Shehata, Chief Medical Officer – University Medicine Berlin, Department of Haematology, Oncology and Tumor\nimmunology, Berlin, Germany

Background: Combination of ramucirumab and paclitaxel resembles the standard treatment option in second line therapy with improvement of re\ponse rate and overall survival (REGARD, RAINBOW). Response rates to PD\x1D1L blockade in gastro-esophageal cancer patients rank within 10-20%, whereas PD-1L blockade is reported to impressively extend survival rates in res\ponders. Trials investigating either the synergistic effect of anti\x1D1angiogenesis and anti-PD-L1 or chemotherapy combined with anti-PD-L1 are promising. Based on these data we hypothesize benefit from combining immunotherapy by checkpoint inhibition with VEGF-directed treatment and chemotherapy induced increase of immunogenicity of tumor cells. This study investigates the incorporation of PD-L1 blockade by avelumab in the second line setting by combination with the actual best second-line chemotherapy regimen in metastatic gastric cancer patients (paclitaxel+ramucirumab).

Methods: The RAP trial (AIO-STO-0218, registered at ClinicalTrials.gov) is a single\x1D1arm phase II trial. A total of 59 patients with metastatic or locally advanced gastric or gastro-esophageal junction adenocarcinoma, ECOG 0\x1D1–1, who progressed after having received first-line therapy with platinum and fluoropyrimidine doublet with or without anthracycline, docetaxel or trastu\zumab within the last six months will receive avelumab and ramucirumab on day 1, 15 and paclitaxel on day 1, 8 and 15 of a 28-day cycle until disease progression (RE\x1D1CIST v1.1). intolerable toxicity, withdrawal of consent or a maximum treatment of 1 year. The primary endpoint is the overall survival rate (OSR) at 6 months. Sample size calculation is based on a Simon 2-stage design with a one-sided alpha error of 10% and a power of 80%, an expected OSR of 20%, and an expected OSR of 0% for both a hypothesis of 0% and a hypothesis of 20%. Secondary endpoints include OS, OSR at 12 months, PFS, safety and tolerability, duration of re\ponse. Ethics commission approved the study protocol in January 2019. Updated patient accrual will be presented. Clinical trial information: AIO-STO-0218.

TPS4150 Poster Session (Board #250b), Mon, 8:00 AM-11:00 AM
Ramucirumab and irinotecan in patients with previously treated gastro\x1D1x1esophageal adenocarcinoma. First Author: Haesung Park, Washington University School of Medicine, St. Louis, MO

Background: Ramucirumab is used for treatment of metastatic gastro\x1D1esophageal adenocarcinoma after disease progression on first-line chemotherapy. Superior survival outcome is expected when combined with paclitaxel. However, many patients suffer from neuropathy after oxaliplatin\x1Dcontaining first-line chemotherapy and are unable to tolerate paclitaxel. Irinotecan has shown survival benefit as a single agent or in combination with other agents, but has not been used in combination with ramucirumab for treatment with gastroesophageal cancer. We hypothesize that this combination regimen of irinotecan plus ramucirumab administered as second-line treatment will be well-tolerated with improved outcomes similar to paclitaxel plus ramucirumab in patients with advanced gastroesophageal cancer. Circulating levels of angiogenic factors are correlates of particular interest in this study.

Methods: This is a multi-institutional, single-arm phase II clinical trial of ramucirumab and irinotecan. Primary objective of the study is to determine the progression-free survival in patients treated with this combination after disease progression on first-line chemotherapy. Secondary objectives are to determine other indices of efficacy including overall survival, time to progression, objective response rate, and clinical benefit rate; and to evaluate toxicity and tolerability. Patients with confirmed diagnosis of gastroesophageal adenocarcinoma with measurable disease are included. Patients are required of have disease progression within 4 months of first line chemotherapy. Key exclusion criteria include squamous histology; prior irinotecan or ramucirumab use; active brain metastases; or other contraindications to ramucirumab including recent history of gastrointestinal bleeding or perforation, thromboembolic event, and uncontrolled hypertension. Patients receive ramucirumab 8mg/kg with irino\x1D1tec 180mg/m² IV every 14 days. We plan to enrol 40 patients which will provide 85% power at a 0.05 significance level to detect a median progression free survival time of 4 months compared to historic control of 2.5 months. 25% of patient accrual is complete as of February 2019. Clinical trial information: NCT03141034.

TPS4149 Poster Session (Board #250a), Mon, 8:00 AM-11:00 AM
A phase II study of TAS-102 in combination with ramucirumab in advanced, refractory gastric or gastroesophageal junction (GEJ) adenocarcinoma. First Author: Indira Mehta, Cleveland Clinic Florida, Buffalo, NY

Background: Patients with advanced gastric cancer experience a 5 year survival rate <10% even with multimodality therapy representing the unmet need for improved treatment. In advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma, ramucirumab (a monoclonal antibody against VEGFR2) has demonstrated clinical activity and has been approved as second line therapy in combination with paclitaxel with a response rate of 28% and an overall survival benefit of 8 weeks when compared to placebo. However, there are many patients that cannot tolerate paclitaxel due to prior exposure to oxaliplatin causing neuropathy. Therefore, novel combinations with ramucirumab, is highly desirable. TAS-102 is an oral cytotoxic agent with two active components; trifluridine (TDF) which inhibits tumor cell growth by being incorporated into DNA during DNA synthesis and tipiracil (TPI) which inhibits the metabolism of TDF, thereby prolonging its ability to exert effect. TPI also inhibits platelet derived endothelial cell growth factor which plays a key role with VEGF in tumor angiogenesis. The combination of a cytotoxic agent with an antiangiogenic agent has demonstrated a significant antitumor activity in multiple cancers. In a recent Phase III study, TAS-102 significantly prolonged overall survival as compared to best supportive care in patients with GEJ and gastric cancers that had received at least 2 prior lines of treatment. We hypothesize that a combination of TAS-102 and ramucirumab might increase efficacy without causing unmanageable toxicity.

Methods: This is a single institutional phase II single arm two-stage design trial using the combination of TAS-102 and ramucirumab in advanced, refractory gastric or GEJ adenocarcinoma. Eligible patients include those with histologically confirmed gastric or GEJ adenocarcinoma that have received at least 1 prior line of treatment with performance status 0 or 1 and preserved organ function. Ramucirumab will be administered every 2 weeks and TAS-102 at a dose of 35 mg/m² twice daily. Each cycle length will be 28 days. The primary endpoint is 6 months OS and secondary endpoints are safety, objective response rate and PFS. Fifteen patients will be enrolled in the first stage. If <7 of the 15 are alive at 6 months, an additional 10 patients will be enrolled in the second phase. Enrolment is currently ongoing. Clinical trial information: NCT03684588.

TPS4151 Poster Session (Board #251a), Mon, 8:00 AM-11:00 AM
Assessment of ramucirumab plus paclitaxel as switch maintenance versus continuation of first-line chemotherapy in patients (pts) with advanced HER2-negative gastric or gastroesophageal junction cancers: The ARMANI phase III trial. First Author: Federica Morano, Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Platinum/fluoropyrimidine regimens are the backbone of first-line therapy for advanced gastric cancer (AGC). The optimal duration of first-line therapy is still unknown and its continuation until disease progression represents the standard. However this strategy is often associated with cumulative toxicity and rapid development of drug resistance. Moreover, only 40% of AGC pts are eligible for second-line treatment. This study aims at assessing whether switch maintenance to ramucirumab plus paclitaxel will extend the progression-free survival (PFS) of subjects with HER-2 negative AGC who have not progressed after a first-line with a platinum/fluoropyrimidine regimen. The hypothesis is that the early administration of an active, non-cross resistant regimen may delay disease progression and, consequently, improve pts' quality of life. This strategy may also rescue all those subjects that become ineligible for a second-line therapy due to the rapid clinical deterioration. Methods: This is a randomized, open-label, multicenter, phase III trial. Eligibility criteria are: unresectable/metastatic HER-2 negative AGC or gastroesophageal junction (GEJ) cancer; ECOG PS 0-1; measurable and/or evaluable disease by RECIST v1.1; no progression after 3 months of therapy with either FOLFOX4, mFOLFOX6 or XELOX. The primary endpoint is to compare PFS of pts in ARM A (continuation of the same first-line therapy with oxaliplatin/ fluoropyrimidine) versus ARM B (switch maintenance to ramucirumab and paclitaxel). Secondary endpoints are: overall survival, time-to-treatment failure, overall response rate, duration of response, percentage of pts receiving a second-line therapy per treatment arm, safety and quality of life. Exploratory analyses to identify primary resistance and prognosis biomarkers are planned, including Next-Generation Sequencing (NGS) on archival tumor tissues. The ARMANI study is sponsored by the Fondazione IRCCS Istituto Nazionale dei Tumori and it is ongoing at 29 Italian centers with a planned population of 280 pts. Clinical trial information: NCT02934464.
Lenvatinib (len) plus pembrolizumab (pembro) for the first-line treatment of patients (pts) with advanced hepatocellular carcinoma (HCC): Phase 3 LEAP-002 study. First Author: Josep M Llovet, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Len, an inhibitor of VEGF receptors 1-3, FGFR receptors 1-4, PDGF receptor α, RET, and KIT, is approved for first-line treatment of unresectable HCC (uHCC) based on the open-label phase 3 REFLECT study in which len showed noninferior overall survival (OS) and significantly improved objective response rate (ORR), progression-free survival (PFS), and time-to-progression (TTP) vs sorafenib. In the phase 2 KEYNOTE-524 study, pembrolizumab (a PD-1 inhibitor) as second-line treatment of advanced HCC, pembro showed meaningful clinical efficacy in pts previously treated with sorafenib, with median PFS 4.9 mo, median OS 12.9 mo, and a manageable safety profile. In results from the phase Ib KEYNOTE-524 trial, len+pembro was well-tolerated, with promising antitumor activity in pts with uHCC. LEAP-002 is a phase 3 study to evaluate the safety and efficacy of len+pembro vs len+placebo as first-line therapy for advanced HCC. Methods: Eligible pts are ≥18 y and have HCC confirmed by radiology, pathology, or cytology; ECOG PS 0/1; BCLC stage C or stage D disease not amenable to locoregional therapy or curative treatment approach; CP class A liver score within 7 days before study; and ≥1 measurable lesion by RECIST v1.1. Pts with past or ongoing HCV infection and steroid use. Primary objective is to evaluate progression-free survival (PFS) rate at 4 months. Secondary objectives include evaluation of objective response rate per immune related (ir)RECIST criteria, median PFS and OS, and safety in this patient population. Exploratory objectives include identification of predictive biomarkers of response and mechanisms of resistance through serial biopsies and blood collection (pre, on and post therapy), including sequential whole exome/transcriptomic analysis with immune cell subset analysis. Treatment includes lenvaparib 600 mg PO BID on days 1-28 with nivolumab 240 mg on days 1, 15 Q4 weeks. In absence of disease progression, pts may continue therapy up to 2 years. Accrual goal is 32 evaluable pts. Using a null hypothesis value of a 63% PFS rate at 4 months, and an 85% alternative hypothesis, the ongoing study has 80% power, with a one-sided alpha of 0.05 to identify treatment efficacy in the study arm. Clinical trial information: NCT03639935.

A multi-center phase Ib/I study of nal-inotriocin, 5-fluorouracil and leucovorin in combination with nivolumab as second line therapy in pts with advanced unresectable biliary tract cancer. First Author: Vaibhav Sahai, University of Michigan, Ann Arbor, MI

Background: Patients (pts) with advanced biliary tract cancers (BTC) have poor prognosis despite systemic chemotherapy, and treatment beyond first-line platinum doublet remains investigational. The immunomodulatory properties of conventional cytotoxic therapy, particularly in regard to the upregulation of PD-1/L1 expression rendering tumor cells more sensitive to T cell-mediated lysis and neoantigen production, rapid emergence of chemotherapy resistance, and known modest efficacy of single agent PD-1 antibody in BTC provide a rationale for combining chemotherapy and immunotherapy. This multi-center, phase Ib/I, single-arm study is designed to investigate the role of nal-inotriocin, 5-FU and leucovorin in combination with nivolumab as second-line therapy in pts with advanced BTC. Methods: Key eligibility criteria include histologically confirmed advanced, unresectable biliary carcinoma (intra- or extra-hepatic and gallbladder) with progression or intolerance of first-line systemic therapy (excluding inotriocin and PD-1/PD-L1 antibody), measurable disease per RECIST v1.1, ECOG PS 0-1, Child Pugh A or B7, and absence of autoimmune disease or chronic steroid use. Primary objective of the phase Ib portion is to determine the recommended phase 2 dose, and of the phase II portion is to evaluate the median progression-free survival. Secondary objectives include evaluation of objective response rate per immune related (ir)RECIST, median OS and safety in this patient population. Exploratory objectives include identification of biomarker predictors of response and mechanisms of resistance through serial biopsies and blood collection (pre, on and post therapy), including sequential whole exome/transcriptomic analysis and immune cell subset analysis (tissue and blood). Therapy includes inotriocin 70 mg/m², leucovorin 200 (dose level -1) or 400 mg/m² (dose level 0), 5-fluorouracil 2400 mg/m² IV over 46 hours, and nivolumab 240 mg on day 1 every 2 weeks for 6 months. In the absence of disease progression, pts may continue therapy for up to 2 years. Accrual goal is 30 evaluable pts. Using a null hypothesis value of median PFS of 2.9 months, and an alternative hypothesis of 6.8 months, this ongoing study has >80% power, with a two-sided alpha of 0.05 to identify treatment efficacy of study arm. Clinical trial information: NCT03785873.

A multicenter phase II trial of rucaparib in combination with nivolumab as maintenance therapy for patients with advanced biliary tract cancer. First Author: Vaibhav Sahai, University of Michigan, Ann Arbor, MI

Background: Patients (pts) with advanced biliary tract cancers (BTC) have a poor prognosis with a median overall survival (OS) less than 12 months. Using whole exome NGS, 26 (49%) pts in a 53 pt cohort had either DNA damage repair (DDR) pathway mutations (somatic and/or germline, n = 18), or isocitrate dehydrogenase 1 (IDH1) mutations (n = 8), and may have potentially benefited from PARP inhibition. Further, disruption of the mutated DDR pathways with a PARP inhibitor may result in increased mutational burden and neoantigens leading to immunogenicity, thus providing the rationale for combination with a PD-1 antibody. This phase 2 trial is designed to investigate the role of a PARP inhibitor in combination with a PD-1 antibody in pts with advanced BTC. Methods: Key eligibility criteria include histologically confirmed advanced, unresectable biliary adenocarcinoma (intra- or extra-hepatic, and gallbladder) without progression after 4-6 months of 1st line platinum-based systemic chemotherapy, measurable disease per RECIST v1.1, ECOG PS 0-1, Child-Pugh A or B7, and absence of autoimmune disease or chronic steroid use. Primary objective is to evaluate progression-free survival (PFS) rate at 4 months. Secondary objectives include evaluation of objective response rate per immune related (ir)RECIST criteria, median PFS and OS, and safety in this patient population. Exploratory objectives include identification of predictive biomarkers of response and mechanisms of resistance through serial biopsies and blood collection (pre, on and post therapy), including sequential whole exome/transcriptomic analysis with immune cell subset analysis. Treatment includes rucaparib 600 mg PO BID on days 1-28 with nivolumab 240 mg on days 1, 15 Q4 weeks. In absence of disease progression, pts may continue therapy up to 2 years. Accrual goal is 32 evaluable pts. Using a null hypothesis value of a 63% PFS rate at 4 months, and an 85% alternative hypothesis, this ongoing study has 80% power, with a one-sided alpha of 0.05 to identify treatment efficacy in the study arm. Clinical trial information: NCT03639935.

Infigratinib versus gemcitabine plus cisplatin multiterior, open-label, randomized, phase 3 study in patients with advanced cholangiocarcinoma with FGFR2 gene fusions/translocations: The PROOF trial. First Author: Milind J. Javle, MD Anderson Cancer Center, Houston, TX

Background: Cholangiocarcinoma is the most common biliary tract malignancy with approximately 5,000–10,000 new cases annually in the USA. The fibrolast growth factor receptor (FGFR) family plays an important role in cholangiocarcinoma, with FGFR2 gene fusions detected in about 15% of patients with cholangiocarcinoma. Infigratinib is an ATP-competitive, FGFR1–3-selective oral tyrosine kinase inhibitor. First-line treatment with chemotherapy offers only modest benefit and more effective treatment options are needed. Based on preliminary response data of infigratinib in relapsed/refractory cholangiocarcinoma with FGFR2 gene fusions/translocations (Phase 2 Study CBJG398X2204), the PROOF trial is evaluating infigratinib versus gemcitabine + cisplatin in front-line patients with advanced cholangiocarcinoma with FGFR2 gene fusions/translocations. Methods: Patients with advanced/metastatic or inoperable cholangiocarcinoma are randomized 1:1 to oral infigratinib once daily for 21 days of a 28-day treatment cycle versus IV gemcitabine (1000 mg/m²) + cisplatin (25 mg/m²) on days 1 and 8 of a 21-day cycle. Treatment will continue until confirmed progressive disease by central review, intolerance, withdrawal of informed consent, or death. After 8 cycles of gemcitabine + cisplatin, patients can continue treatment if the investigator considers that they are deriving continued benefit. Patients on the gemcitabine + cisplatin arm who progress can cross-over to infigratinib. The primary endpoint is progression-free survival (PFS, per RECIST v1.1 central review). Secondary endpoints include overall survival, PFS (investigator determined), overall response rate, disease control rate, duration of response, and safety. Quality of life, PK and exploratory genetic alterations/biomarkers will also be measured. Current status: The study was initiated in February 2019 with planned enrollment of 350 patients with confirmed FGFR2 gene fusions/translocations. Clinical trial information: NCT03773302.
Background: Cisplatin and gemcitabine (CisGem) is the global standard of care for first-line treatment of advanced BTC. NUC-1031, a phosphoramidate transformation of gemcitabine, is designed to overcome resistance mechanisms associated with poor gemcitabine response. Promising signs of efficacy have been observed with single agent in a phase I study in solid tumors (Blagden et al 2018) and in the phase Ib ABC-08 study of NUC-1031 + cisplatin 25 mg/m² d1, d8 q 21 days for the first-line treatment of advanced BTC. 14 pts have been enrolled across 2 cohorts (NUC-1031: 625 mg/m² and 725 mg/m²). In 11 pts evaluable for response ORR was 64% (1 CR, 6 PRs) and DCR was 73%. PFS/OS data is maturing. The combination was very well-tolerated with no unexpected adverse events or dose-limiting toxicities. The RP2D in combination with cisplatin is 725 mg/m². Safety, coupled with encouraging efficacy signal has led to the initiation of a global Phase III development program A Phase III, open-label, randomized head-to-head study of NUC-1031 + cisplatin versus CisGem for the first-line treatment of advanced BTC will include pts ≥18 years with histologically- or cytologically-proven BTC (including cholangiocarcinoma, gallbladder, or ampullary cancer), that is not resectable and who are not eligible or prior to eligible for advanced metastatic disease. A total of 828 pts will be randomized (1:1) to either 725 mg/m² NUC-1031 + 25 mg/m² cisplatin or 1000 mg/m² gemcitabine + 25 mg/m² cisplatin, administered on Days 1 and 8 of a 21-day cycle, respectively. Primary objectives are OS and ORR. Secondary objectives include further assessments of efficacy endpoints and patient-reported quality of life. The study will be conducted at approximately 120 sites across North America, Europe and Asia Pacific countries. Clinical trial information: NCT02351765.

TPS4157 Poster Session (Board #254a), Mon, 8:00 AM-11:00 AM Phase 3 (COSMIC-312) study of cabozantinib (C) in combination with avelumab (A) versus sorafenib (S) in patients (pts) with advanced hepatocellular carcinoma (HCC) who have not received previous systemic anticancer therapy. First Author: Robin Kate Kelley, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Background: C inhibits tyrosine kinases involved in tumor growth, angiogenesis, and immune regulation, including MET, VEGFR, and TAM kinases (Tyro3, AXL, MER). C is approved for treatment of aHCC after prior S based on improved overall survival (OS) vs placebo in the phase 3 CELESTIAL trial (Investigator-NEJM 2018). Standard of care for first-line treatment of aHCC is tyrosine kinase inhibition with S or lenvatinib, and phase 3 trials of immune checkpoint inhibitors (ICIs) in first- and second-line aHCC are ongoing. C may promote an immune-permissive tumor environment, which could enhance response to ICIs. C is being evaluated in combination with the anti-PD-L1 antibody A in multiple tumor types including HCC in a phase 1 study, and dose, preliminary clinical activity, and safety have been established in aRCC (Agarwal Ann Oncol 2018). A in combination with bevacizumab, an anti-VEGF antibody, has shown preliminary clinical activity in first-line aHCC (Fishtyan Ann Oncol 2018). Here, we present the study design of a phase 3 trial of C+A vs S as first-line treatment for aHCC. Eligibility criteria include age ≥18 years, BCLC stage B or C, Child-Pugh A, ECOG PS 0 or 1, and measurable disease per RECIST 1.1. Prior therapies are limited to 6±3; to an experimental arm of C (400 mg qd), A (1200 mg infusion q3w), a control arm of S (400 mg bid), and an exploratory arm of C monotherapy (60 mg qd). 640 pts are planned at ~200 sites globally. Randomization is stratified by disease etiology (HBV [with or without HCV], HCV [without HBV], or other), region (Asia, other), and the presence of extrahepatic metastases (yes, no). Resistant or macrovascular invasion (yes, no). OS and progression-free survival are coprimary endpoints and objective response rate is a secondary endpoint. Additional endpoints include safety, pharmacokinetics, and correlation of biomarker analyses with clinical outcomes. Enrollment in COSMIC-312 is ongoing. Clinical trial information: NCT03755791.
TPS4160
Poster Session (Board #255b), Mon, 8:00 AM-11:00 AM
A randomized noncomparative phase II study of maintenance therapy with multiparttate vaccine Tedopi (OSE22101) + nivolumab or FOLFIRI after induction chemotherapy (CT) with FOLFIRINOX in patients (Pts) with advanced pancreatic ductal adenocarcinoma (aPDAC) (TEDOPaM – PRODIGE 63 GER-COR D17-01 study). First Author: Cindy Neuzillet, Medical Oncology Department, Cure Institute, Versailles Saint-Quentin University, Saint Cloud, France
Background: FOLFIRINOX (5-fluorouracil (5FU), folinic acid (FA), irinotecan (Iri), and leucovorin (LV)) is a standard 1st-line treatment in fit Pts with aPDAC. Anti-PD-1/L1 PD-L1 as single agents have failed in PDAC so far and new combination immunotherapies are needed. Tedopi (OSE2101) is a multipeptide vaccine restricted to HLA-A2 positive Pts, targeting 5 tumor-associated antigens (CEA, HER2, MSH6, PALB2, TP53) that are frequently expressed in PDAC. This study aims to assess the efficacy and safety of Tedopi alone and in combination with anti-PD-1 nivolumab, or FOLFIRI as maintenance therapy in Pts with aPDAC after FOLFIRINOX induction CT. Methods: TEDOPaM – PRODIGE 63 is a 3-arm, Fleming 2-stage, open-label, randomized, non-comparative phase II study. 156 Pts with locally advanced or metastatic, pathologically proven PDAC, ECOG performance status 0-1, HLA-A2 genotype; controlled disease (objective response or stable disease) after 8 cycles of modified FOLFIRINOX; and adequate organ functions, are randomized (1:1:1, stratified on center, tumor stage, and best response to FOLFIRINOX) into 3 arms:
Clinical trial information: NCT03806309. In Arms B and C, FOLFIRI is reintroduced at disease progression or unacceptable toxicity. Primary endpoint: overall survival rate at M12. Secondary endpoints: progression-free survival (CT-scan Q3W), creation of disease control, safety, adverse event rate, RECIST v1.1 (RECIST comparison, HRQoL (EORTC QL-Q30), QoL. An interim analysis is planned after inclusion of 20 Pts in each arm. Translational research will be performed on tumor tissue (initial FFPE biopsy and optional re-biopsy at inclusion): cytokine panel, PBMC phenotyping, planned after inclusion of 20 Pts in each arm.

TPS4162
Poster Session (Board #256b), Mon, 8:00 AM-11:00 AM
Improving cascade genetic testing for families with inherited pancreatic cancer (PDAC) risk: The genetic education, risk assessment and testing (GENERATE) study. First Author: Matthew B. Yurgelun, Dana-Farber Cancer Institute, Boston, MA
Background: 4-10% of PDAC patients harbor pathogenic germline variants in cancer susceptibility genes, including APC, ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PM25, STK11, and TP53. For families with such pathogenic variants, the greatest potential impact of genetic counseling is to identify relatives with a high risk of PDAC (cascade testing), thereby providing the opportunity for early detection and cancer interception of PDAC and other associated malignancies. Numerous factors limit cascade testing in real-world practice, including family dynamics, widespread geographic distribution of relatives, access to genetic services, and misconceptions about the importance of germline testing, such that the preventive benefits of cascade testing are often not fully realized. The primary aim of this study is to analyze two alternative strategies for cascade testing in families with inherited PDAC susceptibility. Methods: 1000 individuals (from approximately 200 families) with a confirmed pathogenic germline variant in any of the above genes in a 1st/2nd degree relative and a 1st/2nd degree relative with PDAC will be remotely enrolled through the study website (www.gene-astudy.org) and randomized between two different methods of cascade testing (individuals with prior genetic testing will be ineligible): Arm 1 will undergo pre-test genetic education with a pre-recorded video and live interactive session with a genetic counselor via a web-based telemedicine platform (Doxys, me). followed by germline testing through Color Genomics; Arm 2 will undergo germline testing through Color Genomics without dedicated pre-test genetic education. Color Genomics will disclose results to study personnel and directly to participants in both arms. Participants in both arms will have the option of pursuing additional telephone counseling through Color Genomics. The primary outcome will be uptake of cascade testing. Secondary outcomes will include participant self-reported genetic knowledge, cancer worry, distress, decisional preparedness, familial communication, and screening uptake, which will be measured via longitudinal surveys. Enrollment will begin February, 2019. Clinical trial information: NCT03762590.

TPS4161
Poster Session (Board #256a), Mon, 8:00 AM-11:00 AM
A randomized phase II trial of niraparib plus either nivolumab or ipilimumab in patients with advanced pancreatic cancer whose cancer has not progressed in platinum-based therapy. First Author: Kim Anna Reiss, University of Pennsylvania Abramson Cancer Center, Philadelphia, PA
Background: The treatment paradigm for advanced pancreatic ductal adenocarcinoma (PDAC) typically involves ongoing chemotherapy until either disease progression or clinical deterioration. A subset of patients with advanced PDAC have exceptional responses to platinum-based chemotherapy. We hypothesized that durable platinum sensitivity in patients with advanced PDAC might be indicative of a DNA repair deficiency, and that these patients may respond to a combination of niraparib, a PARP inhibitor, plus immune checkpoint blockade. Methods: We have enrolled 25 of 84 planned patients on study NCT 03404960. Eligibility criteria include inoperable PDAC and stability on platinum-based chemotherapy for ≥16 weeks without evidence of progressive disease. Patients who have progressed on platinum-based treatment or who have received prior therapy with PARP inhibitors are excluded. Patients are randomized to receive oral niraparib 200mg PO daily plus nivolumab 240mg IV every two weeks in continuous 28 day cycles or oral niraparib 200mg PO daily plus ipilimumab 3mg/kg IV every three weeks for four doses in continuous 21 day cycles. The primary endpoint is progression-free survival at 6 months. Secondary endpoints include response rate, duration of response and overall survival. Paired biopsies are obtained, as well as serial blood collections for circulating tumor cells (CTCs), circulating tumor DNA (ctDNA) and peripheral blood mononuclear cells (PBMC). Correlations will include immune gene sequencing and analyses of serially collected PBMCs, CTCs and ctDNA to identify genomic and immunologic innate and adaptive resistance mechanisms. Clinical trial information: NCT 03404960.

TPS4163
Poster Session (Board #257a), Mon, 8:00 AM-11:00 AM
Phase II multi-institutional study of nivolumab (Nivo), cabiralumab (Cabira), and stereotactic body radiotherapy (SBRT) for localized advanced resectable pancreatic cancer (LAUPC). First Author: Deirdre Jill Cohen, Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY
Background: Treatment of LAUPC most commonly involves chemotherap...
TPS4164  Poster Session (Board #257b), Mon, 8:00 AM-11:00 AM  
Adaptive Dose Escalation Trial of Stereotactic Body Radiation Therapy (SBRT) in combination with GC4419 in pancreatic cancer.  
First Author: Jon Holtmann, Ascension Wisconsin, Milwaukee, WI

**Background:** Local progression causes up to 30% of deaths from pancreatic cancer (PC) and is also a significant source of morbidity. Stereotactic body radiotherapy (SBRT) offers the potential for improved therapeutic index over standard fractionation, but current regimens of 5-7 Gy/fraction x 5 are constrained by nearby organ tolerance and offer only palliation without improving survival. Safe dose escalation is necessary to improve SBRT efficacy. GC4419, a superoxide dismutase mimetic, selectively converts superoxide (O2•−) to hydrogen peroxide (H2O2) and oxygen. O2•− initiates normal tissue damage due to RT. GC4419 is in a Phase 3 trial (NCT03689712) to RT-induced oral mucositis in head and neck cancer, based on positive results in a randomized Phase 2 trial for that indication (Anderson, ASCO 2018). GC4419 improved the survival of mice receiving 8.5 Gy x 5 to the upper abdomen. Cancer cells are less tolerant to elevated H2O2, and more tolerant to elevated O2•− than normal cells, and GC4419 demonstrated mechanism-dependent synergy with high dose-fraction RT in a human tumor xenograft with inducible expression of catalase (Sish, AACR 2018). Thus, adding GC4419 to SBRT may increase both the efficacy and the safety of the latter.

**Methods:** 48 patients with localized, unresectable PC without frank duodenal invasion, who have received 3+ cycles of induction chemotherapy, are to be randomized 1:1 to placebo or GC4419, 90 mg IV, prior to each of 5 consecutive daily (M-F) SBRT fractions. A phase I/II Late Onset Efficacy/Toxicity traded (LO-ET) balanced adaptive design adaptive model drives SBRT dose escalation in each arm based on a dual endpoint (Gr 3-4 GI toxicity or death; stable disease or better) by 90 days post SBRT. The planned dose levels are 10, 11 and 12 Gy x 5 fractions (BED10=100,112.5 and 132Gy, respectively) as an integrated boost to the gross tumor volume (GTV). Primary endpoints: Maximum tolerated dose of SBRT with GC4419 or placebo. Exploratory endpoints include change in tumor radiographic resectability, correlative studies (ctDNA, exosomal DNA, tumor exome/transcriptome sequencing, immune profiling). Supported by Galera Therapeutics, Inc.

Clinical trial information: NCT03340974.

TPS4165  Poster Session (Board #258a), Mon, 8:00 AM-11:00 AM  
A phase I/II study of GS3145095 alone and in combination with anticancer agents including pembrolizumab in adults with selected solid tumors.  
First Author: Dandrei JH Cohen, Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY

**Background:** The immunosuppressive myeloid infiltrate characteristic of the tumor microenvironment in pancreatic cancer represents a major therapeutic barrier in this disease. Modulation of this infiltrate may increase sensitivity to immune checkpoint blockade in this and other tumors with a similar phenotype. The receptor interacting protein 1 (RIP1) is a serine/threonine kinase that becomes active upon homoeostatic disruptions. Block of RIP13-3 and mixed lineage kinase domain-like protein (MLKL), RIP1 kinase activity drives necroptosis. However, RIP1 also signals in response to inflammatory stimuli independently of its association with RIP3. A correlation between increased RIP1 protein expression and a worse prognosis has been reported in a variety of solid tumors. Furthermore, in an unbiased screen RIP1 was identified as a top gene contributing to resistance to immunotherapy (Manguso 2017). In murine models, RIP1 kinase activity has been reported to drive pancreatic oncogenesis. Inhibition of RIP1 in the pancreatic TME leads to the replacement of tumor-permissive myeloid infiltrates with innate cells promoting an anti-tumor response by the available immune system (Seefeld 2018). We hypothesized that providing RIP1 inhibitors in a safe form and synergized with anti-PD-1 treatment. These data suggest that the small molecule RIP1 inhibitor GS3145095 may have therapeutic potential in multiple tumor types. Methods: This is a four-part phase 1/2 study designed to evaluate the safety, PK, PD, and preliminary activity of GS3145095 given orally to advanced oncologic patients with selected advanced oncologic diseases. GS3145095 will be conducted in approximately 30 adults with pancreatic cancer with escalating doses of GS3145095. Part 2 will combine escalating doses of GS3145095 with 200 mg pembrolizumab and may be conducted in a broader population of selected solid tumors. Part 3 represents a cohort expansion of Part 2. Part 4 may investigate the combination of additional anti-tumor agents with one or more doses of GS3145095 identified as safe in a randomized fashion.

Author: Deirdre Jill Cohen, Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY

**Background:** There is increasing evidence suggesting benefit from a neo-adjuvant approach to PC. However, the optimal regimen is unclear and will likely require a precision medicine approach, where patient and tumor attributes define therapy. Platinum-containing regimens have shown survival benefit for PC, with exceptional responders, but biomarkers (BM) of response are not well defined and treatment decisions are often based on patient performance status (PS) and co-morbidity. Tumors with defects in BRCA1/2 and other Fanconi Anemia genes show defective DNA damage response (DDR), conferring potential selective sensitivity to DNA-damaging agents (e.g. platinum) and newer targeted agents. We have shown that DDR deficiency (DDRd) is present in up to 20% of PC. This study aims to exploit DDRd as a therapeutic vulnerability, with integrated analysis to define candidate BM for FA and AG response. Methods: PRIMUS-002 will enroll patients registered on the Precision-Panc Master Protocol who are molecularly profiled using the Precision-Panc Clinical Cancer Genome including a novel DDRd assay, and the transcriptome with longitudinal sampling (pre, during, and post-treatment). Patients receive either FA (nab-paclitaxel 150mg/m² IV,oxaliplatin 85mg/m²,5-fluorouracil 600mg/m² IV, folinic acid 350mg flat dose, fluorouracil infusion 2400mg/m² continuous IV infusion), or AG (nab-paclitaxel 125mg/m², gemcitabine 1000mg/m²) for 3 months, based on patient age and PS. Following initial safety analysis, chemoradiation may be introduced. The primary endpoint is disease progression (DP) during neo-adjuvant therapy. The study is designed to detect a 20% difference in DP between the BM–ve (10%) and BM+ve (30%) in patients treated with FA (90% power, 5% 1-sided level of statistical significance). Exploratory translational endpoints include surrogate therapeutic response assessment using CA19.9, PET-CT SUV, DWI-MRI and ctDNA. Current Enrollment: 2 patients enrolled to date: 1 to receive FA and 1 to AG treatment. Clinical trial information: ISRCTN34129115.

TPS4166  Poster Session (Board #258b), Mon, 8:00 AM-11:00 AM  
PRIMUS-002: A multicentre, open-label, phase II study examining FOLFOX and nab-paclitaxel (FA) and nab-paclitaxel and gemcitabine (AG) for locally advanced or metastatic pancreatic cancer.  
First Author: William Adrian Hall, Medical College of Wisconsin, Milwaukee, WI

**Background:** There is growing consensus for the use of neoadjuvant therapy in patients with potentially operable pancreatic adenocarcinoma (PC). However, there is no consensus on the type and duration of chemotherapy or radiation therapy (RT) in the preoperative setting. Stereotactic body radiation therapy (SBRT) has gained popularity despite the absence of prospective data for its use in the preoperative setting. Furthermore, SBRT preoperatively has not been standardized. At present, there exists no randomized data comparing preoperative SBRT with conventionally fractionated concurrent chemo-RT. We designed this trial to examine differences between pre-op RT dose and fractionation schedules. Methods: This study is a prospective, randomized, two-arm, phase II clinical trial. Eligible patients must have cytologically confirmed PC and be deemed suitable for surgical resection with resectable, borderline-resectable, or locally advanced type A disease based on cross-sectional imaging. Before randomization patients are stratified by clinical node positivity, neoadjuvant chemotherapy, and stage of disease. Patients are then randomized to either 50.4 Gy over 28 fractions with concurrent weekly Gemcitabine vs SBRT to a total dose of 25.35 Gy over 5 fractions. The primary endpoint of the study is pathologic node positivity. We hypothesize that patients treated with neoadjuvant chemotherapy followed by conventionally fractionated chemo-RT will have a lower rate of pathologic node positivity as compared to those patients treated with neo-adjuvant chemotherapy followed by SBRT. Secondary endpoints include patient reported quality of life, local recurrence, primary tumor pathologic response, margin status, surgical complications, MR based treatment response, and overall survival. We anticipate a node positivity rate of 37% when using preoperative chemotherapy followed by conventionally fractionated concurrent chemo-RT. We designed this trial to examine differences between pre-op RT dose and fractionation schedules. Methods: This study is a prospective, randomized, two-arm, phase II clinical trial. Eligible patients must have cytologically confirmed PC and be deemed suitable for surgical resection with resectable, borderline-resectable, or locally advanced type A pancreatic adenocarcinoma. First Author: William Adrian Hall, Medical College of Wisconsin, Milwaukee, WI

**Background:** There is growing consensus for the use of neoadjuvant therapy in patients with potentially operable pancreatic adenocarcinoma (PC). However, there is no consensus on the type and duration of chemotherapy or radiation therapy (RT) in the preoperative setting. Stereotactic body radiation therapy (SBRT) has gained popularity despite the absence of prospective data for its use in the preoperative setting. Furthermore, SBRT preoperatively has not been standardized. At present, there exists no randomized data comparing preoperative SBRT with conventionally fractionated concurrent chemo-RT. We designed this trial to examine differences between pre-op RT dose and fractionation schedules. Methods: This study is a prospective, randomized, two-arm, phase II clinical trial. Eligible patients must have cytologically confirmed PC and be deemed suitable for surgical resection with resectable, borderline-resectable, or locally advanced type A pancreatic adenocarcinoma. First Author: William Adrian Hall, Medical College of Wisconsin, Milwaukee, WI
Niraparib in metastatic pancreatic cancer after previous chemotherapy (NIRA-PANC): A phase 2 trial. First Author: Anup Kasi, University of Kansas Cancer Center, Westwood, KS

**Background:** Attempts to improve therapy for patients with pancreatic adenocarcinoma with traditional chemotherapy have largely failed to meaningfully improve survival. Therefore, there is a critical need for identification of specific molecular changes that define prognosis and potentially guide therapy decisions. Defective DNA damage response pathways in pancreatic cancer represent a targeted opportunity for treatment. PARP inhibitors exert activity in tumor cells that may not be effectively able to repair initially single-stranded and cumulatively double-stranded DNA breaks and can have a heightened susceptibility in tumor cells over normal tissue. This concept is referred to as synthetic lethality. Niraparib is an orally available, potent, highly selective PARP-1 and -2 inhibitor. We are studying the efficacy of Niraparib in pancreatic cancer patients that harbor DNA repair defects.

**Methods:** This study is funded by a research grant from TESARO. Pre-screening of patients to find biomarker positive patients is funded by KU Cancer Center. This is a phase II open label single arm trial in metastatic pancreatic cancer patients with germline or somatic mutations, either already known, or tested after consent to pre-screening tumor tissue analysis in BRCA1/2, PALB2, ATM, NBN, ATR, BRRP1, IDH1/2, RAD51, RAD51B/C/D, RAD54L, CDK12, BARD1, FAM175A, BAP1, CHEK1/2, GEN1, MRE11A, XRCC2, SHFM1, FANCD2, FANCA, FANCC, FANCG, RPA1, ARID1A. Patients are being treated with Niraparib 300mg or 200mg by mouth daily for 28 days (1 cycle = 28 days) (200mg dose is for participants whose baseline weight is < 77 kg [169.756 lbs] or baseline platelet count is < 150,000 μL). The primary objective is to assess antitumor efficacy of niraparib using Objective Response Rate per RECIST 1.1. Secondary objectives include PFS, OS, DCR, DOR, and safety. Eligible patients received > 1 line of therapy, no prior PARP inhibitor(s), have measurable disease, and ECOG PS 0-1. Accrual target enrollment of 18 patients over a period of 24 months with a study duration of 30 months. Correlative studies include assessment of pharmacokinetics, circulating tumor cells and storing samples for future research. The trial is currently enrolling. Clinical trial information: NCT03553004.
4500 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for metastatic renal cell carcinoma (mRCC): Outcomes in the combined IMDC intermediate/poor risk and sarcomatoid subgroups of the KEYNOTE-426 study. First Author: Brian I. Rini, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Background: In KEYNOTE-426, pembro + axi significantly improved OS (HR 0.53, P < .0001), PFS (HR 0.69, P = .0001), and ORR (59.3% vs 35.7%, P < .0001) vs sunitinib and had manageable toxicity as first-line therapy for mRCC (NCT02853331). The pembro + axi benefit was observed across all IMDC risk groups and regardless of PD-L1 expression. We present data for the combined intermediate/poor risk group and for patients (pts) with sarcomatoid features. Methods: 861 eligible pts with clear-cell mRCC, no prior systemic therapy for mRCC, and PFS ≥ 70 were randomized 1:1 to pembro 200 mg IV Q3W for a maximum of 35 cycles plus axi 5 mg orally BID (N = 432) or sunitinib 50 mg orally QD (4 wk on/2 wk off) (N = 429). Primary endpoints were OS and PFS (RECIST v1.1 by blinded, independent central review [BICR]). ORR (RECIST v1.1 by BICR) was the key secondary endpoint. The intermediate/poor risk group was prespecified; the sarcomatoid group was exploratory. HRs and their 95% CIs were calculated with a Cox proportional hazards model. None of the analyses were multiplicity-corrected. Results: 592 (68%) of all randomized pts were of IMDC intermediate/poor risk — 294 in the pembro + axi arm, 298 in the sunitinib arm. Pembro + axi improved OS (HR 0.52, 95% CI 0.37-0.74; 12-mo rate 87.3% vs 71.3%), PFS (HR 0.67, 95% CI 0.53-0.85; median 12.6 vs 8.2 mo), and ORR (55.8% vs 95% CI 49.9-61.5) vs 29.5% (24.4-35.1) in pts with intermediate/poor risk; CR rates were 4.8% (95% CI 2.6-7.9) vs 0.7% (0.1-2.4). Of the 578 pts with known status, 105 (18.2%) had sarcomatoid features — 51 in the pembro + axi arm, 54 in the sunitinib arm. Pembro + axi improved OS (HR 0.58, 95% CI 0.21-1.59; 12-mo rate 83.4% vs 79.5%), PFS (HR 0.54, 95% CI 0.29-1.00; median not reached vs 8.4 mo) and ORR (58.8% vs 95% CI 44.2-70.7) in pts with sarcomatoid features; CR rates were 11.8% (95% CI 4.4-23.9) vs 0% (0.0-6.6). Conclusions: Pembro + axi provides benefit in the combined population of pts with IMDC intermediate or poor risk and in pts whose tumors had sarcomatoid features. The observed benefits were consistent with those seen in the total population. Clinical trial information: NCT02853331.

4502 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Randomized, double-blind phase III study of pazopanib versus placebo in patients with metastatic renal cell carcinoma who have no evidence of disease after metastasectomy: A trial of the ECOG-ACRIN cancer research group (E2810). First Author: Leonard Joseph Appleman, UPMC Hillman Cancer Center, Pittsburgh, PA

Background: Patients with no evidence of disease (NED) after metastasectomy for metastatic renal cell carcinoma (mRCC) are at high risk of recurrence, but no systemic therapy has been shown to benefit this population. Pazopanib is an inhibitor of VEGFR and other kinases that improves progression-free survival in patients with measurable RCC metastatic disease. We performed a randomized, double-blind, placebo-controlled multicenter study to test the hypothesis that pazopanib would improve disease-free survival in patients with mRCC rendered NED after metastasectomy. Methods: Patients with NED following metastasectomy were randomized 1:1 to receive pazopanib starting at 800 mg daily vs placebo for 52 weeks. Patients were stratified by 1 vs > 1 site of resected disease, and by disease-free interval ≤ vs > 1 year. Clinical assessment for toxicity and patient-reported outcomes were performed every 4 weeks, and restaging scans every 12 weeks. The study was designed to observe a 42% improvement in disease-free survival (DFS) from 25% to 45% at 3 years. Results: From August 2012 to July 2017, 129 patients were enrolled. The study was unblinded after 83 DFS events had been observed (92% information). The median follow-up from randomization was 30 months (range 0.4 – 66.5 months). The study did not meet the primary endpoint: hazard ratio (95% CI) for DFS was 0.85 (0.55, 1.31) (p = 0.47) in favor of pazopanib. At the time of unblinding, 22/129 (17%) of subjects had died. The HR for overall survival (OS) was 2.65 (1.02, 6.9) in favor of placebo (p = 0.05). Patient-reported outcomes and laboratory correlates will be reported separately. Conclusions: 52 weeks of pazopanib did not improve DFS compared to blinded placebo in patients with mRCC who were NED after metastasectomy. There was a trend toward worse PFS in pazopanib vs placebo. Clinical trial information: NCT01575548.

4503 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

CALGB 90601 (Alliance): Randomized, double-blind, placebo-controlled phase III trial comparing gemcitabine and bevacizumab or placebo in patients with metastatic urothelial carcinoma. First Author: Jonathan E. Rosenberg, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The combination of gemcitabine (G) and cisplatin (C) is a standard therapy for metastatic urothelial carcinoma (mUC). Based on data that angiogenesis plays a role in UC growth and progression, a randomized placebo-controlled trial was performed. Methods: Patients mUC, no prior chemotherapy for metastatic disease and ≥12 months from prior (neo) adjuvant chemotherapy and ECOG PS 0-1 were randomized 1:1 to G 1000 mg/m² IV days 1 and 8 and C 70 mg/m² day 1 with bevacizumab (GCB) 15 mg/kg IV or placebo (GCP) day 1 every 21 days. Randomization was stratified by the presence of visceral metastases and prior chemotherapy. The primary endpoint was overall survival (OS) defined as the time from randomization to death or last follow-up (FU). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and ≥ 3 grade toxicity. With 445 deaths, the log-rank test had an 87% power to detect a hazard ratio (HR) of 0.74 with a 2-sided α=0.05. The primary analysis was based on the stratified log-rank test adjusting on stratification factors. Alliance Data Safety and Monitoring Board approved the final OS analysis be performed at 420 events due to lower than expected event rates. Results: 506 patients were randomly assigned (252 GCB, 254 GCP) stratified by the presence of visceral disease and prior chemotherapy for UC. The median FU for patients still alive was 46.2 months. Median OS was 14.5 months for patients treated with GCB and 14.3 months for patients treated with GCP with a HR of 0.87 (95%CI 0.72-1.06; 2-sided Wald p=0.17). The HR for PFS was 0.77 (95%CI 0.63-0.93) in favor of GCB (p=0.0074). Grade 3 or greater adverse event rate was 83.5% with GCB compared to 80.7% with GCP. Conclusions: The addition of bevacizumab to GC chemotherapy did not result in improved OS (primary endpoint) in patients with mUC but there was a PFS improvement. The observed median OS of about 14 months is consistent with prior phase III trials of cisplatin-based chemotherapy. Support: U10CA180821, U10CA180882, U10CA180820, U10CA180853, U10CA180888, Genentech. https://acknowledgments.alliancefound.org. Clinical trial information: NCT00942331.
Response to 1st line chemotherapy

<table>
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<tr>
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<th>Placebo (N=52)</th>
<th>Pembro (N=55)</th>
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<tr>
<td>CR/PR</td>
<td>32 (62%)</td>
<td>39 (71%)</td>
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<tr>
<td>SD</td>
<td>20 (38%)</td>
<td>16 (29%)</td>
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**Background:** Platinum-based chemotherapy for 1st-line treatment of pts with metastatic urothelial cancer (mUC) is typically administered for a fixed duration followed by observation until recurrence. PD-1 blockade with pembrolizumab improves survival of pts with mUC progressing despite platinum-based chemotherapy. We explored the potential benefit of earlier use of PD-1 blockade using a “switch maintenance” approach.

**Methods:** Pts with mUC achieving at least stable disease after up to 8 cycles of 1st-line platinum-based chemotherapy were enrolled. Pts were randomized 1:1 to pembrolizumab 200 mg IV q3 weeks versus placebo for up to 24 months; pts progressing on placebo could cross over to pembrolizumab. Randomization was stratified based on pre-chemotherapy visceral metastases (Y/N) and response to 1st-line chemotherapy (CR/PR vs. SD). The primary objective was to determine the progression-free survival (PFS) as per irRECIST among pts treated with placebo vs pembrolizumab.

**Results:** Between 12/2015 and 11/2017, 107 pts were randomized to placebo (n=52) versus pembrolizumab (n=55). The baseline pt characteristics are shown in the Table. Pts randomized to placebo and pembrolizumab received a median of 6 and 8 cycles, respectively. Excluding pts with baseline <p value=0.05| evaluable pts on placebo and 25% (104/416) on pembrolizumab. Grade 3-4 treatment emergent adverse events occurred in 48% of pts on placebo and 56% on pembrolizumab. PFS was significantly longer in patients randomized to pembrolizumab versus placebo (Maximum Efficiency vs. Clinical Setting).

**Conclusions:** Switch maintenance pembrolizumab prolongs PFS in pts with mUC completing 1st-line platinum-based chemotherapy. Clinical trial information: NCT02550012.

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**5056 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**SWOG S1314: A randomized phase II study of co-expression extrapolation (COXEN) with neoadjuvant chemotherapy for localized, muscle-invasive bladder cancer.** First Author: Thomas W. Flagg, Division of Medical Oncology, School of Medicine, University of Colorado, Aurora, CO

**Background:** Both dose-dense Methotrexate-Vinblastine-Adriamycin/doxorubicin-Cisplatin (ddMVAC) and Gemcitabine-Cisplatin (GC) are accepted neoadjuvant agents for muscle-invasive bladder cancer (BC). We investigated COXEN, a gene expression extrapolation model, as a predictive biomarker. Most pts enrolled had Stage cT2-cT4a N0 M0, urothelial BC (histology allowed), >5 mm of viable tumor, Cisplatin eligible, with plan for cystectomy. 237 patients were randomized between ddMVAC, given every 14 days for 4 cycles, and GC, given every 21 days for 4 cycles. The primary objective was to assess whether the pre-specified dichotomous treatment-specific COXEN gene expression profile is prognostic of pT0 rate or ≤ pT1 at surgery, and to assess whether COXEN score is a predictive factor between regimes and response. Logistic regression was used to model response, adjusting for stratification factors. **Results:** 167 patients were included; the ddMVAC/GC arms had a median age of 65.84, PS = 0 in 80%75%, Male proportion of 88%79% and T2 stage of 87%92%. All had at least 3 cycles of chemo and surgery/progression within 100 days of last chemo. There were favorable COXEN ddMVAC scores in 32% and GC score in 26%. The pT0 rates for ddMVAC and GC were 32% and 35%; the rates of ≤ pT1 were 55% and 49%, respectively. **Conclusion:** The COXEN scores were not significantly prognostic for response in their individual arms; The COXEN GC score was significant predictor for downstaging in pooled arms. There was no evidence of an interaction between COXEN score and regimen in predicting response. The prospective data and samples from this study will allow for further development of COXEN and other predictive biomarkers. Clinical trial information: NCT02177695.

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Infigratinib (BGJ398) is a potent and selective FGFR1 inhibitor with significant activity in patients (pts) with advanced or metastatic urothelial carcinoma (mUC) bearing FGFR3 mutations or fusions (M/F), which may result in lower sensitivity with an encouraging ORR and prolonged PFS in the WT cohort; greater than 1 prior line of chemotherapy or recurrence within 12 months of (neo)adjuvant chemotherapy, measurable disease and baseline, most patients (37/43) had visceral metastasis. Fourteen (32.6%) patients had received at least 1 line of prior chemo and 60% had Bellmunt scores of 3. Results: Patient enrollment for this study was completed in November 2018. A total of 43 patients were enrolled, with a median age of 64 years old. At baseline, most patients (37/43) had visceral metastasis. Fourteen (32.6%) patients had received >2 lines treatment and 8 (18.6%) patients had prior immune checkpoint inhibitor (CPI) therapy in second line treatment. The objective response rate was 60.5% (95% CI: 44.4%, 75.0%) and the DCR was 90.7% (39/43). As of Jan 23, 2019, the median PFS for the overall study population was not yet reached, and the median PFS was 7.8 months (95% CI: 4.9, 10.7) for the 9 patients (5.8%) who received RC48-ADC (arm A) compared with 7.1 months (95% CI: 4.1, 10.7) for the patients who received sunitinib alone (arm B). The ORR was 70.6% (12/17) in patients with HER2 FISH+ or IHC3+. The ORR was 64.3% in patients post to 2 lines treatment and 75.0% in patients post to immunotherapy. Common treatment-related AEs of any grade in arm A were 94.1% with fatigue (51.2%), neutropenia (41.9%), neuropenia (37.2%), fatigue (34.9%), ALT increase (32.6%), and AST increase (32.6%); Most were Grade 1 or 2. Conclusions: RC48-ADC has demonstrated a clinically meaningful ORR of 60.5% in pretreated HER-2 positive mUC patients including those who underwent failure to the immunotherapy. Clinical trial information: NCT03507166.
4512 Poster Discussion Session: Displayed in Poster Session (Board #338), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Atezolizumab (atezo) + bevacizumab (bev) versus sunitinib (sun) in pts with untreated metastatic renal cell carcinoma (mRCC) and sarcomatoid (sarc) histology: IMmotion151 subgroup analysis. First Author: Brian I. Rini, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Background: In the Phase 3 IMmotion151 trial, atezo + bev showed improved PFS vs sun in untreated mRCC pts expressing PD-L1. Here we report results of a pre-specified subgroup analysis in pts whose tumors have sarcom histology, an independent predictor of poor survival. Methods: Pts were randomized to receive atezo 1200 mg IV q3w + bev or sun 15 mg/kg IV q3w or sun 50 mg po qd for 4 wk on, 2 wk off. Co-primary endpoints were reported previously (Motzer ASCO GU 2018). Secondary endpoints included iv-I/P-TTs and PFS in atezo + bev vs sun and atezo vs sun. Grade 3-4 AEs were reported.

Results: 142 randomized pts (16%) from IMmotion151 had tumors with any component of sarc histology; mPFS was 8.3 vs 5.3 mo with atezo + bev vs sun and mOS was NR vs 15.0 mo, respectively (see Table for PD-L1+). ORR was 49% vs 14% and CR rate was 10% vs 3% in the atezo + bev vs sun arms. Grade 3-4 AEs occurred in 27 pts (40%) with atezo + bev and 34 (49%) with sun. Using the MDASI scale, sarc pts reported longer median time to deterioration (TDD) of symptom interference with daily activities with atezo + bev vs sun (11.3 vs 4.9 mo). Prevalence of Angiogenesis High gene expression (GE) signature subset was lower (34% vs 65%) and T-effect® GE subset was higher (54% vs 40%) in sarc vs non-sarc tumors. PD-L1+ disease was more common in sarc vs non-sarc tumors (63% vs 39%). Conclusions: mRCC pts with sarc histology had longer OS and PFS and a higher ORR/CR rate when treated with atezo + bev vs sun, regardless of PD-L1 status. Biomarker data support a biological correlate for the increased responsiveness to atezo + bev in sarc pts. Clinical trial information: NCT02420821.

4513 Poster Discussion Session: Displayed in Poster Session (Board #339), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

CheckMate 214 post-hoc analyses of nivolumab plus ipilimumab or sunitinib in IMDC intermediate/poor-risk patients with previously untreated advanced renal cell carcinoma with sarcomatoid features. First Author: David F. McDermott, Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA

Background: Pts (pts) with advanced renal cell carcinoma with sarcomatoid features (sRCC) have poor prognosis and suboptimal outcomes with anti-VEGF targeted therapy. Nivolumab plus ipilimumab (N+I) demonstrated superior objective response rate (ORR) and overall survival (OS) vs sunitinib (S) in previously untreated pts with International Metastatic RCC Database Consortium (IMDC) intermediate/poor (Ip)-risk, clear-cell, advanced RCC in the phase 3 CheckMate 214 trial. Methods: We performed a post-hoc exploratory analysis of N vs S in CheckMate 214 sRCC pts. The presence of sarcomatoid features was assessed by keyword search for “sarco-matoid” in pts with available local pathology reports accompanying pretreatment tumor samples. Results: 842 (77%) of 1096 included pts had clear-cell sarcomatoid RCC (N+I, 60; S, n = 58). Baseline characteristics of sRCC pts were balanced between arms. Notably, 47% vs 53% of Ip-risk sRCC pts in the N+I and S arms had tumor PD-L1 expression ≥ 1% at baseline, which was higher than in all Ip-risk pts (N+I, 26% vs S, 29%). In descriptive analyses performed at a minimum follow-up of 30 months, confirmed ORR and complete response rate per investigator (RECIST v1.1), OS, and progression-free survival (PFS) per investigator were improved with N+I vs S in Ip-risk pts with sRCC (Table). No new safety signals were seen in sRCC pts. Conclusions: In this post-hoc descriptive subgroup analysis of CheckMate 214, N+I demonstrated promising efficacy and prolonged survival vs S, with consistent safety, in previously untreated, Ip-risk, advanced clear-cell RCC with sarcomatoid features. Prognostic studies of N+I that include pts with sRCC are ongoing. Clinical trial information: NCT02317493.

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Genitourinary (Nonprostate) Cancer 267s
4516 Poster Discussion Session; Displayed in Poster Session (Board #342), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Active surveillance in metastatic renal cell carcinoma (mRCC): Results from the Canadian Kidney Cancer Information system (CKCis). First Author: Igal Kushnir, Ottawa Hospital Cancer Centre, Ottawa, ON, Canada

**Background:** Active surveillance (AS) is a commonly used strategy in patients (pts) with low tumor burden or slow growing disease. However, few studies have assessed AS for mRCC compared to immediate treatment. We aimed to assess the outcomes and safety of AS in comparison to immediate systemic treatment for mRCC pts. **Methods:** Using CKCis, mRCC pts diagnosed between January 1, 2011 and December 31, 2016 were identified. AS strategy was defined as: (1) start of systemic therapy ≥ 6 months after diagnosis of mRCC; or (2) never receiving systemic therapy for mRCC with an overall survival (OS) ≥ 1 yr (OS ≥ 1 yr is a surrogate to exclude pts not started on treatment due to poor prognosis). Pts starting systemic treatment < 6 months after diagnosis of mRCC were defined as receiving immediate systemic treatment.

**OS and time until 1st line treatment failure (TTF) between the two cohorts were compared. Results:** A total of 863 pts met criteria for AS (cohort A). Of these, 370 started treatment ≥ 6 months after their initial diagnosis (cohort A1) and 493 never received systemic treatment and were alive for ≥ 1 year (cohort A2). 848 pts received immediate systemic treatment (cohort B). Median age for pts in cohort A and B was 65.1 (19.0-91.5) vs. 62.2 yrs (23.1-87.1) (p < 0.0001). Sex distribution was not statistically different. Pts in cohort A had fewer sites of metastatic disease vs. cohort B (0.4 vs. 0.7; p < 0.0001). Median number of cycles of systemic treatment in cohort B (P = 0.0001). Five-year OS probability was significantly greater for cohort A than for cohort B (70.2% vs. 32.1%; P < 0.0001). After adjusting for IMDC risk criteria and age, both OS (HR 0.46, 0.38-0.56, P < 0.0001) and TTF (HR 0.79, 0.69-0.92, P = 0.0021) were greater in cohort A than in cohort B. For cohort A1 the median time AS was 1.4 months (range 1-8) and median follow-up was 3.6 (0.3-8.8) months. 13 patients had undergone at least one scan; ORR was 31% (4/13, 80%CI: 14-52%), Median number of cycles of ipilimumab plus nivolumab received was 6.47 months, grade 3-4 IMAEs within 100 days of last dose were reported in 6.4% of pts. The safety and efficacy of AS in mRCC to date, our data suggest that a subset of pts may be safely observed without immediate initiation of systemic therapy. Prospective validation is required in the contemporary immunotherapy era.

4518 Poster Discussion Session; Displayed in Poster Session (Board #344), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Phase II study of nivolumab and ipilimumab for advanced bladder cancer of variant histiogtis (BCVH). First Author: Bradley Alexander McGregor, Dana-Farber Cancer Institute, Boston, MA

**Background:** Patients with BCVH have poor outcomes and data regarding the management of this heterogeneous group of patients is limited. Nivolumab and ipilimumab has demonstrated safety and efficacy in urothelial carcinoma and other malignancies. In this multicenter, single-arm, multi-cohort phase II trial we evaluate the efficacy of nivolumab and ipilimumab in patients with BCVH and other advanced rare genitourinary cancers (NCT 03333616). Herein, we report the preliminary results of the fully accrued BCVH cohort. **Methods:** Eligible patients had metastatic BCVH, ECOG performance status of 0-2, and were either untreated or had received any prior therapy excluding prior immunotherapy. Patients were treated with nivolumab 3 mg/kg and ipilimumab 1 mg/kg intravenously every 3 weeks for 4 cycles with continued maintenance of NIVO 480 mg every 4 weeks. The primary endpoint was overall response rate (ORR) by RECIST 1.1. **Results:** 19 BCVH patients were enrolled at 4 institutions between 4/2018 and 1/2019: squamous cell (n = 6), small cell (n = 3), adenocarcinoma (n = 3), urachal (n = 5), plasmacytoid (n = 1), and spindle cell (n = 1). 13 (68%) patients had prior systemic therapy including platinum-based chemotherapy in 92% patients. Median number of cycles of ipilimumab plus nivolumab received was 1.4 months (range 1-8) and median follow-up was 3.6 (0.3-8.8) months. 13 patients had undergone at least one scan; ORR was 31% (4/13, 80% CI: 14-52%), with partial responses seen in small cell carcinoma (n = 2), urachal (n = 1) and a complete response in 1 patient with plasmacytoid carcinoma. 3 patients (16%) developed treatment-related grade 3 toxicities with 1 (5%) grade 4 toxicity. **Conclusions:** Nivolumab and ipilimumab resulted in objective responses in a subset of patients with BCVH with manageable toxicities. Updated clinical and correlative data will be presented. This combination may be a promising further therapeutic option for patients with BCVH, who currently have substantial unmet needs. Clinical trial information: NCT 03333616.

4517 Poster Discussion Session; Displayed in Poster Session (Board #343), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Safety and efficacy of nivolumab plus ipilimumab (NIVO+IPI) in patients with advanced renal cell carcinoma (aRCC) with brain metastases: Interim analysis of CheckMate 920. First Author: Hamid Emanemakou, University of Wisconsin School of Medicine and Public Health, Madison, WI

**Background:** Previous clinical trials of patients (pts) with aRCC, including CheckMate 214, have mostly excluded pts with brain metastases. However, antitumor activity in pts with brain metastases has been observed in pts with melanoma treated with NIVO 1 mg/kg + IPI 3mg/kg and pts with non-small cell lung cancer treated with NIVO 240 mg + IPI 1mg/kg. CheckMate 920 is an ongoing, phase 3b/4 clinical trial of NIVO + IPI treatment in pts with aRCC with a high unmet medical need. Here, we present the safety and efficacy interim results for the cohort of pts with brain metastases. **Methods:** Pts with previously untreated aRCC of any histology, with asymptomatic brain metastases (not on corticosteroids or receiving radiation), and Karnofsky performance status ≥ 70% were assigned to treatment with NIVO 3 mg/kg + IPI 1 mg/kg every 3 weeks for 4 doses, followed by NIVO 480 mg every 4 weeks. Pts were treated until disease progression, unacceptable toxicity, or for a maximum of 2 years. The primary endpoint was the incidence of high-grade immune-mediated adverse events (IMAEs). Key secondary endpoints included progression-free survival (PFS) and objective response rate (ORR) by RECIST v1.1. **Results:** Overall, 28 pts were enrolled in the brain metastases cohort. With a median follow-up of 6.47 months, grade 3-4 IMAEs within 100 days of last dose were reported in 6.4% of pts. The 3-4 grade IMAEs observed in ≥ 1 patient were diarrhea, colitis, diabetic ketoacidosis, immune-mediated hepatitis, hypophysitis, and rash of any type (n = 1 each). No treatment-related grade 5 IMAEs were reported. ORR by RECIST v1.1 per investigator in all treated subjects is 28.6% (95% CI 13.2-48.7). Median PFS in all treated subjects was 9.0 months (95% CI 2.9- not estimable (NE)). Median OS has not been reached (95% CI 13.1–NE). **Conclusions:** In pts with aRCC and brain metastases who are often excluded from clinical trials, NIVO + IPI treatment showed a safety profile consistent with previous reports of this dosing regimen, with encouraging antitumor activity. Clinical trial information: NCT02982954.

4519 Poster Discussion Session; Displayed in Poster Session (Board #345), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Clinical outcomes according to PD-L1 status and age in the prospective international SAUL study of atezolizumab (atezo) for locally advanced or metastatic urothelial carcinoma (UC) or non-UC of the urinary tract. First Author: Cara N. Stenberg, Weill Cornell Medicine, New York, NY

**Background:** Atezo, a monoclonal antibody targeting PD-L1, is an approved therapy for locally advanced/metastatic UC based on IMvigor210 and IMvigor212 phase II and III trials. The single-arm SAUL study (NCT02928406), with a broader patient (pt) population demonstrated median overall survival (OS) of 8.7 months and a safety profile consistent with previous atezo trials. **Methods:** Pts with locally advanced/metastatic UC or non-UC of the urinary tract received atezo 1200 mg every 3 weeks until disease progression or unacceptable toxicity. Populations excluded from IMvigor211 (renal impairment, ECOG PS 2, treated asymptomatic CNS metastases, stable controlled autoimmune disease, comitant steroids, HIV positive, non-UC) were eligible. The primary endpoint was safety; OS and overall response rate (ORR) were secondary endpoints. Predefined subgroup analyses included outcomes according to PD-L1 status (VENTANA SP142) and age in the overall population (and in the IMvigor211-like subgroup for PD-L1). **Results:** Between Nov 2016 and Mar 2018, 1004 pts were enrolled; 997 received atezo. Efficacy is summarized below. Incidences of grade ≥ 3 treatment-related adverse events were similar irrespective of PD-L1 status (overall IC ≥ 1/3 vs. 2/3: 11% vs 16% IMvigor211-like IC ≥ 1/3 vs 2/3: 11% vs 15%) and age (≥ 65 y: 13%; ≤ 75 y: 12%; ≥ 80 y: 10%). **Conclusions:** OS and ORR appear more favorable in IC 2/3 vs IC 0/1 subgroups (overall and in the IMvigor211-like population). Atezo was effective and well tolerated across subgroups including elderly pts. Clinical trial information: NCT02984046.
Correlation of methylthioadenosine phosphorylase (MTAP) loss with response to anti-folate therapy in urothelial bladder carcinoma (UBC). First Author: Omar Alhalabi, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The MTAP gene encodes an essential enzyme for the salvage pathway of nucleotide synthesis and is frequently deleted in UBC. Anti-folate agents such as pemetrexed can effectively inhibit the de novo pathway of nucleotide synthesis and as a result, create a synthetic lethality in MTAP deficient UBC. We hypothesize that MTAP gene loss correlates with enhanced response to pembrolizumab (Pemb) in UBC patients.

Methods: We investigated MTAP gene deletion rates in the TCGA database and determined MTAP protein loss rates by immunohistochemistry (IHC) using a UBC tissue microarray (TMA) from 151 patients (pts). We then performed in vitro and in vivo studies using MTAP proficient and MTAP deficient bladder cancer cell lines. At the clinical level, we performed a retrospective analysis based on MTAP status of pts treated with pemetrexed as 2nd line at our institution between 2014 and 2018. We are now performing a retrospective analysis based on MTAP status of pts treated with pembrolizumab (Pemb) who had MTAP loss.

Results: The frequency of MTAP deletion in TCGA was 25.9% by IHC and 27.8% by NanoString (NS) technology. In 55% of 59 UTUC and 27% of 92 MIBC specimens, MTAP deficiency was confirmed by NS. 11% of the 29 patients (pts) with MTAP deletion responded to Pemb whereas 35% of the 62 pts with MTAP proficient UBC responded to Pemb. Of the 6 pts enrolled on the clinical trial, 3 (50%) had complete response whereas only 1 of 8 (12.5%) MTAP proficient UBC pts responded. Of the 6 pts enrolled on the clinical trial, 3 (50%) had complete response whereas only 1 of 8 (12.5%) MTAP proficient UBC pts responded. Of the 6 pts enrolled on the clinical trial, 3 (50%) had complete response whereas only 1 of 8 (12.5%) MTAP proficient UBC pts responded.

Conclusions: Our clinical and clinical data demonstrate that MTAP loss in UBC leads to a state of synthetic lethality when treated with Pemb and should be further investigated as a novel biomarker to predict response to anti-folate agents.

Circulating cell-free DNA (cfDNA) levels and fragmentation pattern can distinguish nonsmall cell lung cancer (NSCLC) from small cell lung cancer (SCLC). First Author: Jaleh Falahal, Cleveland Clinic Foundation, Cleveland, OH

Background: Occult MI and met BC may be under-staged. Circulating cfDNA may be a dynamic, low-cost and minimally invasive biomarker. We evaluated correlations between total circulating cfDNA and presence of MIBC and met BC. We hypothesized that the relative abundance of circulating low molecular weight cfDNA would correlate with BC stage. Methods: Peripheral blood from pts with BC was collected in Streck BCT tubes and processed to obtain cfDNA extract. Total cfDNA quantity (ng/ml) was assessed by fluorometry. cfDNA fragment size was measured by Bioanalyzer DNA analysis. Wilcoxon rank sum test and Fisher’s Exact test were used to compare cfDNA quantity and fragmentation pattern among pts with NMIBC, MIBC, met BC.

Results: Blood was obtained from 58 pts with BC (20% women, 34% never smokers, median age 71 (29-89). There was no significant difference in cfDNA between MIBC and met BC, however, it was significantly lower in pts with NMIBC vs MIBC and met BC (table). The concentration of low molecular weight fragments (LMW-frags) (100 – 400) base pairs and the ratio of LMW-frags to cfDNA were significantly different between pts with NGIBC and pts with MIBC or met BC (table). Using median values as the cutoff, there was a significantly higher proportion of pts with cfDNA > 7 ng/ml and LMW-frags > 1.6 ng/ml, in MIBC & met BC vs NMIBC (p < 0.001). The % of pts with LMW-frags to cfDNA > 30%, was significantly different among NMIBC, MIBC and met BC groups: 16%, 53%, 78%, respectively (p < 0.001). Conclusions: This exploratory study suggests that cfDNA levels may correlate with BC stage. Measuring the relative abundance of LMW-frags with the expected size of cfDNA can enhance the specificity of cfDNA analysis for distinction between MIBC and met BC. Future studies are needed to confirm findings and define the optimal cutoffs for the diagnosis of BC stage.

Nivolumab monotherapy in patients with advanced platinum-resistant urothelial carcinoma: Efficacy and safety update from CheckMate 275. First Author: Arlene O. Siefker-Radtke, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: In the open-label, single-arm, phase 2 CheckMate 275 trial, objective response rate (ORR) for patients (pts) with metastatic urothelial carcinoma (mUC) with nivolumab (NIVO) was 20.4% with minimum follow-up of 21.3 mo. Here, we report updated efficacy and safety data with minimum follow-up of 33.7 mo. Methods: pts with platinum-resistant locally advanced or metastatic urothelial carcinoma received NIVO 3 mg/kg until disease progression or unacceptable toxicity. The primary endpoint was ORR by blinded independent review committee (BIRC) by RECIST v1.1 (including duration of response [DOR]). Secondary endpoints included progression-free survival (PFS) by BIRC, overall survival (OS), and ORR per investigator. Efficacy was evaluated in all treated pts and by tumor PD-L1 expression. Safety and PFS by investigator were exploratory endpoints.

Results: ORR by BIRC was 20.7% (95% CI 16.1–26.1) including 18 (7%) complete responses (CR; with 1 additional CR since the last report; Table). ORR per investigator was similar (24.8%). Median DOR by BIRC was 20.3 mo (95% CI 11.5–31.3). Of 56 pts with best overall response (BOR) of CR or partial response (PR), 59 had a DOR >12 mo. Median PFS (mPFS) was 1.9 mo per BIRC (95% CI 1.9–2.3; Table) and 2.0 mo per investigator (95% CI 1.9–2.5). Median OS (mOS) was 8.6 mo (95% CI 6.1–11.3; Table). 12, 24, and 36-mo OS rates were 40%, 30%, and 22%. While efficacy was numerically higher in pts with tumor PD-L1 expression >1%, efficacy was observed in all pts (Table). Any-grade treatment-related adverse events occurred in 69% of pts (grade 3–4, 25%), mostly (59%) within the first 3 mo of initiating therapy. Conclusions: With long-term follow-up from CheckMate 275, NIVO continues to provide durable antitumor activity in pts with mUC. No new safety signals were noted. Clinical trial information: NCT02387996.
Outcomes of patients (pts) with metastatic urothelial cancer (mUC) and poor performance status (PS) receiving anti-PDL1 agents. First Author: All Raza Khaki, University of Washington, Seattle, WA

Background: Anti-PDL1 immune checkpoint inhibitors (ICI) prolong overall survival (OS) after platinum chemotherapy in mUC. However, clinical outcomes in pts with poor PS at time of ICI initiation are unknown. We hypothesized that ICI initiation in pts with ECOG PS 2-3 would be associated with worse outcomes vs. pts with ECOG PS < 2, and impact death location.

Methods: A retrospective cohort study in 8 institutions identified pts with mUC who received ICI. Demographic, clinicopathologic, treatment (tx) patterns, response, and outcomes were collected. Primary endpoint: overall response rate (ORR). Secondary endpoints: median (m) OS in pts receiving ICI as 1L and 2L; odds of dying in hospital (vs elsewhere) for pts receiving ICI (vs no tx) within 30 days of death; and estimated drug cost for pts with ICI within 30 days of death based on average wholesale price. Unadjusted logistic regression was used to assess association between ORR and ECOG PS (2-3 vs < 2) andwald test was used to compare mOS between ECOG PS (2-3 vs < 2). Results: 194 consecutive pts (30% women, 41% never smokers, median age at diagnosis 69) treated with ICI for mUC were identified. Median number of tx lines was 2; all pts received >1 ICI line (6 pts received >3 ICI lines); 97, 79, 17 and 7 pts received ICI in 1L, 2L, 3L and 4L, respectively; 26% pts with ICI in 1L and 2L had ECOG PS 2-3. ORR and mOS are shown in table. Among 106 pts who died, 96 had available death location; of those, 8% received ICI within 30 days of death. Starting ICI within 30 days of death (vs no tx) was associated with better odds of hospital death (OR 2.6; 95% CI 1.0-6.8; P = 0.034). Median time to CR (range) was 2.0 (2-12), 3.5 (3-15) and 3.0 (3-12) mo, respectively. Median doses to first response (range) were 2 (17), 0 (30) and 8 (36) nIICI. Median atezo duration (range), mo was 3.5 (3-15), 1.0 (0-3) and 0.8 (0-2) for 1L, 2L and 3L, respectively. Median time to CR (range), mo was 2.0 (2-12), 2.0 (2-12) and 1.0 (0-3) for 1L, 2L and 3L, respectively. Estimated average ICI cost/pt within 30 days of death was $1400.58. Conclusions: Pts with ECOG PS 2-3 at time of ICI initiation had similar ORR vs ECOG PS < 2 but worse mOS. ICI initiation within 30 days from death was associated with higher likelihood of hospital death. ICI may not circumvent the negative prognostic role of poor PS, so biomarker-based pt selection is critical. Limitations include lack of adjustment for selection bias and other confounders at time of ICI initiation; data validation is ongoing.

4525 Poster Session (Board #351), Mon, 1:15 PM-4:15 PM

Durability of complete response (CR) with (atezolizumab (atezo)) or without (no ICI) anti-PD-L1 ICI therapy in patients (pts) with muscle invasive (MI) and metastatic (met) urothelial carcinoma (mUC). First Author: Yoann Loriot, Institut de Cancérolgie Gustave Roussy, Villejuif, France

Background: Atezo (anti-PD-L1) has been shown to elicit CRs in a number of mUC patients (pts) in clinical trials. We sought to describe the kinetics, durability and outcomes associated with these CRs in Ph I (PCD) and II (IMvigor210) atezolizumab atezo) studies, each with long-term follow-up. Methods: In PCD (pre-treated mUC) and IMvigor210 (Cohort 1, cisplatin-ineligible untreated mUC; Cohort 2, platinum-treated mUC), pts received atezo per protocol (Petrylak JAMA Oncol 2018; Balar Lancet 2017; Rosenberg Lancet 2016). This post hoc analysis descriptively assessed pt disposition, time to and duration of RECIST 1.1 response and overall survival in pts with CR. Results: CR rates were 13%, 8% and 7% in PCD, IMvigor210 Cohort 1 and Cohort 2, respectively. First response was PR in most pts with CR. Median CR duration was > 3 y in PCD, not estimable (NE) in IMvigor210 Cohort 1 and > 2 y in Cohort 2 (Table). At data cutoff, all but 2, 0 and 1 pts were alive, respectively; across studies, ≥40% of pts with CR were on treatment. CR pts had a first response (PRCR) by a median of 3.5 cycles. Further pt characteristics and survival outcomes will be reported. Conclusions: Across Ph III atezo mUC studies, CRs appeared durable (median duration > 2) despite small pt numbers. Most pts with CR were alive, with responses ongoing after long-term follow-up (median follow-up > 30 mo). Clinical trial information: NCT01375842, NCT02951767, NCT02108652.

4527 Poster Session (Board #353), Mon, 1:15 PM-4:15 PM

Association of cell-free DNA (cfDNA) levels with myeloid-suppressor derived circulating miRNA (MDSC) levels in blood of patients (pts) with muscle invasive (MI) and metastatic (met) bladder cancer (BC). First Author: Jaleh Fallah, Cleveland Clinic Foundation, Cleveland, OH

Background: cfDNA can be detected in healthy individuals but higher concentrations are present in pts with cancer. MDSC are immuno-suppressive cells that can be mobilized from bone marrow by tumor-related factors. Higher blood MDSC levels have been associated with worse outcomes in pts with solid tumors including BC. We assessed correlations between cfDNA and MDSC levels in pts with MIBC and met BC. Methods: Peripheral blood from pts with MIBC and met BC was collected in Streck BCT tubes and processed to obtain cf DNA acid extracts. Total cfDNA was determined by fluorometry. Cell-free DNA fragment size was measured by Bioanalyzer DNA analysis; 100-400 bp fragments (mono- and di-nucleosomal fragments linked to granulocytic processing of apoptotic and necrotic tumor cells) were detected. cfDNA levels were associated with worse survival and were negatively associated with total MDSC count in several studies. Here, we describe the largest analysis of Rw CPI use in mUC to date. Overall, this unadjusted descriptive analysis showed relative comparability of pt and tx characteristics and TTO among 3 Ls. Insights into Rw tx allow for an understanding of how clinical trial data translate to broader pt populations, including those with ECOG PS > 1, and may be useful for practitioners.

4526 Poster Session (Board #352), Mon, 1:15 PM-4:15 PM

4528 Poster Session (Board #354), Mon, 1:15 PM-4:15 PM

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4529 Poster Session (Board #355), Mon, 1:15 PM-4:15 PM
Molecular biomarker analysis and survival in patients (pts) with advanced urothelial cancer (UC) previously treated with chemotherapy. First Author: Bernadette Szabados, Beat Cancer Centre, Queen Mary University of London, United Kingdom
Background: The biomarkers PD-L1, FOXP3, and CD8 have been explored in pts with advanced UC who progressed after platinum-based chemotherapy (CTx). However, their relevance earlier in the disease process is less well understood. Methods: The Phase 2/3 LaMB study (NCT00949455) compared maintenance lapatinib vs placebo after first-line (1L) platinum-based CTx in pts with HER1/HER2-overexpressing stage IV advanced UC. Pre-CTx archival samples from this study were retrospectively analyzed and included both randomized and screen failure pts. PD-L1 expression was assessed (VENTANA SP263 Assay) and categorized as high (>25% of tumor cells [TC] and/or immune cells [IC]) or low/negative (<25% TC and IC). Overall survival (OS) and progression-free survival (PFS) were estimated via Kaplan-Meier method; results were stratified by PD-L1 expression. The exploratory biomarkers CD8 and FOXP3 were also analyzed. The prognostic significance of the biomarkers was explored by multivariable Cox proportional hazards models and a bootstrap method for model selection. Results: Of 446 pts (232 randomized; 214 screened), 243 (54.5%) were assessed for PD-L1 expression, with 61 (25.1%) PD-L1 high vs low/negative. In PD-L1 high and low/negative pts, 12.5 months (10.4 PD-L1 high and 15.5 PD-L1 low/negative) were associated with OS. PD-L1 expression was not associated with OS or PFS in univariate analysis or in multivariable models for OS (HR 1.4 [95% CI, 0.8–2.3]) and PFS (6.3 [3.5–8.8] vs 5.0 months [4.3–6.3]). PD-L1 expression was associated with OS in a univariate model for OS (HR 1.4 [95% CI, 0.8–2.3]). In a multivariable model for OS, PD-L1 expression improved accuracy of the model by 23% and was a significant variable (HR, 2.1 [95% CI, 1.2–3.5]). Results of analyses of CD8 and FOXP3 will also be reported. Conclusions: Overall, these data suggest a lack of association between PD-L1 expression and OS. Future platinum-based CTx. Mechanisms underlying the potential association of PD-L1 expression with OS still remain unclear. CD8 and FOXP3 exploratory analyses may help to elucidate these results. Clinical trial information: NCT00949455.

4531 Poster Session (Board #357), Mon, 1:15 PM-4:15 PM
Impact of immune-related adverse events on survival in patients with metastatic urothelial carcinoma treated with immune-checkpoint. First Author: Rafael Morales-Barrera, Vall d’Hebron Institute, Barcelona, Spain
Background: Immune-checkpoints inhibitors (ICIs) represents the standard of care for platinum-pretreated advanced urothelial cancer patients (pts). By enhancing T-cell activation, a unique spectrum of inflammatory side effects has emerged, also known as immune-related adverse events (irAEs). Data regarding the association between irAEs and pts outcomes are conflicting. Here we conducted a retrospective analysis to investigate the association between irAEs profile and disease outcome in metastatic urothelial carcinoma (mUC) pts. Methods: Medical records from pts with mUC included in clinical trials between July 2013 and June 2018 and treated with ICIs were reviewed. Pts previously treated with platinum-based chemotherapy or cisplatin-ineligible pts who had not been previously treated with chemo-therapy were included. Clinical responses were assessed as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to RECIST v1.1. Adverse events were graded based on NCI CTCAE v2.0. Key end point was survival (OS) from the date of irAE and follow-up was assessed. Results: From a total of 52 pts, 44 (84.6%) were treated withICI monotherapy and 8 (15.3%) in combination (anti-CTLA4 or targeted ther-apy). Median age was 65 years, 42 pts (80.8%) were male, 44 patients (84.6%) had ECOG PS 0–1, 14 pts (26.9%) had liver metastasis. Overall irAEs were observed in 30 pts (57.7%) and 10 pts (19.2%) developed grade 3/4 irAEs. Most common grade 3/4 irAEs were diarrhea (6.6%), rash (6.6%) and hepatitis (6.6%). Disease control rate (CR [26%]+PR [33%]+SD [20%]) was higher for patients with irAEs compared to those patients who did not developed irAEs (CR [13.6%]+PR[0%]+SD [22.7%]), this difference was statically significant (P = 0.002). Median OS was 11.23 mo (CI 95%, 3.6–18.70) for the overall cohort, while median OS was 21.91 mo for those patients with irAEs compared to 6.47 mo in patients who did not developed irAEs (HR 1.38, 95% CI 0.22 – 1.10, p = 0.008, and ≥moderate renal dysfunction (OR 0.20, 95% CI 0.08 – 0.51, p = 0.001) were associated with lower odds of SOC NAC. Non-SOC NAC was associated with higher BCSM (competing risk) and lower OS (KM) vs. IC and SOC NAC. On multivariable analysis, non-SOC NAC was associated with higher risk of BCSM (HR 1.35, 95% CI 1.06 – 1.72, p = 0.01) and lower OS (HR 1.38, 95% CI 1.11 – 1.70, p = 0.003) vs. SOC NAC. Conclusions: About 50% of pts receiving NAC were not treated with SOC regimens. Non-SOC NAC was associated with higher bladder cancer death risk. This stresses the role of SOC NAC ideally in a multidisciplinary expert setting, as well as the need for timely RC and neoadjuvant clinical trials, including cisplatin-ineligible pts.

4532 Poster Session (Board #358), Mon, 1:15 PM-4:15 PM
Increasing use of neo-adjuvant chemotherapy (NAC) in muscle-invasive bladder cancer (MIBC): Prognostic impact of non-standard of care (SOC) regimens. First Author: Yaw A. Nyame, Department of Urology, University of Washington Medical Center, Seattle, WA
Background: Cisplatin-based NAC can prolong overall survival (OS) in patients (pts) with MIBC. Utilization of NAC has increased to about 20% of pts with MIBC over the last decade. We evaluated NAC utilization with and without SOC cisplatin-based combination regimens and oncologic outcomes using registry data. Methods: This is a population-based analysis of linked SEER-Medicare data (2004-2011). We identified 4534 pts with MIBC (ct2-4NO-L1) undergoing radical cystectomy (RC). Based on pharmacy records data, pts were stratified into 3 groups: SOC, non-SOC, and immediate cystectomy (IC). We used de-scriptive statistics to compare groups, and multivariable logistic regression to define factors associated with receiving SOC NAC. Competing risk bladder-specific mortality (BCSM) incidence curves were generated and KM analysis was used to assess OS from time of RC. The impact of NAC on OS was evaluated with Cox regression analysis. Results: 694 (15.3%) pts received NAC, increasing from 1% in 2004 to 24.8% in 2011, with 345 (50%) receiving non-SOC, e.g. gemcitabine/carboplatin (49.3%), gemcitabine alone (21.2%), carboplatin alone (14.8%), cisplatin alone (8.4%), and methotrexate/vinblastine/ Adriamycin/carboplatin (0.8%). On logistic regression, increasing age (OR 0.91, 95% CI 0.88 – 0.94, p < 0.0001), Hispanic/Latino ethnicity (OR 0.49, 95% CI 0.22 – 1.10, p = 0.08) and ≥moderate renal dysfunction (OR 0.20, 95% CI 0.08 – 0.51, p = 0.001) were associated with lower odds of SOC NAC. Non-SOC NAC was associated with higher BCSM (competing risk) and lower OS (KM) vs. IC and SOC NAC. On multivariable analysis, non-SOC NAC was associated with higher risk of BCSM (HR 1.35, 95% CI 1.06 – 1.72, p = 0.01) and lower OS (HR 1.38, 95% CI 1.11 – 1.70, p = 0.003) vs. SOC NAC. Conclusions: About 50% of pts receiving NAC were not treated with SOC regimens. Non-SOC NAC was associated with higher bladder cancer death risk. This stresses the role of SOC NAC ideally in a multidisciplinary expert setting, as well as the need for timely RC and neoadjuvant clinical trials, including cisplatin-ineligible pts.
4533 Poster Session (Board #359), Mon, 1:15 PM-4:15 PM
Adenocarcinoma (ABC), uterine carcinosarcoma (UCS) and squamous cell carcinoma (SCCB) of the bladder: A Comprehensive Genomic Profiling (CGP) Study. First Author: Joseph Jacob, SUNY Upstate Medical University, Syracuse, NY

Background: We performed a CGP to compare the genomic alterations (GA) in ABC, UCS and SCCB. Methods: 143 cases of ABC, 2,142 cases of UCS and 83 cases of SCCB were subjected to CGP using a hybrid-capture based assay. Tumor mutational burden (TMB) was determined on 1.1 Mb of sequenced DNA and microsatellite instability (MSI) was determined on 14 loci. PD-L1 expression was determined by IHC. Results: ABC patients were younger and more often female than UCS and SCCB (P < 0.0001). UCS and SCCB had a higher TMB than ABC (P = 0.01). Targetable GA in ABC was similar in all 3 groups involving TP53 and KRAS/ACC. ABC cases were more frequent in ABC whereas TERT, CDK12/4/6 and DNA-repair genes (ARID1A and KOMED1) were more frequently altered in UCS and SCCB. Targetable MTOR pathway GA (PIK3CA, TSC1, PTEN) were more frequent in UCS and SCCB as were targetable kinase alterations (FGFR3 and ERBB2). The UCB and SCCB had a significantly higher TMB than ABC (P < 0.0001) including mean TMB and TMB > 20 mut/m (P < 0.0001). CD274 (PD-L1) was amplified more frequently in SCCB than ABC or UCS (P < 0.0001). MSI high status was very uncommon in all tumor types. Conclusions: Deep sequencing reveals that ABC features a wider different genomic profile from UCS and SCCB. UCS has the highest frequencies of targetable kinase GA and high TMB. SCCB has the highest frequencies of IO efficacy predicting biomarkers including mean TMB and PD-L1. Nonetheless, ABC does feature potential kinase targets such as FGFR3 and ERBB2.

4535 Poster Session (Board #361), Mon, 1:15 PM-4:15 PM
Squamous-cell carcinoma variant histology (SCC-VH) in muscle-invasive bladder cancer (MIBC): A comprehensive clinical, genomic, and therapeutic assessment from multiple datasets. First Author: Marco Bandini, Vita-Salute San Raffaele University, Milan, Italy

Background: Pure or predominant SCC-VH is not uncommon in MIBC. Nevertheless, very few data are available about the efficacy of neoadjuvant chemotherapy (NAC). Here, we examined the outcomes after NAC, explored novel therapeutic targets, and propose new results in these patients (pts) by integrating multiple datasets. Methods: Within RISC and San Raffaele databases (1990-2018), we identified 2858 MIBC pts with urothelial cancer (UC, N = 2229) or VH (N = 629) who received RC +/- NAC. Kaplan-Meier and Cox regression analyses compared cancer-specific survival (CSS) between SCC and UC with NAC stratification. Logistic regression models tested the odds of clinical-to-pathological downstaging (cT > pT), Foundation Medicine (FM) database was queried for SCC-VH, 97 pts were assayed with hybrid-capture based comprehensive genomic profiling (CGP). Finally, we looked at the results from the PURE-01 study, that is now amended and enrolling pts with VH that previously reported improved responses to cisplatin-based NAC associated with favorable hematologic toxicity profile. GemOx may be used as a new option for UCC patients who are not suitable for platinum-containing chemotherapy.

Conclusions: Long-term follow up reveals that pre-treatment tumor tissue was sequenced for coding exons of 287 cancer-related genes and analyzed for mutations. Survival in patients with one or more mutations in ATM, RB1, or FANCC genes was compared to those without mutations. Results: Of 58 pts treated, 38% (22/58 pts) had relevant mutations in the combined group of MVAC (13/34 pts) and GC (9/24 pts) trials. At a median follow-up of 56 months and minimum follow up of 16 months, patients with mutations had statistically significantly greater OS (p = 0.0043) and DSS (p = 0.0015). Median OS/DSS was not reached for patients with a mutation in any group. At 5 years post treatment, OS/DSS were greater in mutated vs. non-mutated patients in all groups (see table). Conclusions: Long-term follow up reveals that previously reported improved responses to cisplatin-based NAC associated with mutations in ATM, RB1 and FANCC also confer a clinically meaningful and statistically significant survival benefit in these patients. These alterations may be useful as predictive biomarkers to allow clinicians to prioritize patients most likely to benefit from NAC prior to radical cystectomy.

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**Poster Session (Board #363), Mon, 1:15 PM-4:15 PM**

Bladder Cancer Multidisciplinary Clinic (BMC) model: Impact on imaging, pathology and treatment recommendations. 

**First Author:** Brian Winters, Department of Urology, University of Washington Medical Center, Seattle, WA

**Background:** Despite guideline-based standard of care recommendations in BC and upper tract urothelial carcinoma (UTUC), treatment remains variable across US. Experts recommend focusing BC care in tertiary centers. We hypothesized that a BCMC model, with expert central pathology and radiology review, may result in changes in corresponding reports, and, thus, treatment recommendations. 

**Methods:** Our BCMC clinic format includes simultaneous consultation with Urologic, Medical and Radiation Oncology, with real time expert genitourinary pathology and radiology review. We retrospectively assessed the concordance between outside (pre-BMC) imaging & pathology review and BCMC review. Differences between pre- and post- BCMC recommendations on management were also assessed; descriptive statistics were used. 

**Results:** We identified 233 BC/UTUC patients (pts) referred to BCMC. Complete radiographic and pathologic data were available for 209 pts. Median age at time of evaluation was 68 (27-93) and 85% were PS ECOG 0-1. After BCMC review of outside records, 112 (53.6%) imaging and/or pathology changes were noted, with 57 (27%) pts upstaged. Overall, imaging interpretation was changed in 25% of cases, and 20% of pts were upstaged. BCMC pathology review resulted in changes in 59 (28%) pts. Among those, 42 (71%) had histologic subtype addition or change, 9 (15%) had LVICIS status change, and 2 (3.4%) had low to high grade conversion. In terms of pathology staging, 7 (12%) were downstaged, and 5 (8.5%) upstaged. Further diagnostic work-up was recommended in 71/209 (34%) pts, resulting in upstaging in 11/71 (15.5%) of cases. Pre- and post- BCMC-recommended treatment modality differed in 55/209 (26%) pts, while a new treatment modality was added in 28/209 (13%) pts. These recommendations were followed 91.4% of the time (191/209 pts). 

**Conclusions:** BCMC initiation at our institution resulted in imaging and/or pathology diagnostic changes in almost half of cases, with approximately a quarter of pts being upstaged. Findings reveal the importance of expert radiology and pathology review in BC. Further study is needed to confirm the proposed benefits and impact of BCMC on treatment response and outcomes.

**Poster Session (Board #367), Mon, 1:15 PM-4:15 PM**

Treatment sequencing of anti-PD-1/PD-L1 and carboplatin (carbo)-based chemotherapy (chemo) in cisplatin-ineligible patients (pts) with metastatic urothelial cancer (mUC). 

**First Author:** Xiao X. Wei, Dana-Farber Cancer Institute, Boston, MA

**Background:** Anti-PD-1/PD-L1 agents and carbo-based chemo are therapy options in 1L setting for cisplatin-ineligible pts with mUC. However, optimal sequencing is unclear. 

**Methods:** We conducted a multicenter retrospective analysis of cisplatin-ineligible pts with mUC treated with 1L PD-1/PD-L1 monotherapy followed by carbo-based chemo (IO—Cb) or the reverse order (Cb—IO) without intervening systemic therapy. Perioperative cisplatin-based chemo was allowed if completed > 1 year from 1L mUC therapy initiation. To assess association between overall survival (OS) and therapy sequence, a multivariate analysis (MVA) was performed from initiation of 2L therapy, adjusted for treatment sequence, time interval between initiation of 1L and 2L therapies, Hb (< 10 vs ≥10 g/dl), EGCG PS (0-1 vs 2-3), and metastatic site (LN/soft tissue only vs non-liver vs liver). 

**Results:** 146 pts (IO—Cb n = 43, Cb—IO n = 103) were evaluable with median age 72, 76% men, 78% ECOG PS 0-1, 17.8% with liver metastasis. Baseline factors were balanced except for higher proportion of men in IO—Cb group (91% vs 70%, p = 0.01). Median time interval between initiation of 1L and 2L therapy for IO—Cb and Cb—IO were 15.6mo (4.8-7.8-1) and 23.0mo (2.1-10.3-3). Response rates are summarized (Table). On MVA, treatment sequence was not associated with OS (HR 1.05, p = 0.85). Site of metastasis was the only factor significantly associated with OS (p = 0.002). 

**Conclusions:** In our retrospective analysis of cisplatin-ineligible pts with mUC regardless of PD-L1 expression, anti-PD-1/PD-L1 followed by carbo-based chemo or the reverse sequence appeared to confer comparable OS. The observed response rates and time interval between initiation of 1L and 2L therapy are likely contributed by pt selection, where all pts received 2L. Further investigation of the ‘PD-L1 high’ population is warranted, given higher response rates with anti-PD-1/PD-L1 vs ‘PD-L1 low’ population. 

Ongoing phase III trials will help inform optimal sequencing.
4542 Poster Session (Board #368), Mon, 1:15 PM-4:15 PM
FGFR-altered, advanced urothelial carcinoma (UC) and response to chemotherapy prior to receiving erdafitinib. First Author: Andrea Necchi, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

**Background:** FGFR-altered, advanced UC has predominantly a luminal 1 subtype, which is associated with lower response rates to immunotherapy and possibly also to chemotherapy. Objective response rates (ORR) for first-line cisplatin-based regimens, such as gemcitabine-cisplatin (gem/cis) and methotrexate-vinblastine-doxorubicin-cisplatin (MVAC), historically range between 45-60% and for gemcitabine-carboplatin (gem/carbo) 35-45%. However, the ORR on chemotherapy for the ~20% of patients with FGFR-3 altered tumors is unknown. **Methods:** BLC2001 (NCT02365597) is an ongoing global open-label phase 2 study of the pan-FGFR inhibitor erdafitinib in patients with locally advanced or metastatic UC with specific FGFR2/3 gene alterations. Patients who had received first-line (1L) or second-line (2L) chemotherapy for advanced UC were identified. Investigator-reported ORR (complete + partial responses) and median time to progression (TTP) on these pretreatments were analyzed. **Results:** Of 210 patients treated with erdafitinib in BLC2001, 191 had received prior systemic therapy including 184 and 83 patients who had received 1L and 2L chemotherapy, respectively. ORR were 29.3% (54/184, 95% CI 22.8%, 35.9%) to 1L chemotherapy and 24.1% (20/83; 95% CI 14.9%, 33.3%) to 2L chemotherapy. 1L therapy consisted of gem/cis in 94 patients, gem/carbo in 59 patients, and MVAC in 22 patients, with ORR (95% CI) of 35.1% (25.5%, 44.8%), 25.4% (14.3%, 36.5%), and 22.7% (5.2%, 40.2%), respectively. In the 2L setting, of 46 patients who had received a regimen containing a taxane (paclitaxel [taxane] or docetaxel) or vinflunine, 25 patients (17.4%; 95% CI 6.4%, 28.3%) achieved an objective response. Patients who had received first-line (1L) or second-line (2L) chemotherapy with ORR (95% CI) of 35.1% (25.5%, 44.8%), 25.4% (14.3%, 36.5%), and 22.7% (5.2%, 40.2%), respectively. In the 2L setting, of 46 patients who had received a regimen containing a taxane (paclitaxel [taxane] or docetaxel) or vinflunine, 25 patients (17.4%; 95% CI 6.4%, 28.3%) achieved an objective response. Patients who had received a regimen containing a taxane (paclitaxel [taxane] or docetaxel) or vinflunine, 25 patients (17.4%; 95% CI 6.4%, 28.3%) achieved an objective response. 1L therapy was lower, but within the range expected based on historical data. **Conclusions:** In this post-hoc analysis, the overall ORR to prior chemotherapy was lower, but within the range expected based on historical data. Further investigation into the response to chemotherapy in FGFR alteration positive patients is warranted and may be useful for the development of 1L trials of combination therapy. Clinical trial information: NCT02365597.

4544 Poster Session (Board #370), Mon, 1:15 PM-4:15 PM
Prognostic value of sequential 18F-FDG + Na18F PET/CT (NaF+FDG PET) in metastatic genitourinary (GU) cancer patients (pts) treated with chemotherapy/nivolumab/Ipilimumab (CaboNivoIpi). First Author: Nicholas Peter Verdinii, National Cancer Institute at the National Institutes of Health, Bethesda, MD

**Background:** NaF+FDG PET imaging are used to assess soft tissue and bone metastases. The prognostic value of NaF+FDG PET in GU cancer pts was assessed as a secondary endpoint within a phase I trial of combination CaboNivoIpi. **Methods:** NaF+FDG PET scans were collected at baseline and cycle (C) 2, 4, and 6 (2L) for 50pts. Up to 50 pts/patient were analyzed at baseline, up to 10 lesions/organ in case of extensive disease. Lesion number and whole-body metabolic tumor volume (wMTV) were recorded at baseline, C3D1 and percent change for FDG and NaF scans. Whole-body tissue lesion glycolysis (wTLG) and its percent change was obtained for FDG scans. Parameters were evaluated with respect to OS using Kaplan-Meier and log-rank, with quartiles, then refined to show strongest distinction, adjusting p-values to account for this exploration. Parameters with strongest OS association were also analyzed for associations with OS in urothelial carcinoma (UC) pts. **Results:** 50 pts, (UC (n = 20); others (renal cell, prostate, urachal/adenocarcinoma, germ cell, penile, bladder squamous cell (n = 2-7 each)). Median (m) overall survival (OS) was 23.9 months (mo) (95% CI: 13.7mo – NE) with 29.7 mo potential follow up and mOS of 24.7mo (95% CI: 13.7mo – NE) for UC. For FDG in all pts, wMTV: baseline ≤ vs > 51.6, mOS (NR vs 10mo, p = .0006), C3D1 ≤ vs > 85 mOS (25.9mo vs 5.1mo, p = .0001), percent change (0/increase vs decrease, mOS 14mo vs 25.9mo, p = .0015), wTLG: baseline ≤ vs > 178mOS (NR vs 11.5mo, p = .011), C3D1 ≤ vs > 300, mOS (25.9mo vs 8.3mo, p < .0001), percent change decrease vs increase, mOS (25.9mo vs 14.0mo, p = .016); and lesion number: baseline ≤ vs > 13, mOS (25.9mo vs 9.9mo, p = .0090), C3D1 ≤ vs > 13 mOS (25.9mo vs 9.9mo, p < .0001) significantly predicted OS. In UC pts, wMTV percent change (0/increase vs decrease, mOS 14mo vs 25.9mo, p = .057), wTLG percent change decrease vs increase, mOS (NR vs 8.4mo, p = .0015), and lesion number C3D1 ≤ vs > 13 mOS (25.9mo vs 2.8mo, p = .022) significantly predicted OS. NaF parameters failed to do so. **Conclusions:** FDG wMTV and wTLG at baseline and C3D1, predicted OS in GU cancer pts CaboNivoIpi. Clinical trial information: NCT02496208.

4543 Poster Session (Board #369), Mon, 1:15 PM-4:15 PM
Erdafitinib in high-risk patients (pts) with advanced urothelial carcinoma (UC). First Author: Se Hoon Park, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

**Background:** The pan-FGFR inhibitor erdafitinib exhibited a robust objective response rate (ORR) and tolerability among pts with FGFR2/3-altered advanced UC in the BLC2001 (NCT02365597) phase 2 study (Sieferl-Radko ASCO 2018 #4503). Here we report a post hoc subgroup analysis to explore efficacy among high-risk pts. **Methods:** The analysis included 99 BLC2001 pts who received the optimized dose regimen of 8 mg/d continuous (pharmacodynamically guided) up to 9 months per serum phosphate. Results: for ORR, duration of response (DOR), progression-free survival (PFS), and overall survival (OS) were analyzed by select baseline variables, with high-risk defined as age ≥75 y, EGCG Ps 2, hemoglobin ≤10 g/dL, visceral metastases, and 2 or 3 Bellmunt risk factors. **Results:** Efficacy results (Table) show investigator-assessed ORR >35% and median PFS >6 mo across all subgroups except EGCG P 2. OS data are immature but generally follow the trend of PFS. With the exception of EGCG 2, there were no differences in G3/4 serious AE proportions by subgroup. **Conclusions:** The post hoc subgroup findings support that erdafitinib generally provides comparable efficacy in high-risk pts with FGFR-altered AD as the overall population. Clinical trial information: NCT02365597.
KEYNOTE-052: Phase 2 study evaluating first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC)—Updated response and survival results. First Author: Peter H. O'Donnell, The University of Chicago, Chicago, IL

Background: Initial results of the phase 2 KEYNOTE-052 (NCT02335424) study led to approval of pembro for cisplatin-ineligible patients (pts) with advanced UC. Updated results representing follow-up of 2 y since last pt enrolled are presented. Methods: Pts had confirmed advanced UC, were cisplatin-ineligible (ECOG PS 2, CrCl ≥30 to 60 mL/min, grade ≥2 neuropathy/hearing loss, NYHA Class III heart failure), and received pembro at 200 mg IV Q3W until progression, unacceptable toxicity, withdrawal, or 24 mo of therapy, whichever occurred first. Primary end point was confirmed ORR (RECIST v1.1, independent central review). Key secondary end points: duration of response (DOR), overall survival (OS), and safety. Data cutoff was September 26, 2018. Results: Among pts assessed (N = 370), median age was 74 y, 85% had visceral disease, and 30% were PD-L1 positive (combined positive score [CPS] ≥10). Median follow-up was 11.4 mo (range, 0.1-41.2) for all pts and 29.3 mo (range 7-41.2) for responders. Confirmed ORR was 29% (95% CI, 24-34); complete response, 9% (n = 33); partial response, 20% (n = 73). Median DOR was 30.1 mo (95% CI, 18.1-not reached [NR]); 67% and 52% of pts had DOR ≥12 and ≥24 mo, respectively. Median OS was 11.3 mo (range 9.7-13.1); 12- and 24-mo OS rates were 47% and 31%, respectively. In pts with CPS ≥10 (n = 251) and ≥10 (n = 110), respectively, confirmed ORR was 20% (95% CI, 16-26) and 47% (95% CI, 38-57). Median DOR for pts with CPS < 10 and ≥10 was 18.2 mo (95% CI, 9.7-NR) and NR (95% CI, 18.1-NR); DOR ≥24 mo was 45% and 57%, respectively. Median OS for pts with CPS < 10 and ≥10 was 9.7 mo (95% CI, 7.6-11.5) and 18.5 mo (95% CI, 12.2-28.5); 24-mo OS rates were 24% and 47% respectively. Treatment-related AEs (AEs) occurred in 67% of pts. Most common were fatigue and pruritus (18% each); 21% were grade ≥3, including 1 death (myositis). Conclusions: With extended follow-up, pembro continued to elicit clinically meaningful, durable antitumor activity in cisplatin-ineligible pts with advanced UC and was more pronounced in those with PD-L1 CPS ≥10. Pembro safety profile was as expected. Clinical trial information: NCT02335424.

Immune correlates of CD73 expression in patients with urothelial carcinoma (UC). First Author: Edwin Lin, University of Utah Huntsman Cancer Institute, Salt Lake City, UT

Background: Checkpoint inhibitors have improved outcomes in UC. However, response rates are low and additional mechanisms of immune evasion need to be ascertained. CD73 (encoded by NT5E) converts extracellular AMP to adenosine, which exerts an immunosuppressive effect in the tumor microenvironment by inhibiting infiltrating T and NK cells. Utilizing The Cancer Genome Atlas (TCGA) bladder cancer dataset, we evaluated correlations between NT5E expression and the immune milieu in UC. Methods: RNA-seq data from 411 primary UC tumor samples were obtained from the TCGA. Patients were split into low, intermediate, and high NT5E expression groups (≤1, -1 to 1 and ≥1 standard deviation from the overall mean). A tumor inflammation signature (TIS) reflecting an inflamed tumor phenotype was calculated based on the averaged expression of 18 previously validated genes (Ayers et al, 2017). NT5E expression was compared between tumors with high and low TIS scores and among the TCGA molecular subtypes. Abundance of infiltrating immune cell subsets was estimated based on expression of previously identified 782 immune metagenes and compared between NT5E expression groups (Charoentong et al, 2017). The Mann-Whitney U test assessed statistical significance, and the Bonferroni correction was used to control for false discovery rate. Results: NT5E expression was significantly higher in tumors with a high TIS score compared to those with low TIS score (P < 0.0001) and correlated with expression of other immune checkpoint such as PD-L1, IDO and LAG-3 (each P < 0.01). Patients with basal/squamous subtype had the highest NT5E expression compared to luminal or neuronal subtypes. High NT5E expression was associated with increased infiltrating NK cells, neutrophils, Tregs and decreased Type 2 helper cells. Conclusions: High expression of NT5E in UC patients with an inflamed tumor phenotype was associated with an increase in infiltrating Tregs, and the basal/squamous subtype. Our findings highlight a potential role of CD73-adenosine pathway as a mechanism of immune evasion and a novel therapeutic target in UC. Further studies to assess the clinical impact of NT5E expression on outcomes in UC patients treated with immunotherapy are needed. AT and NA: equal contribution.

An FDA analysis of the association between adverse events and outcome in patients with urothelial cancer receiving a programmed death protein 1 or programmed death ligand 1 (anti-PD-1/L1) antibody. First Author: Chana Weinstock, U. S. Food and Drug Administration, Silver Spring, MD

Background: To assess the relationship between tumor response rate, overall survival, and the development of related adverse events of special interest (AESIs) or related immune-mediated adverse events (imAESIs) in patients with urothelial cancer treated with anti-PD-1/L1 antibodies. Methods: We examined seven trials that led to drug approval and which included 1747 patients with metastatic or locally advanced urothelial cancer treated with an anti-PD-1/L1 antibody. Five trials enrolled patients who had received prior platinum-based therapy and two enrolled patients who were cisplatin-ineligible. The datasets were searched for AESIs, related imAESIs, and related imAESIs. The relationship to study drug was determined by the Investigator. Immune-mediated adverse events were defined as AESIs treated with topical or systemic corticosteroids. Results: In these exploratory analyses, a related AESI was reported in 64% of responding patients and in 34% of patients who did not respond to the anti-PD-1/L1 antibody while a related imAE occurred in 28% and 12% of patients who did and did not respond to study drug, respectively. In a responder analysis, an increase in overall survival was seen in patients with related AESIs compared to those with no related AESI (hazard ratio [HR] 0.42; 95% CI: 0.37, 0.49). Fifty-seven percent of responding patients with a related AESI reported a related imAE prior to documentation of response. Conclusions: Patients who responded to treatment with an anti-PD-1/L1 antibody were more likely to report a related AESI or related imAE. This relationship did not appear to be due to the increased duration of exposure in responding patients. Systemic corticosteroid use did not appear to affect the duration of response.
Background: Intravesical BCG instillation (IBI) is the gold standard adjuvant therapy for muscle invasive bladder cancer (MIBC) ineligible for cisplatin-containing therapy. Therefore, we propose this pre-surgical trial with durva + treme for this population of pts. Methods: This is a single-arm, pre-surgical clinical trial with durva + treme in pts with localized, high-risk MIBC (CT2-T4a) who are ineligible for cisplatin-based NAC followed by cystectomy. Overall, we recruited 154 pts with MIBC, who had undergone IBI in 1/19 to 1/20. With a median follow up of 10.2 months, 9 of 154 pts (5.84%) developed grade ≥3 immune-related toxicity including hepatitis and amylase/lipase elevation, and two (7%) resulted in surgery delay for >30 days. Immune profiling with CyTOF analysis of baseline peripheral blood indicates that pts with PCR may have significantly lower frequency of a Th2 subset as compared to pts with up-staging of disease. In addition, gene expression profiling of baseline lymphocyte ratio (NLR; HR 1.94; 95% CI [1.57-2.40]) and lactate dehydrogenase (LDH; HR 1.60; 95% CI [1.28-1.99]). There was robust association of candidate prognostic factors with OS. Factors were dichotomized as predictor of BCG response in HR-NMIBC. These results build a scientific rationale for pharmacological intervention on a molecular target using immuno-oncology.

Conclusions: Our data indicate that durva plus treme is an effective and safe neoadjuvant therapy for pts with MIBC ineligible for cisplatin-based therapy. Therefore, neoadjuvant therapy with durva + treme and a number of potential biomarkers warrant testing in a larger phase 3 trial. Clinical trial information: NCT 02812420.
4554 Poster Session (Board #380), Mon, 1:15 PM-4:15 PM

Recombinant humanized anti-PD-1 monoclonal antibody toripalimab in patients with metastatic urothelial carcinoma: Preliminary results of an open-label phase II clinical study. First Author: Xinan Sheng, Peking University Cancer Hospital, Beijing, China

Background: Patients with advanced metastatic urothelial carcinoma (UC) who experience disease progression after standard therapy have limited treatment options. Phase I studies of toripalimab in subjects with heavily pretreated metastatic UC have demonstrated an acceptable safety profile and promising clinical activity. Here we report the preliminary safety and efficacy result of toripalimab in a phase II clinical study in Chinese patients with refractory/metastatic urothelial carcinoma. (Clinical trial ID: NCT03131266).

Methods: Metastatic UC Patients will receive toripalimab, also known as JS001, 3 mg/kg Q2W until disease progress or unacceptable toxicity. All patients with measurable disease will be assessed for clinical response every 8 weeks according to RECISTv1.1. Tumor PD-L1 expression and tumor mutation burden will be measured for correlation with clinical response.

Results: From May 2017 to February 10, 2019, 79 patients were enrolled from 7 participating centers. The median age was 61 years with 57.5% male. By the cut-off date of Jan 20, 2019, common treatment related AEs were mostly grade 1 or 2, including anemia, hyperglycemia, ALT increased, AST increased and hypothyroidism. Among 65 evaluable patients, 2 complete responses, 18 partial responses, and 13 stable diseases were observed, for an objective response rate (ORR) of 30.8% and a disease control rate of 50.8%. 70% (14/20) responses were ongoing by the cut-off date. PD-L1 expression results were obtained from 56 subjects. PD-L1+ patients (n=16, 28.6%) had significantly higher ORR than PD-L1- patients (n=40), 62.5% versus 15.0% (p<0.01).

Conclusions: Toripalimab has demonstrated encouraging clinical activity in chemo-refractory UC patients and a manageable safety profile. Toripalimab elicited a favorable 62.5% ORR in PD-L1 positive patients, while PD-L1 negative patients also achieved a 15% ORR, including one complete response. Patients will be continuously monitored for additional safety and efficacy readouts (DOR, PFS and OS). Clinical trial information: NCT03131266.

4555 Poster Session (Board #381), Mon, 1:15 PM-4:15 PM

Circulating tumor cell (CTC) enumeration in patients (pts) with metastatic genitourinary (mGU) tumors treated in a phase I study of cabozantinib and nivolumab (CaboNivo) and CaboNivo/Ipi. First Author: Andrea B. Apolo, Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: CTCs may serve as biomarkers for clinical outcomes in GU tumor pts. We examined the association between baseline CTC enumeration, CTC heterogeneity, CTC morphologic subtypes, and progression-free-survival, overall survival and response to therapy with combination CaboNivo or CaboNivo/Ipi. Methods: 123 samples from 52 pts with mGU tumors treated with CaboNivo (38 pts) or CaboNivIpi (14 pts) drawn at Baseline, Cycle (C) 2 Day (D) 1, and C2D1 were processed using the Epic Sciences platform. CTCs were defined as cytokeratin (CK)+, CD45-, distinct morphology, intact nucleus. PD-L1 expression was also assessed. Results: From 07/20/2016-09/01/2018, 122 pts (urothelial carcinoma) were enrolled. Clear cell renal cell carcinoma N = 4; bladder adenocarcinoma N = 8; bladder squamous cell carcinoma N = 2; bladder small cell N = 2; renal medullary N = 2) were treated. Median age was 61.5 years (range 20-82); 35 (67%) were male. N = 37 (71%) had visceral involvement, N = 15 (29%) with liver involvement. N = 11 (22%) had unknown site of disease and N = 1 (2%) had bone involvement and lung involvement, N = 1 (2%).

CTCs were detected in multis with mGU tumors treated with CaboNivo and CaboNivIpi. CTC values were somewhat but not statistically lower in responders vs. non-responders. On treatment lower CTCs and the absence of aggressive CTC subtypes were associated with better clinical outcomes. On-going analyses include single cell genomics, and analysis of T-cell populations. Clinical trial information: NCT02496208.

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Background: Objective: To examine in a cohort of anti-PD-L1 (I) immune checkpoint inhibitors (ICP) treated urothelial cancer patients a strategy combining treatment outcomes with molecular alterations, pathways, and immune/tumor microenvironment features to determine potential responder and rapid-progression signatures. Methods: De-identified clinical history and treatment outcomes were collected on 109 MIBC patients treated with ICP agents. Archived FFPE samples from these patients were obtained and processed for mRNAseq, exome-seq, tumor mutation burden (TMB), microsatellite instability (MSI) and mutation panel testing. Comprehensive tumor/immune profiling is being analyzed in the context of ICP treatments and RECIST 1.1 outcomes. A 60 gene MIBC 4-typer expression subtype and other response associated predictors are used to stratify and identify positive/negative ICP response indicators. Results: 109 patients were identified (median age 75, 64% male, 78% white, 17% black). 74% of patients had hemoglobin < 10, 30% had liver metastases, and 59% had ECOG performance status > 0. Mutation analysis of the first 66 patients showed TP53 (n = 34, 52%), FGFR3 (n = 17, 26%), CDKN2A (n = 13, 20%) and RB1 (n = 12, 18%) as the top alterations. No patients (0/8) with known pathogenic mutations in FGFR3 (S249C and TACC3-fusion) responded to ICP. Of patients with T2 staging prior to ICP (37/66), overall survival was markedly shorter (2.7 years) in those possessing FGFR3 mutations (n = 6/37) compared to that for FGFR3 WT patients (5.7 years, n = 31/37; p = 0.045). Further analyses of molecular features relative to treatment outcomes are ongoing to characterize response signatures. Conclusions: Our preliminary cohort of patients with pathogenic FGFR3 alterations showed 0% favorable response to ICP. We are expanding on this observation with further comprehensive molecular analyses and retrospective treatments/outcomes data. We anticipate identifying expression signatures that reflect ICP patient responder/non-responder signatures that may aid in future therapy decisions.

Background: Upper-tract urothelial carcinomas (UTUC) may harbor similar genetic profile as compared to bladder cancer, although frequencies of mutated genes have been shown to differ between them. However, to the best of our knowledge, the epigenetic landscapes of UTUC and their association with genetic alterations and clinico-pathological tumor features remain unknown. Methods: We collected 40 UTUC samples (20 non-muscle invasive (NMI) and 20 muscle-invasive (MI)) and carried out whole-exome sequencing (n = 30), DNA methylation using Infinium EPIC arrays (n = 35) and RNA sequencing (n = 20). Validation was performed on TCGA bladder cancer dataset. Results: We identified 3232 putative somatic mutations with an average of 2.1+/-2.6 mutations per megabase. Significantly mutated genes were FGFR3 (50%), KDM6A (27%), MLL2 (27%) and ARID1A/B (23%). No difference in term of genetic alterations were identified between MI- and NMI- UTUC. Unsupervised hierarchical clustering using most variable DNA methylation probes uncovered two robust DNA methylation epi-clusters. Epi-cluster C1 (n = 23; 65.7%) displayed markedly higher DNA methylation relative to Epi-cluster C2 (n = 12; 34.3%). Notably, all muscle-invasive samples were enriched in C1 (16/17, 94.1%); conversely, C2 was enriched with non-muscle-invasive samples (p = 0.0009). Overall, 14,209 probes were significantly hypermethylated in C1 as compared to C2 epi-cluster; Gene Set Enrichment Analysis (GSEA) demonstrated that those were enriched for PRC2 targets (p = 6x10^-33). Integrative analysis with tumor genetic landscape showed that C1 epi-cluster was enriched for mutations in SWI/SNF complex as compared to C2 (p = 0.02). We then applied our epi-signature to bladder TCGA cohort and obtained two similar epi-clusters associated with patients overall survival (p = 0.035). Conclusions: Our study demonstrate for the first time that difference between MI- and NMI- invasive UTUC might be related to epigenetic rather than genetic alterations. This might pave the way for testing epigenetic therapies in non-muscle invasive tumors with the aim to prevent recurrence and distant metastasis.

Background: Patients with non-muscle-invasive bladder cancer (NMIBC) unresponsive to BCG therapy have limited treatment options. N-803 (also known as ALT-803) is an IL-15-based immunostimulatory protein complex (IL-15/Perifin Fc) that promotes proliferation and activation of natural killer (NK) cells and CD8+ T cells, but not regulatory T cells. Phase Ib data in BCG-naïve patients with NMIBC demonstrate that intravesical administration of N-803 with BCG induced complete response in all patients, without recurrences for the study duration of 24 months. Methods: An open-label, single-arm multicenter Phase 2 study of intravesical BCG plus N-803 in patients with BCG-unresponsive high-grade NMIBC (NCT03022825) was open. The study has two cohorts: Cohort A, patients with BCG-unresponsive carcinoma in situ (CIS) (with or without Ta or T1 disease) and Cohort B, patients with BCG-unresponsive high-grade Ta/T1 disease. All treated patients receive intravesical N-803 plus BCG, similar to a standard induction and maintenance treatment schedule. The primary endpoint for Cohort A is incidence of complete response (CR) of CIS at any time, and the primary endpoint for Cohort B is disease-free rate at 12 months. Results: To date, sixty-six patients have enrolled in this phase 2 trial (Cohort A (CIS), n = 23; Cohort B (Papillary), n = 24). Of eleven evaluable patients in Cohort A, nine patients (82%) have a reported CR. In addition, seven out of nine (78%) patients in Cohort A demonstrated CR at their 6-month response assessment. Of thirteen evaluable patients in Cohort B, ten patients (77%) showed no evidence of recurrence at their 3-month response assessment; of these, none (0/8) evaluated past 3 months have had disease recurrence. Three serious adverse events (AEs) (fatigue, dizziness, and bladder pain) have been reported. In Cohort B, four patients (36%) have a reported CR. In addition, seven out of nine (78%) patients in Cohort B have shown no evidence of recurrence at their 3-month response assessment; of these, none (0/8) evaluated past 3 months have had disease recurrence. Three serious adverse events (AEs) (fatigue, dizziness, and bladder pain) have been reported. In Cohort B, four patients (36%) have a reported CR. Conclusions: Nine out of eleven (82%) patients with BCG-unresponsive CIS of the bladder demonstrated a complete response. Ten out of thirteen patients with BCG-unresponsive papillary NMIBC show no evidence of disease at first assessment. Intravesical N-803 plus BCG was well-tolerated and no patients experienced immune-related AEs. Clinical trial information: NCT03022825.
Background: We previously reported no difference in favorable response rate (FRR) or PFS for TIP vs BEP. Here we present results of a pre-planned analysis of biomarkers of outcome. Methods: HCG and AFP were drawn on days 1 and 15 of each cycle and rates of decline classified as satisfactory (S) or unsatisfactory (US) by MSK (Motzer JCO 2014) and GETUG (Fazio Lancer Oncot 2014) methods. HIC for PR (PR + CR) and PFS. Patients (pts) who received disease-stabilizing chemotherapy were excluded from marker analyses. Results: Of 91 pts, 80 did not receive disease-stabilizing treatment with 79 having sufficient marker values for analysis by the MSK method and 76 by GETUG. By MSK, 49 had 5 decline vs 30 US; by GETUG, 34 vs 41 US. FRR and PFS were improved for pts with S vs US decline by both methods and remained significant by the MSK method when stratified by IGCCCG group (Table). IHC (n=17) quality was adequate in 71 to 73 pts (varied by stain) and was positive (H>0) for PARP in 68/73, ERCC1 in 54/71, RAD51 in 54/73, p-AKT in 57/2, and HER2 in 4/72. Only PARP1 was associated with outcome with worse PFS for the lowest expression tertile (H< 180; p=0.013). Conclusions: PARP1 expression and tumor marker decline rates, particularly by MSK method, were significantly associated with outcome to initial chemotherapy in int/poor risk GCT. Future trials incorporating marker decline into treatment allocation and validating the prognostic effect of PARP1 expression are warranted. Clinical trial information: NCT01873326.

5046 Poster Session (Board #389), Mon, 1:15 PM-4:15 PM A reduced pazopanib dose with food: Is it more patient-friendly and does it reduce drug costs? First Author: Meredith M. Regan, 1 Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA

Background: Immuno-oncology therapies (IOs) and tyrosine kinase inhibitors (TKIs) are recommended for the treatment of aRCC. As new drugs and combination regimens emerge, there is interest in gaining a deeper understanding of optimal treatment sequencing. We aimed to assess clinical and economic outcomes associated with sequential treatment in patients with metastatic renal cell carcinoma (mRCC) patients with mRCC with TKI intermediate/low risk. Methods: A discrete event simulation model was developed to estimate the total costs and survival (in life-years; LYs) over patients' lifetimes when receiving sequential treatment with nivolumab + ipilimumab (N+I), sunitinib (SUN), pazopanib (PAZ), or cabozantinib (CAB) as first-line (1L) treatment, and nivolumab (NIVO), axitinib (AXI), PAZ, CAB, or lenvatinib + everolimus (LEN+EVE) as second line (2L). Efficacy inputs were derived from the CheckMate 214 trial and a network meta-analysis based on available literature. Safety and cost data were obtained from literature and publicly available sources. Results: N+I initiating sequences were estimated to provide longer survival in mean LYs and lower mean costs/LY versus sequences with 1L TKIs (table). The estimates of incremental cost-effectiveness ratio (ICER) for N+I initiating sequences with 2L TKI monotherapy were well below the willingness-to-pay threshold of $50,000. Using 2L LEN+EVE, compared with 2L monotherapies, provided an incremental survival benefit of 0.012/LY (95% CI 0.003–0.020) at an additional cost of $221,597 vs $264,722 or $343,874. Conclusions: Use of 1L N+I followed by TKI monotherapy is estimated to provide longer survival while being more cost-effective versus TKIs followed by IOs or sequences cycling TKIs, mainly driven by a longer time to 2L treatment and longer treatment-free survival with N+I. Clinical trials with head-to-head comparisons of treatment sequences would be necessary to validate the findings of the study.

# Genitourinary (Nonprostate) Cancer

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Drug combinations targeting vascular endothelial growth factor (VEGF) and the programmed death one (PD-1) pathway have demonstrated efficacy of PD-1 blockade in metastatic clear cell renal cell carcinoma (mRCC). First Author: Jean-Christophe Pignon, Brigham and Women’s Hospital, Boston, MA

Background: hERV levels positively correlate with tumor immune infiltrate and were recently shown to be associated with clinical benefit to PD-1/PD-L1 blockade in two small cohorts of patients (pts) with mRCC (Smith C.C. et al and Panda A. et al; 2018). We tested whether hERV levels correlate with efficacy of nivolumab in a prospective phase II study of pts with mRCC (Checkmate 010). Methods: Reverse transcription RNA extracted from 99 FFPE pretreatment tumors were analyzed by RT-qPCR to assess levels of pan-ERV4, pan-ERV3,2, hERV4700 GAG or ENV, and the reference genes 18S and HPRT1. Normalized hERV levels were transformed as categorical value (high or low) using population quartiles as cutoffs. For each cutoff, samples with non-quantifiable hERV levels for which the limit of quantification was above the tested cutoff could not be categorized and were excluded from analysis. Log rank test was used to test the association of hERV levels with PFS/rPFS. At the 25th percentile cutoff, 45 pts had high levels of hERV4700 ENV and 24 pts had low levels of hERV4700 ENV. Median PFS and rPFS were significantly longer in the high-hERV4700 ENV group (HR: 0.66; 95% CI: 0.45-0.97, P = 0.019; P = 0.013, respectively) versus the low-hERV4700 ENV group (2.6 (95% CI: 1.4 - 5.4) and 2.9 (95% CI: 1.4 - 5.7) months, respectively, P = 0.010 for PFS and P = 0.028 for rPFS). At the same cutoff, ORR and rORR rates were significantly higher in the high-hERV4700 ENV group (35.6 (95% CI: 26.9-45.1) and 22.8 (11.1-34.7), respectively, P = 0.036 for ORR and P = 0.012 for rORR). Conclusions: hERV4700 ENV levels may predict outcome on nivolumab in mRCC. Results of our validation and correlation of hERV levels with immune markers in a controlled phase III trial (CheckMate 025) is ongoing.
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Consistent efficacy of nivolubam plus ipilimumab across number of International Metastatic Database Consortium (IMDC) risk factors in CheckMate 214. First Author: Bernard Escudier, Quaffer Roussy, Villepin 1 Factor

Background: The IMDC prognostic model was created based on anti-VEGF treatments for advanced renal cell carcinoma (aRCC), and may not be relevant for immunotherapy. Methods: In a post hoc analysis of CheckMate 214, we compared efficacy of nivolubam + ipilimumab (N-I) vs sunitinib (S) by number of IMDC risk factors present. Results: Among 1096 intent-to-treat (ITT) patients (pts) in both arms, 21%, 61%, and 18% had favorable, intermediate (int), or poor-risk, respectively. Of int-risk pts, 58% had 1 factor (most commonly <1 yr from diagnosis (Dx), 52%; <1 LLN, 27%; or KPS ≤70%, 10%); and 42% had 2 factors (of these pts, the most common combination of 2 factors was <1 yr from Dx and Hb < LLN, 59%). Of poor-risk pts, 58% had 3 factors, 29% had 4 factors, and few had 5 (10%) or 6 (3%) factors. Due to small numbers, pts with 4-6 factors were pooled. At 3 mo minimum follow-up, RECIST v1.1 confirmed objective response rate (ORR) and complete response (CR) rate per investigator remained consistently higher with N-I vs S across pts with 1–4 factors, although with S, ORR decreased with increasing number of factors (Table). Improved progression-free survival (PFS) and overall survival (OS) were seen with N-I vs S respectively, of the number of factors present, including in pts with only 1 risk factor (Table).

Conclusions: N-I showed consistent efficacy across number of IMDC risk factors, while S decreased in efficacy with increasing number of factors. Efficacy of N-I was superior to S in all int- and poor-risk pts. These CheckMate 214 data, along with prior CheckMate 025 data, suggest that N-I may enhance benefit with N monotherapy across IMDC risk categories show a need for improved prognostic models for immunotherapies in aRCC. Clinical trial information: NCT02231749.

4575 Poster Session (Board #401), Mon, 1:15 PM-4:15 PM

Systemic therapy for advanced clear cell renal cell carcinoma (ccRCC) after progression on immuno-oncology plus VEGF targeted therapy combinations (IO-VEGF). First Author: Yasser Ged, Memorial Sloan Kettering Cancer Center, New York, NY

Background: IO-VEGF combinations are the backbone for current and future therapeutic developments in RCC with several IO-VEGF regimens reporting positive results in phase 3 trials. However, limited data exists on outcomes to subsequent therapy in patients progressing on IO-VEGF regimens. Methods: A retrospective analysis was performed on patients with ccRCC at the Memorial Sloan Kettering Cancer Center and Cleveland Clinic Cancer Institute who initiated systemic therapy post IO-VEGF regimens including combinations with VEGF tyrosine kinase inhibitors (IO-TKI) and combinations with anti-VEGF monoclonal antibodies (IO-mAB). Patients treated on unreported clinical trials were excluded from the outcomes analysis. The primary objective was to evaluate the overall survival (OS) post IO-VEGF. The secondary objectives included objective response rate (ORR) and progression-free survival (PFS) according to RECIST v1.1. Kaplan-Meier methods and the log-rank test were used to evaluate time from start of systemic therapy post IO-VEGF to the event of interest. Results: Fifty-nine patients were treated after discontinuation of IO-VEGF regimens. Prior IO-VEGF regimens included IO-mAB (n = 35, 59%) and IO-TKI (n = 24, 41%). IMDC scores at the start of next line of therapy were favorable in 20%, intermediate in 60% and poor in 20%. Next line of therapy included VEGF-targeted therapy (n = 45, 76%), VEGFR-TKI based combinations (n = 6, 10%), mTOR inhibitors (n = 3, 5%), and unreported clinical trials (n = 5, 9%). EPR-TKI combinations including cabozantinib (n = 22), axitinib (n = 17), lenvatinib/evelomilus (n = 4), pazopanib (n = 4), and others (n = 4). Median OS was 24.5 months (95% CI 12-NE) with a 12 months OS rate of 63%. The ORR was 27% (14/51) and the median PFS was 6.8 months (95% CI 4.8-11). No difference in post IO-VEGF OS was observed when comparing IO-TKI vs IO-mAB (log rank p = 0.7). Conclusions: Post combination IO-VEGF treatment, most patients received VEGFR-TKIs. In this setting, VEGFR-TKIs continue to show clinical activity similar to historic experiences of patients post VEGF monotherapy.

4577 Poster Session (Board #403), Mon, 1:15 PM-4:15 PM

Deferred cytoreductive nephrectomy among patients with newly diagnosed metastatic renal cell carcinoma treated initially with sunitinib. First Author: Bimal Bhindi, University of Calgary, Calgary, AB, Canada

Background: While the CARMENA trial prompts more caution with upfront cytoreductive nephrectomy (CN) in patients with metastatic renal cell carcinoma (mRCC), 17% of patients in the sunitinib-alone arm underwent deferred CN (dCN). Upfront systemic therapy has been proposed as a potential litmus test to identify patients suitable for CN, but data on outcomes are limited. We sought to characterize outcomes of dCN after upfront sunitinib relative to sunitinib alone. Methods: Patients with newly diagnosed mRCC receiving upfront sunitinib were identified from the International mRCC Database Consortium (IMDC) from 2006-2018. All CNs done after initial sunitinib were included, excluding CNs performed after sunitinib failure. The outcomes were overall survival (OS) and time to treatment failure (TTF). Kaplan Meier and multivariable Cox regression analyses were performed; dCN was analyzed as a time-varying covariate to account for immortal time bias. Results: The cohort included 708 patients of whom 53 (7.5%) underwent dCN at a median of 6.5 months (IQR 3.5,10.5) from diagnosis. Patients in the dCN group were more likely to have better Karnofsky performance status (KPS), intermediate IMDC risk, fewer metastatic sites, and response to upfront sunitinib (Table). There were 604 deaths during a median follow-up of 63 months. Median OS and TTF with dCN were 43.5 and 19.8 months vs. 9.4 and 4.3 months without, respectively. Upon multivariable analysis, dCN remained significantly associated with OS (HR 0.45, 95%CI 0.3-0.65; p < 0.001) but not TTF (HR 0.73, 95%CI 0.52-1.01; p = 0.056). Conclusions: Patients who received dCN were carefully selected and achieved long OS. With these benchmark outcomes, optimal selection criteria need to be identified and confirmation of the role of dCN in a clinical trial is warranted.
4579 Poster Session (Board #405), Mon, 1:15 PM-4:15 PM
Meta-analysis of randomized clinical trials (RCT) for the adjuvant treatment of renal cell carcinoma (RCC) with vascular endothelial growth factor receptor tyrosine-kinase inhibitors (VEGFR TKIs). First Author: Daniel Vargas Almeida, BP-A Beneficência Portuguesa de São Paulo, São Paulo, Brazil.

**Background:** Although surgery is the cornerstone in the treatment of most cases of localized kidney cancer, up to 30% of patients will experience disease recurrence at three years of follow-up. Three RCTs with VEGFR TKIs (ASSURE, PROTECT and ATLAS) failed to demonstrate improvement in disease-free survival (DFS). Only S-TRAC trial showed a significant improvement in DFS, and was approved by the Food and Drug Administration (FDA). However, the matter remains controversial among genitourinary oncologists. Therefore, we performed a meta-analysis to better evaluate the potential benefit of adjuvant VEGFR TKIs after curative intent nephrectomy.

**Methods:** Eligible studies were searched in PubMed databases and limited to phase 3 RCT published from January 1996 to December 2018 of US FDA-approved VEGFR TKIs reporting on patients with RCC treated in the adjuvant setting. A summary hazard-ratio (HR) of disease-free survival (DFS) was calculated using 95% CIs by random-effects or fixed-effects models on the basis of the heterogeneity of included studies.

**Results:** Four RCT (ASSURE, S-TRAC, PROTECT and ATLAS trials) were selected for analysis, including a total of 4,820 patients. A VEGFR TKI (sunitinib, sorafenib, pazopanib or axitinib) was administered in 2,737 patients, and 2,083 received placebo. The summary DFS HR for the overall population was 0.89 (95% CI 0.79-1.00; p = 0.06). When including the report of the ASSURE with the sub-group analysis with high-risk patient population (n = 1,143), the DFS HR was 0.74 (95% CI 0.62-0.89) for DFS with HR < 1 for DFS with HR > 1. When performing the cox regression analysis, no evidence of publication bias was found. Conclusions: This is the first meta-analysis including the four RCTs in RCC adjuvant setting. This meta-analysis failed to demonstrate improvement in DFS for patients receiving a VEGFR TKI after curative intent nephrectomy. A modest benefit in DFS was observed in a selected sub-group of patients with higher risk for recurrence. There is no data regarding overall survival.

4580 Poster Session (Board #406), Mon, 1:15 PM-4:15 PM
Dynamic contrast-enhanced MRI to predict intratumoral molecular heterogeneity in clear cell renal cell carcinoma. First Author: Durga Udayakumar, University of Texas Southwestern, Dallas, TX.

**Background:** Mutation inactivation of VHL in clear cell renal cell carcinoma (ccRCC) leads to upregulation of hypoxia inducible factors (HIFs) and angiogenesis. However, ccRCC is characterized by high intra-tumor heterogeneity (ITH). Random small samples such as those in percutaneous biopsies are likely limited for characterization of molecular alterations in heterogeneous ccRCCs. We hypothesize that whole-tumor dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) is useful to noninvasively identity ITH in ccRCC.

**Methods:** This IRB-approved, prospective, HIPAA-compliant study, included 62 ccRCCs. 3T DCE MRI was obtained prior to nephrectomy. Surgical specimens were sectioned to match MRI acquisition plane. 182 snap frozen samples (49 tumors) and adjacent uninvolved renal parenchyma (URP) were collected.

**Results:** 1,1 Mbp of sequenced DNA and microsatellite instability (MSI) were determined on tumors (MT) from unmatched patients (pts) underwent hybrid-capture based therapy. Tumor mutational burden (TMB) was determined on 1.1 Mbp of sequenced DNA and microsatellite instability (MSI) was coexisted in 25% of tumors. DCE-MRI % enhancement was observed in a selected sub-group of patients with high CD73 expression. There is no data regarding overall survival.

4581 Poster Discussion Session; Displayed in Poster Session (Board #346), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM
Comprehensive genomic profiling (CGP) of upper-tract (UTUC) and bladder (BUC) urothelial carcinoma reveals opportunities for therapeutic and biomarker development. First Author: Andrea Necchi, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

**Background:** To understand the genomic landscape and inform the therapeutic development of UC, 2463 cases were analyzed by CGP for genomic tumors [MT] from unmatched patients [pts] undergoing hybrid-capture based CGP to evaluate all classes of GA. Tumor mutational burden (TMB) was determined on 1.1 Mbp of sequenced DNA and microsatellite instability (MSI) was coexisted in 25% of tumors. DCE-MRI % enhancement was observed in a selected sub-group of patients with high CD73 expression. There is no data regarding overall survival.

4582 Poster Session (Board #408), Mon, 1:15 PM-4:15 PM
Prognostic significance of CD73 expression in localized renal cell carcinoma (RCC). First Author: Abhishek Tripathi, University of Oklahoma, Stephenson Cancer Center, Oklahoma City, OK.

**Background:** CD73 or ecto-5’-nucleotidase mediates the de-phosphorylation of adenosine monophosphate to adenosine which promotes immunosuppression in the tumor microenvironment. Its prognostic significance in localized RCC has not been well characterized. Methods: We assessed CD73 protein expression using immunohistochemistry (Cell Signaling Technology, D7F9A, 1:25) on tissue microarrays (TMAs) containing tumor tissue from patients with pT1-4,N0-1, M0 RCC who underwent nephrectomy. CD73 expression was quantified using a combined score (CS: intensity x percentage of cells staining positive). CD73 positivity was defined as any CD73 expression on tumor cells (CS ≥ 0). Patients were categorized into CD73 negative (CS = 0), low (< median CS) and high (> median CS) groups. Clinical data was collected retrospectively. Baseline patient characteristics were compared between CD73 negative and positive (high + low) groups using the Cochran-Armitage trend test. Multivariable Cox regression evaluated associations of CD73 expression with disease-free and overall survival (DFS, OS) after adjusting for other baseline prognostic variables.

**Results:** Of the 112 patients included, clear cell was the most common histology (70%) followed by chromophobe (12.5%), and papillary (12%) RCC. CD73 expression (CS > 0) was noted in 22% (n = 25) of tumors and was associated with more advanced stage (T3-4/N=; 37.5% vs. 25%; p = 0.02) and a trend towards higher nuclear grade (≥3: 48% vs. 35%; p = 0.07). Median follow-up from nephrectomy was 9.7 yrs. In multivariable analysis adjusting for nuclear grade (< 3 vs. ≥3) and stage (T1-2, NO vs. T3-4+N), tumors with high CD73 expression had significantly worse DFS and OS (Table). Conclusions: CD73 expression was found in 22% of RCC patients and was associated with adverse pathologic features and poor prognosis independent of tumor stage and histologic grade. Our results provide strong rationale for further investigation of the CD73/adenosine pathway as a therapeutic target in RCC.

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**4583** Poster Session (Board #409), Mon, 1:15 PM-4:15 PM

Atezolizumab plus bevacizumab in non-clear cell renal cell carcinoma (NccRCC) and clear cell renal cell carcinoma with sarcomatoid differentiation (ccRCCsd): Updated results of activity and predictive biomarkers from a phase II study. First Author: Ronan Flippot, Dana-Farber Cancer Institute, Boston, MA

Background: NccRCC and ccRCCsd are aggressive tumors associated with poor prognosis and response to therapy. Combination strategies co-targeting VEGF signaling and inhibitory immune checkpoints are highly active in clear-cell renal cell carcinoma, but data is lacking in NccRCC and ccRCCsd. We conducted a multicenter, open-label, single arm phase II trial of atezolizumab plus bevacizumab in NccRCC and ccRCCsd. Methods: Patients with NccRCC and ccRCCsd (≥ 20% sarcomatoid differentiation), and EOCG performance status of 0-2 were eligible. Prior systemic treatment was allowed with the exception of prior PD-1/PD-L1-directed therapy. Atezolizumab 1200mg and bevacizumab 15mg/kg were administered every 3 weeks until progression, unacceptable toxicity, or patient withdrawal. Primary endpoint was objective response rate (ORR) per RECIST 1.1. Exploratory biomarker analyses included PD-L1 expression on tumor (TC) and immune cells (IC), and spatial analysis of the immune infiltrate. Results: Sixty patients received at least 1 cycle of treatment, among whom 56 were evaluable for response (17 ccRCCsd and 39 NccRCC). ORR was 34% in the overall population, 53% in NccRCC, and 26% in ccRCCsd. Median progression-free survival was 8.4 months (95%CI, 6.9-16.5). Baseline tumor tissue was available for 36 patients. TC PD-L1 expression ≥1% was associated with improved ORR (9/14, 64%) compared to patients with PD-L1 expression < 1% (4/20, 20%). Patients with TC PD-L1 expression ≥1% who experienced progression as best response had shorter average distance between tumor cells and nearest neighboring immune cells at baseline. Further analysis of the immune tumor microenvironment on an expanded cohort, including IC PD-L1 expression and correlation with clinical outcomes, is ongoing and will be updated. Conclusions: The combination of atezolizumab plus bevacizumab is active in NccRCC and ccRCCsd. Candidate predictive biomarkers include PD-L1 expression in TC and topological analysis of the immune infiltrate. Clinical trial information: NCT02724878.

**4585** Poster Session (Board #411), Mon, 1:15 PM-4:15 PM

Metastatic penile (mPSCC), uterine cervical (mSCC), and skin (mSSCC) squamous cell carcinomas: A comparative genomic profiling (CGP) study. First Author: Joseph Jacob, SUNY Upstate Medical University, Syracuse, NY

Background: We compared the genomic alteration (GA) profiles of mSCC, mPSCC and mSSCC to study impact on the targeted and immunotherapy options for the men and women suffering from these refractory cancers. Methods: 78 mPSCC, 604 mSCC and 336 mSSCC underwent CGP using a hybrid-capture based assay. Tumor mutational burden (TMB) was determined on 1.1 Mb of sequenced DNA and microsatellite instability (MSI) was determined on 114 loci. Results: The TMB > CDKN2A- status was significantly more frequent in the mSCC than mPSCC or mSSCC (P < 0.0001). The GA/ tumor frequencies were similar in mSCC and mPSCC, but significantly lower in mSSCC (P < 0.0001). TP53 mutations were more common in mSCC (UV light exposure) and mPSCC (likely due to loss of an original HPV+ status). TERT, NOTCH1 and FAT1 GA were more frequent in mPSCC and mSCC whereas PIK3CA GA were more common in mSCC. MTOR pathway target (GA were more frequent in mPSCC and mSSCC whereas PIK3CA GAs were more common in mSCC. MBRM1-0.0063 in the ORR scale is observed between 2.3 GA/tumor. The most frequent un-targetable GA were ATRX (25%), TP53 (13%) SDHB (13%), CTNNB1 (7%), VHL (7%), and CDKN2A/2B, PIK3CD, NOTCH2 and MEN1 (all 5%). The most frequent potentially targetable GA included RET (9%), NF1 (9%) and FGFR1 (5%). TP53 GAs were more common in mSSCC. STK11 mutations were more common in mSSCC (UV light exposure) and mPSCC (likely due to loss of an original HPV+ status). TERT, NOTCH1 and FAT1 GA were more frequent in mPSCC and mSCC whereas PIK3CA GA were more common in mSCC. MTOR pathway target (GA were more frequent in mPSCC and mSSCC. MSI high status was extremely rare in mCSCC, mPSCC and mSSCC share a variety of clinicopathologic features, the 3 tumor types suggest that immunotherapies would be beneficial in a large subset of patients.

**4584** Poster Session (Board #410), Mon, 1:15 PM-4:15 PM

Malignant phaeochromocytoma (MP): A comprehensive genomic profiling (CGP) study. First Author: Vennady Bratslavsky, Urologic Oncology Branch, National Cancer Institute at the National Institutes of Health, Bethesda, MD

Background: We CGP to characterize the genomic alterations (GA) in MP and to enable the search for potential therapy targets. Methods: From a series of 201,766 consecutive clinical cases, 44 cases of clinically advanced MP underwent CGP using a hybrid-capture based commercial assay to evaluate all classes of GA. Tumor mutational burden (TMB) was determined on 1.1 Mb of sequenced DNA and reported as mutations/Mb and microsatellite instability (MSI) was determined on 114 loci. PD-L1 expression was determined by IHC (DAKO 22C3 antibody). Results: All patients had clinically advanced recurrent and/or metastatic disease. 23 patients were females and 21 patients were males. There were 34 (77%) of MP known to have originated in the adrenal gland and 10 (23%) of the MP were sequenced from metastatic site where the exact primary site was unknown. The primary tumor was used for sequencing in 14 (32%) of the MP cases and a non-primary tumor metastatic site (liver, lung, bone, soft tissue, lymph node, kidney, peritoneal cavity, and chest wall) in 30 (68%) of the MP cases. There were 2.3 GA/Tumor. The most frequent un-targetable GA were ATRX (25%), TP53 (13%) SDHB (13%), CTNNB1 (7%), VHL (7%), and CDKN2A/2B, PIK3CD, NOTCH2 and MEN1 (all 5%). The most frequent potentially targetable GA included RET (9%), NF1 (9%) and FGFR1 (5%). PBMR1 GA were found in 2% of MAP. Germline mutations in known cancer predisposition genes were predicted in 8 (18%) of cases involving SDHB (5 cases) and BRCA1, MEN1, and MS (1 case each). The genomic signatures of primary MP were not significantly different from that obtained from sequencing of metastatic site biopsies. 0% of MP stained positively for PD-L1 expression. The mean TMB was 2.95 mutations/Mb, the median TMB was 2.4 mutations/Mb. There were 2 (5%) of MP with TMB ≥ 10 mutations/Mb and 0% (0%) with TMB ≥ 20 mutations/Mb. 0% (0%) of MP evaluated for MSI had a MSI-High status. Conclusions: Although the GA/tumor is relatively low for MP, CGP can reveal important potential therapy targets including RET, NF1 and FGFR1. MP do not reveal strong potential for immunotherapies with low TMB, absence of MSI-High status and low (2%) PBMR1 mutation frequencies.

**TPS4586** Poster Session (Board #412a), Mon, 1:15 PM-4:15 PM

A randomized phase II study of atezolizumab plus recombinant human IL-7 (CYT107) vs atezolizumab alone in patients with locally advanced or metastatic urethelial carcinoma (mUC): A Cancer Immunotherapy Trials Network Trial (CITN-14). First Author: Evan Y. Yu, University of Washington, Seattle, WA

Background: Atezolizumab is a regulatory-approved PD-L1 antagonistic antibody for the post-platinum mUC setting. Responses to atezolizumab are highly efficacious in a subset of patients, but suboptimal or absent in most patients. IL-7 (CYT107) is a homeostatic growth factor that promotes proliferation, differentiation, and survival of T lymphocytes. We recently demonstrated CYT107 significantly increases peripheral absolute lymphocyte and T cell numbers in metastatic castration-resistant prostate cancer patients when administered after sipuleucel-T. We hypothesize expansion of T cells by CYT107 may improve responses to PD-L1 inhibition. To test this hypothesis, we designed a randomized trial (NCT03513952) in mUC comparing the combination of CYT107 and atezolizumab to atezolizumab alone. Methods: Patients with ECOG PS ≤ 2 and RECIST v1.1 measurable mUC with disease recurrence after platinum-based chemotherapy are eligible. A safety run-in of 6 patients with staggered enrollment to atezolizumab plus CYT107 will be followed by randomization if < 2 patients experience a DLT. An additional 48 patients will then be randomized 1:1 to atezolizumab 1200 mg IV q3wks or with CYT107 10 μg/kg IM qwk X 4, started 1 wk before atezolizumab. The primary endpoint is RECIST v1.1 ORR, with HR € 14.8% and H (45%, one-sided a 0.10; power 88%). An interim futility analysis will be performed after 24 randomized patients have their first disease assessment; cessation of the trial will occur if an O'Brien-Fleming futility boundary of < -0.0063 in the ORR scale is observed between the experimental and control arm. Secondary endpoints include clinical benefit rate, PFS, DOR, OS, results by PD-L1 expression stratification, and safety. Exploratory correlative evaluations of tumor-infiltrating immune cells, interferon γ expression, inflammatory gene expression, ELISPOT, T cell receptor sequencing, serum metabolite levels, gut microbiome, and PK analyses will be performed. Current status: Trial accrual has begun and is anticipated to complete around mid-2020. Clinical trial information: NCT03513952.
TPS4587 Poster Session (Board #412b), Mon, 1:15 PM-4:15 PM
A phase 3 randomized study of neoadjuvant chemotherapy (NAC) alone or in combination with nivolumab (NIVO) + BMS-986205 in cisplatin-eligible muscle invasive bladder cancer (MIBC). First Author: Guru Sonpavde, Dana-Farber Cancer Institute, Boston, MA

Background: Immuno-oncology (IO) therapies have revolutionized the treatment (tx) of pts with advanced bladder cancer (advBC). For pts with cisplatin-eligible MIBC, the recommended tx regimen is cisplatin-based NAC prior to radical cystectomy (RC). However, since only ~30% of pts achieve a pathologic complete response (pCR) translating to improved long-term outcomes with approved regimens, new therapies are needed. PD-L1 expression is associated with aggressive BC and has been shown to increase in BC after NAC, suggesting that the PD-1/PD-L1 axis is a valid therapeutic target. Additionally, expression of indoleamine 2,3-dioxygenase (IDO) is higher in BC than in normal bladder tissue and is associated with advanced disease and poor clinical outcome. BMS-986205, a selective, potent, once-daily oral IDO1 inhibitor that works early in the IDO1 pathway to reduce kynurenine production, has demonstrated clinical activity in combination with NIVO (anti–PD-1) in pts with IO tx-naive advBC who had >1 prior line of therapy (QRR, 37%). Taken together, these data provide a rationale for investigating NAC + NIVO + BMS-986205 in MIBC. Here we describe a phase 3 study evaluating the efficacy and safety of NAC + NIVO + BMS-986205 followed by RC and continued 10 tx in pts with MIBC (NCT03661320).

Methods: Pts aged ≥18 years with previously untreated MIBC (clinical stage T2-T4a, NO, MO), creatinine clearance ≥50 mL/min, and predominant UC histologies who are eligible for cisplatin-based NAC and RC will be enrolled. Pts with evidence of positive lymph node; metastatic BC; or prior systemic therapy, radiotherapy, or surgery for BC other than TURBT are not eligible. Pts will be randomized to receive NAC (gemcitabine/cisplatin; arm A), NAC + NIVO + oral placebo (arm B), or NAC + NIVO + BMS-986205 (arm C) following neoadjuvant therapy. Patients in arms B and C will receive BMS-986205 for 22 cycles. Pts with a high PIS will be randomized 1:1 to receive cisplatin-based neoadjuvant therapy (22 pt) or DU 1500 mg + TRE 75 mg every 4 weeks x 3 cycles (22 pt). If more than 8 responses (pT0) are observed in first 22 pts included in DU+TRE arm, 24 additional pts will be recruited in this arm. Pts are considered non-responders if no reductions in the anti-tumor activity of DU/TRE measured as pT0 rate in pts with a positive PIS. Disease free survival and safety profile will also be evaluated. Tissue, plasma and urine samples will be collected for translational studies. Clinical trial information: NCT03472274.

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TPS4588 Poster Session (Board #413a), Mon, 1:15 PM-4:15 PM
DUTRENEO Trial: A phase II randomized trial of DUvalumab and TREmelumab as NEOadjuvant approach in muscle-invasive urothelial bladder cancer (UC) patients progressing selected by immune signatures. First Author: Enrique Grande, MD Anderson Cancer Center Madrid, Madrid, Spain

Background: Cisplatin-based neoadjuvant chemotherapy (CT) followed by cystectomy improves overall survival in patients (pts) with MIBC. Immune checkpoint inhibitors as single agents are approved in pts with advanced UC. Combination of both programmed cell death ligand-1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) checkpoints might be synergistic. Durvalumab (DU) is a selective, engineered, human IgG1 monoclonal antibody (mAb) that blocks PD-L1 binding to PD-1. Pembrolizumab and atezolizumab, have shown a promising activity (including significant pathologic complete responses (pT0) in MIBC pts candidate to cystectomy, with better results in those pts with PD-L1 overexpression. It is expected that the dual targeting of the immune system with an anti-PDL1 + anti-CTLA4 such as DU and TRE in the neoadjuvant setting may improve these outcomes. In addition, the most precise selection of pts according to a molecular INF-gamma signature is intended to increase the efficacy.

Methods: This is a prospective and randomized phase II, open-label study conducted in urothelial MIBC pts diagnosed of T2-T4 and/or N+ candidates to cystectomy. ECOG 0-1 and adequate organ function. Pts will be treated according to the score of a pro-inflammatory signature (PIS) determined with Nanostring technology. Pts with a high PIS will receive DUrvalumab and TREmelumab (DU+TRE) at 22 mg/kg every 2 weeks for 12 cycles. Pts with a high PIS will be randomized 1:1 to receive cisplatin-based neoadjuvant therapy (22 pt) or DU 1500 mg + TRE 75 mg every 4 weeks x 3 cycles (22 pt). If more than 8 responses (pT0) are observed in first 22 pts included in DU+TRE arm, 24 additional pts will be recruited in this arm. PD-L1 expression is determined by pS142 (Ventana SP142 immunohistochemistry assay). The primary endpoint is pCR after neoadjuvant tx and event-free survival (arms C vs NAC + NIVO + oral placebo (arm B), or NAC + NIVO + BMS-986205 (arm C) following neoadjuvant therapy. Patients in arms B and C will receive BMS-986205 for 22 cycles. Pts with a high PIS will be randomized 1:1:1 to receive cisplatin-based neoadjuvant therapy (22 pt) or DU 1500 mg + TRE 75 mg every 4 weeks x 3 cycles (22 pt). If more than 8 responses (pT0) are observed in first 22 pts included in DU+TRE arm, 24 additional pts will be recruited in this arm. Pts are considered non-responders if no reductions in the anti-tumor activity of DU/TRE measured as pT0 rate in pts with a positive PIS. Disease free survival and safety profile will also be evaluated. Tissue, plasma and urine samples will be collected for translational studies. Clinical trial information: NCT03472274.
EV (1.25 mg/kg) was generally well tolerated with a confirmed ORR of 43% in of mUC pt samples (Petrylak ASCO 2017). In a phase 1 study (NCT02091999), approach may provide additional benefit. Enfortumab vedotin (EV), an ineligible for first-line (1L) cisplatin (PD-L1 positive), or are ineligible for 1L reserve University, Cleveland, OH TPS4583 Poster Session (Board #425b), Mon, 1:15 PM-4:15 PM until ~550 pts are enrolled. Clinical trial information: NCT03711032. of response (DOR), 12-month DOR rate in pts with CR and safety and applicable) every 12 weeks for years 1-2 and every 24 weeks for years 3-5 and blinded independent central review of urine cytology and biopsy (as and have an ECOG PS score of 0-2. Responses are assessed by cystoscopy and blinded independent central review of urine cytology and biopsy (as applicable) every 12 weeks for years 1-2 and every 24 weeks for years 3-5 and by computed tomography urography every 8 months through year 5. Treatment will continue with pembrolizumab for up to 2 years and BCG for 3 years or until confirmed HR NMIBC persistence, recurrence, or disease progression, unacceptable toxicity, or pt/physician decision to withdraw. Primary end points for safety include completeness rate in pts with CIS. Secondary endpoints are event-free survival (EFS), recurrence-free survival, overall survival, disease-specific survival, time to cystectomy, 12-month EFS rate in all pts, duration of response (DOR), 12-month DOR rate in pts with CR and safety and tolerability. Recruitment began in November 2018 and will continue until ~550 pts are enrolled. Clinical trial information: NCT03711032.

EV-103: Enfortumab vedotin plus pembrolizumab and/or chemotherapy for locally advanced or metastatic urothelial cancer. First Author: Christopher J. Holmes, University Hospitals Cleveland Medical Center/Case Western Reserve University, Cleveland, OH Background: PD-(L)1-targeted immune checkpoint inhibitors (ICIs), such as pembrolizumab (P), are approved for patients with locally advanced or metastatic urothelial cancer (la/MUC) who progress after platinum, are ineligible for first-line (1L) cisplatin (PD-L1 positive), or are ineligible for 1L platinum. The ORR for CPI in all treated pts is ~25%, and a combination approach may provide additional benefit. Enfortumab vedotin (EV), an investigational antibody-drug conjugate, delivers the microtubule-disrupting agent monomethyl auristatin E to cells expressing Nectin-4, found in 97% of mUC pt samples (Petrylak ASCO 2017). In a phase 1 study (NCT02091999), EV (1.25 mg/kg) was generally well tolerated with a confirmed ORR of 43% in 112 MUC pts (Rosenberg ASCO-GU 2019). These encouraging results, with the potential for an enhanced immune response, suggest that EV+P may improve response rates and extend response durability. Methods: EV-103, a phase 1b trial for non-resectable la/MUC pts with no prior CPI, added an additional 4 cohorts (Parts 2 and 3) in an Oct 2018 amendment. It is now expected to enroll ~159 pts. Dose escalation parts (EV+P, 1L or 2L) must be ineligible for 1L cisplatin-based chemotherapy or have disease progression during/following treatment with ≥1 platinum-containing regimen. Dose expansion (Part 1) will evaluate EV+P in 1L (Cohort A) and 2L settings (Optional Cohort B). Part 2 will evaluate 1L EV+cisplatin (Cohort D), 1L EV+carboplatin (Cohort E), and 1L or 2L EV+gemcitabine (Optional Cohort F). Part 3 (Cohort G) will evaluate 1L EV+P+cisplatin or carboplatin, depending on pts cisplatin-eligibility. In all cohorts, pts receive EV on Days 1 and 8 of each 3-week cycle. In combination therapy, pts receive P, cisplatin, and carboplatin on Day 1 or gemcitabine on Days 1 and 8 of each cycle. The primary objective is to assess the safety/tolerability of EV+P and/or chemotherapy. Secondary objectives are establishing EV recommended dose for combination therapies, assessing ORR per RECIST for all cohorts and per iRECIST for therapies with pembrolizumab, as well as assessing disease control rate, duration of response, PFS, OS, PK, and biomarkers. The study opened Oct 2017. Clinical trial information: NCT03288545.
TPS4595  Poster Session (Board #416b), Mon, 1:15 PM-4:15 PM

A phase III randomized open label study comparing bempegaldesleukin (NKTR-214) plus nivolumab to sunitinib or cabozantinib (investigator’s choice) in patients with previously untreated advanced renal cell carcinoma. First Author: Nizar M. Tannir, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Bempegaldesleukin (NKTR-214) is a CD122-preferential IL-2 pathway agonist that stimulates proliferation and activation of tumor antigen-specific CD8+ T cells and natural killer cells within the tumor microenvironment and increases PD-1/PD-L1 expression. These properties make bempegaldesleukin (NKTR-214) a potentially promising agent for combination therapy with checkpoint inhibitors that target and inhibit the PD-1/PD-L1 pathway. In phase 1 studies, NKTR-214 plus nivolumab demonstrated encouraging objective response rates (ORR) in first-line renal cell carcinoma (RCC) and an acceptable safety profile. Immunotherapy with NKTR-214 plus nivolumab may lead to greater clinical benefit than tyrosine kinase inhibitors (TKIs), standard-of-care agents, in this patient population. Methods: This multicenter, randomized, open-label phase 3 study (NCT03720019245) will evaluate the efficacy and safety of bempegaldesleukin (NKTR-214) plus nivolumab compared with investigator’s choice of TKI (sunitinib or cabozantinib) in patients with previously untreated advanced or metastatic RCC with clear cell component. Exclusion criteria include active brain metastasis and autoimmune disease. Approximately 600 patients will be randomized in a 1:1 ratio, stratified by PD-L1 status (≥1% vs <1% or indeterminate). International Metastatic RCC Database Consortium prognostic score (1-2 [intermediate risk] vs 3-6 [poor risk]); and TKI (sunitinib or cabozantinib; cabozantinib percentage to be capped at 50%). Combination therapy will consist of bempegaldesleukin (NKTR-214) 0.006 mg/kg intravenously (IV) every 3 weeks (Q3W) plus nivolumab 360 mg IV Q3W until progression or death or maximum of 2 years. TKI therapy will consist of sunitinib 50 mg orally once daily (QD) for 4 weeks followed by 2 weeks off or cabozantinib 60 mg orally QD. Primary objectives are ORR by blinded independent central radiology (BICR) assessment and overall survival. Secondary objectives are progression-free survival by BICR, safety, predictive value of PD-L1 expression, and quality of life. Enrollment is ongoing. Clinical trial information: NCT03729245.

TPS4596  Poster Session (Board #417a), Mon, 1:15 PM-4:15 PM

PDIGREE: An adaptive phase 3 trial of PD-inhibitor nivolumab and ipilimumab (IPI-NIVO) with VEGF TKI cabozantinib (CABO) in metastatic untreated renal cell carcinoma (Alliance A031704). First Author: Tian Zhang, Duke University Medical Center, Durham, NC

Background: First-line treatment of mRCC has rapidly changed to include IPI-NIVO or CABO, with clinical benefit of each based on the Checkmate 214 and CABOSUN trials. Combination immunotherapy with VEGF therapies have shown benefit in the JAVELIN 101 and KEYNOTE 426 trials over sunitinib. It is yet unclear which patients (pts) benefit most from combination immunotherapy-VEGF inhibitors, and the optimal sequence of drugs. Methods: In an adaptive, randomized, multicenter, phase 3 trial (Alliance A031704, PDIGREE), pts will start treatment with induction IPI 1mg/kg and NIVO 3mg/kg intravenously (IV) once every 3 weeks. Key inclusion criteria include clear cell mRCC, IMDC intermediate or poor risk, Karnofsky performance status (KPS) >70, and no prior treatments for mRCC. Based on 3-month radiographic assessment (after completing IPI-NIVO combination), pts with complete responses (CR) will undergo maintenance NIVO 480mg IV every 4 weeks, pts with progression of disease (PD) will switch to CABO 60mg oral daily, and pts with new/CR/non-PD will be randomized to NIVO 480mg IV every 4 weeks versus NIVO 480mg IV every 4 weeks with CABO 40mg oral daily. Randomization will be stratified by IMDC risk criteria and presence of bone metastases. The primary endpoint of the study is overall survival (OS). We hypothesize that 3-year OS rate will improve to 70% for NIVO-CABO compared to 60% for NIVO alone; to achieve 85% power with a two-sided alpha of 0.05 and exponential distribution, 696 patients will be enrolled. Key secondary endpoints include PFS, 12-month CR rate, ORR based on RECIST 1.1 and irRECIST criteria, and toxicity profiles. Quality of life will be assessed based on the FKS1-19, PROMIS-fatigue, and EQ5D-5L questionnaires. Biomarkers associated with CR and association of IL-6 with treatment benefit will be assessed. Other tissue-based and plasma-based biomarkers are planned. Enrollment will begin this year. Support from UG1CA189823, U24CA196171; https://acknowledgments.alliancefound.org. Clinical trial information: NCT03793166.

TPS4597  Poster Session (Board #417b), Mon, 1:15 PM-4:15 PM

PROSPER: A phase III randomized study comparing perioperative nivolumab (nivo) in observation in patients with renal cell carcinoma (RCC) undergoing nephrectomy (EOCG-ACRIN 8143). First Author: Lauren Christine Harshman, Dana-Farber Cancer Institute, Boston, MA

Background: The anti-PD-1 antibody nivo improves overall survival (OS) in metastatic RCC and is well tolerated. There is no standard adjuvant (adjuv) systemic therapy that increases OS over surgery alone for non-metastatic RCC. Priming the immune system prior to surgery with anti-PD-1 has shown an OS benefit compared to a pure adjuv approach in mouse solid tumor models. Multiple ph 2 studies in bladder, lung and breast cancers have shown remarkable pathologic responses with neoadjuvant (neoadj) PD-1 blockade. Two ongoing ph 2 studies of perioperative nivo in M0 RCC patients are showing preliminary feasibility and safety with no surgical delays (NCT02595918). PROSPER RCC (NCT03055013) aims to improve clinical outcomes by priming the immune system prior to nephrectomy with neoadj RCC and continued engagement with adjuv blockade in patients with high risk RCC compared to surgery alone. Methods: This global, unblinded, phase 3 National Clinical Trials Network study is currently accruing patients with clinical stage ≥T2 or Tany+N+ RCC of any histology planned for nephrectomy. Oligometastases are permitted if can be rendered NED. We amended the study to enhance accrual and patient quality of life by changing nivo dosing to 480mg q 4 wks and requiring baseline tumor biopsy only in the nivo arm. The investigational arm receives 1 dose of nivo prior to surgery followed by 9 adjuv doses. The control arm undergoes standard nephrectomy followed by observation. Randomized patients are stratified by clinical T stage, node positivity, and M stage. Accrual of 805 patients provides 84.2% power to detect a 14.4% absolute benefit in recurrence-free survival (RFS) at 5 years assuming the ASSURE historical control of ~56% to 70% (HR = 0.70). The study is powered to reveal a significant increase in OS (HR = 0.67). Critical perioperative therapy considerations such as safety, feasibility, and quality of life endpoints have been integrated. PROSPER RCC embeds a wealth of translational work aimed at investigating the impact of the baseline immune milieu, the changes induced by neoadjuvant anti-PD-1 priming, and how both may predict clinical outcomes. Clinical trial information: NCT03055013.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Impact of darolutamide (DARO) on pain and quality of life (QoL) in patients (Pts) with nonmetastatic castrate-resistant prostate cancer (nmCRPC).

**Background:** DARO is a structurally distinct androgen receptor antagonist for the third-generation AR antagonists.

**Results:** DARO significantly delayed pain progression vs placebo (PBO) (40.3 vs 25.4 mo; HR 0.65; 95% CI 0.50–0.80; P < 0.001) and delayed metastasis-free survival (MFS) was significantly prolonged vs placebo (PBO) (0.71; 95% CI 0.50–0.99; P = 0.045). Methods: 1509 pts were randomized 2:1 to DARO 600 mg (two 300 mg tablets) twice daily (n = 955) or PBO (n = 554) while continuing androgen deprivation therapy (ADT). Primary endpoint was MFS. Secondary endpoints included OS and time to pain progression (assessed by Brief Pain Inventory Short Form). QoL was assessed by European Organisation for Research and Treatment of Cancer QoL Prostate Cancer module (EORTC-QLQ-PR25) at baseline (BL) and every 16 wk until end of treatment. Analysis of time to deterioration in EORTC-QLQ-PR25 subscales, defined as first occurrence of a minimally important difference (half the standard deviation of BL value), used Kaplan–Meier estimators and stratified Cox proportional hazard models. Results: DARO significantly delayed pain progression vs PBO (40.3 vs 25.4 mo; HR 0.65; 95% CI 0.53–0.79; P < 0.001); this was maintained beyond end of study treatment. Time to deterioration of EORTC-QLQ-PR25 outcomes showed statistically and clinically significant delays with DARO vs PBO for urinary symptoms (25.8 vs 14.8 mo; HR 0.64; 95% CI 0.54–0.76; P < 0.01). Time to deterioration of hormonal treatment-related symptoms was comparable with DARO vs PBO (18.9 vs 18.4 mo; HR 1.06; 95% CI 0.88–1.27; P = 0.52). DARO was well tolerated. Exposure-adjusted incidences (pts per 100 years’ exposure) of AE of interest were similar/lower with DARO vs PBO (fatigue/asthenic conditions [11.3 vs 11.1], hypertension [4.7 vs 5.1], hot flush [3.7 vs 4.1], fracture [3.0 vs 3.5], falls [2.7 vs 4.1], cognitive disorder [0.3 vs 0.2], and seizure [0.2 vs 0.2]). Conclusions: For nmCRPC pts, DARO prolongs MFS, is well tolerated, maintains QoL, and delays worsening of pain and disease-related symptoms compared with PBO. Clinical trial information: NCT02200614.

**PSMA heterogeneity and DNA repair defects in prostate cancer.**

**Background:** Prostate-specific membrane antigen (PSMA) is a promising target for theranostics in metastatic castration resistant prostate cancer (mCRPC). Methods: Membranous PSMA (mPSMA) expression was immunohistochemically evaluated in castration sensitive (CSPC) (n = 38) and mCRPC (n = 60) tissue biopsies, and associations with molecular aberrations (next-generation sequencing; NGS) and clinical outcome were determined. Results: mPSMA expression was significantly higher (p = 0.005) in mCRPC biopsies (median H-score [interquartile range]: 55.0 [2.8-117.5]) compared to CSPC biopsies (17.5 [0.0-60.0]). Furthermore, patients with higher mPSMA expression (> median H-score) at diagnosis had higher Gleason Grade (p = 0.04) and shorter OS (p = 0.006). Critically, 42% (16/38) of CSPC biopsies and 27% (16/60) of mCRPC biopsies were completely negative for mPSMA expression. In addition, CSPC and mCRPC biopsies expressing mPSMA demonstrated marked intra-tumor heterogeneity in expression levels, commonly exhibiting areas without detectable PSMA (CSPC < 100%; mCRPC < 84%), while heterogeneous mPSMA expression between metastases from the same patient was also observed. Subsequent genomic analysis showed that mCRPC patients with deleterious DNA damage repair (DDR) aberrations have higher (p = 0.016) mPSMA expression (87.5 [25.0-247.5]) than those without these (20 [0.3-98.8]). Furthermore, 9 of the 11 patients (82%) responding to PARP inhibition had a mPSMA H-Score above the median. The association between mPSMA expression and DDR aberrations was validated in an independent cohort with known DDR aberrations. Tumors with DDR aberrations had significantly higher mPSMA (median H-score [interquartile range]: 136.3-300) p = 0.005; BRCA2 300 [165-300] p < 0.001) than unselected mPSMA biopsies (55.0 [2.7-117.5]). Finally, analyses of 122 mCRPC biopsy transcriptions confirmed a negative correlation between PSMA and BRCA2 mRNA expression (p = 1.5×10^-10). Conclusions: mPSMA expression in CSPC and mCRPC exhibits marked intra- and inter-patient heterogeneity, limiting the clinical utility of PSMA-targeted theranostics. We show for the first time that DDR gene aberrations associate with high mPSMA expression and may serve as predictive biomarkers for PSMA-targeted therapies.

Interest of short hormonotherapy (HT) associated with radiotherapy (RT) as salvage treatment for metastatic free survival (MFS) after radical prostatectomy (RP). Using data from 9 years of the GETUG-AFU 52 randomized trial (NCT00423475). First Author: Christian Carrie, Leon Berard Center, Radiotherapy Department, Lyon, France

**Background:** RT is the standard salvage treatment after RP. The role of HT is not formally demonstrated to date. This trial assessed the efficacy of RT alone vs RT+HT in terms of progression-free survival (PFS), metastase-free survival (MFS) and overall survival (OS) in patients with biological relapse (BR) after RP. After a median follow-up (FU) duration of 5.3 years, we previously reported (Carrie C, Lancet Oncol 2016) a benefit in PFS (80% vs 62% PFS free at 5 years; p < 0.0001) in the combined arm, whatever the risk subgroups. Methods: Patients (pts) were randomized (1:1) to RT alone or RT+HT (goserelin, for 6 months). The randomization was stratified according to radiotherapy modality and risk group. Short term risk was defined as Gleason score < 8, surgical margins+, psa doubling time ≥ 8 months and no seminal vesicle involvement. Assuming a 45% 5-year PFS of 45% in the RT arm, the trial required 369 pts per arm to detect an improvement of 12% on PFS in RT+HT arm (90% power and 5% bilateral alpha risk), possibly translating into a 10% gain in OS (75% to 85% with 80% power). Biological relapse (BR) was defined according to ASTRO-consensus. Results: At the time of data cutoff (March 2019), the median follow-up duration was 112 months. We confirm the benefit of RT+HT on PFS (HR = 0.54 (C195% = 0.43-0.68) ; P < 0.0001) whatever the risk subgroup (HR = 0.47 (C195% = 0.28-0.80) and 0.56 (C195% = 0.44-0.73) for low and high risk patients, respectively. Metastatic free survival (MFS) is significantly improved in the combined arm (HR = 0.73 (C195% = 0.54-0.98) ; P = 0.034) with 69% [C195% = 63-74] versus 75% [C195% = 70-80] of MFS at 10 years for RT alone and RT+HT, respectively. Conclusions: Salvage radiotherapy combined with short term HT significantly improved 10-years metastatic free survival compared with RT alone. Short term radiotherapy alone. GETUG-AFU 52 confirmed the previously published results from RTG-9601, confirm that this strategy can be considered as the new standard for salvage treatment after radical prostatectomy. Clinical trial information: NCT00423475.

Updated results from a randomized phase II study of cabazitaxel (CAB) versus abiraterone (AB) or enzalutamide (ENZ) in poor prognosis metastatic CRPC. First Author: Kim N. Chi, BC Cancer, Vancouver, BC, Canada

**Background:** The treatment for poor prognosis mCRPC includes taxanes and androgen receptor (AR) targeted therapy, however the optimal treatment is undefined. Methods: Patients (pts) with poor prognosis (liver metastases, early CRPC (> 12 months from ADT start), and/or > 3 of 6 poor prognostic criteria (Chi et al, Annals of Oncol, 2016)) were randomized to receive CAB (Arm A) or AR targeted therapy (Arm B, ABI or ENZ by investigator choice) with cross over at progression, Primary objective was to determine the clinical benefit rate (CBR) (PSA decline ≥50% (PSA50), objective response (OR), or stable disease (SD) ≥12 weeks). Plasma was sampled serially for circulating tumour DNA (ctDNA). Results: 95 pts were randomized (Arm A: 45, Arm B: 50). 18% had liver mets, 88% early CRPC and 30% had > 3 of 6 poor prognostic criteria. 52% of pts had prior docetaxel, half for castration sensitive disease. Table summarizes 1-line therapy outcomes. Baseline ctDNA fraction > 15% (median) was associated with shorter 1-line progression-free survival (PFS) (median 2.8 vs 8.4 m, HR = 2.54, P < 0.001) and overall survival (OS) (median 14.0 vs 38.7 m, HR = 2.64, P < 0.001), ctDNA alterations in AR, TP53, PI3K pathway, RB1 and DNA repair were detected in 53%, 45%, 31%, 23%, and 21% of pts. Shorter PFS and OS were associated with AR gain (HR 2.57 (95% CI 1.63-4.06); HR 3.59 (1.9-6.69), respectively) and TP53 defects (HR 2.62 (CI 1.65-4.19); HR 3.33 (CI 1.86-6.14), respectively). Pts with concurrent defects in TP53 and RB1 had a trend for worse PFS/OS than pts with TP53 defect alone. AR rearrangements predicted to disrupt the ligand binding domain were detected in 6% of pts and had a shorter PFS (HR = 2.60 (1.11 - 6.09)) with a trend for shorter OS (HR = 2.27 (0.89 - 5.81)). Conclusions: In this poor prognosis cohort, 1-line treatment with CAB had a higher clinical benefit rate than treatment with ABI/ENZ. Elevated ctDNA and genomic alterations in TP53 and AR were prognostic. Supported in part by Sanofi. Clinical trial information: NCT02254785.
**5004 Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

**TAXOMET: A French prospective multicenter randomized controlled phase II study comparing docetaxel plus metformin versus docetaxel plus placebo in mCRPC.**

*First Author: MARC Pujalte Martin, Centre Antoine Lacassagne, Nice, France*

**Background:** Docetaxel (DOCE) is a standard of care in metastatic castration-resistant prostate cancer (mCRPC). Several retrospective cohort studies suggest a decrease in PC incidence and mortality with metformin (MET). MET has also demonstrated anti-tumor activity in PC preclinical models, with increased apoptosis when added to DOCE. The addition of MET could enhance DOCE efficacy in mCPRC patients (pts). **Methods:** TAXOMET is a phase II prospective multicentric randomized controlled trial. Non-diabetic mCPRC pts were assigned 1:1 to receive DOCE 75mg/m² every 21 days + prednisone (P) 5mg twice a day and either MET 850mg twice a day (arm A) or placebo (arm B), up to 10 cycles. The primary end point was PSA response rate (=50% decrease). Main secondary endpoints included objective response rate (ORR, according to RECIST v1.1), clinical and biological progression-free survival (PFS), overall survival (OS), toxicity and quality of life (QoL). Comparisons between arm A and B were performed using Chi² test for qualitative data and Log-rank test for survival data. **Results:** From January 2013 to December 2015, 99 pts were randomized (49 pts in arm A and 49 pts in 10 french centers, and 95 pts were evaluable. No difference was observed between arm A and arm B in PSA-response rate (72% in both arms), ORR (28% in both arms), clinical or biological mPFS (7.3 months vs 5.8 months p = 0.848) and mOS (24.2 months (95CI: 17.2 – 33.7) vs 19.7 months (95CI: 14.8 – 36.4) p = 0.53), respectively. There were no severe or fatal adverse events, except a trend for diarrhea to be more common with MET (70% in arm A vs 50% in arm B, p = 0.072), but few grade 3-4 events. There was no difference in QoL according to QLQ-C30 score between the two arms during the treatment period. **Conclusions:** This is the first prospective randomized controlled trial to evaluate the combination of MET with DOCE in mCPRC. The addition of MET has no meaningful clinical benefit in this setting. Clinical trial information: NCT01796028.

**5006 Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

**First results from TITAN: A phase III double-blind, randomized study of apalutamide (APA) versus placebo (PBO) in patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) receiving androgen deprivation therapy (ADT).**

*First Author: Kim N. Chi, BC Cancer, Vancouver, BC, Canada*

**Background:** TITAN was designed to determine whether APA, a selective next-generation androgen receptor inhibitor, plus ADT improves radiographic progression-free survival (rPFS) and overall survival (OS) compared with PBO plus ADT in pts with mCSPC. **Methods:** In this randomized, double-blind phase 3 study, pts with mCSPC regardless of extent of disease were randomized (1:1) to APA (240 mg/d) or PBO, added to ADT, in 28-day cycles. Pts with prior documented adverse events, except a trend for diarrhea to be more common with MET (70% in arm A vs 50% in arm B, p = 0.072), but few grade 3-4 events. There was no difference in QoL according to QLQ-C30 score between the two arms during the treatment period. **Conclusions:** This is the first prospective randomized controlled trial to evaluate the combination of MET with DOCE in mCPRC. The addition of MET has no meaningful clinical benefit in this setting. Clinical trial information: NCT01796028.

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**5005 Oral Abstract Session, Fri, 2-45 PM-5:45 PM**

**TOPARP-B: A phase II randomized trial of the poly(ADP)-ribose polymerase (PARP) inhibitor olaparib for metastatic castration resistant prostate cancer (mCRPC) with DNA damage repair (DDR) alterations.**

*First Author: Johan Mateo, The Institute of Cancer Research & The Royal Marsden, London, United Kingdom*

**Background:** We previously reported the antitumor activity of olaparib (400 mg BID) against molecularly unselected mCPRC (TOPARP-A; Mateo et al NEJM 2015). We now report TOPARP-B, a phase II trial for patients with mCPRC preselected for putatively pathogenic DDR alterations. **Methods:** Patients with mCPRC progressing after ≥ 1 taxane chemotherapy underwent targeted sequencing of tumor biopsies and were deemed eligible when alterations (germline or somatic; mono- or bi-allelic) in any DDR gene were detected. Patients were randomized 1:1 under a “pick-the-winner” design to 400mg or 300mg of olaparib BID, aiming to exclude ≥30% response rate (RR) in either arm. The primary endpoint RR was defined as radiological response (RECIST 1.1) and/or PSAS050% fall and/or CT count conversion (Cellsear; ≥ 5 ≤ 5), confirmed after 4 weeks. Analyses of RR per gene alteration subgroup was pre-planned. Secondary endpoints included progression-free survival (PFS), tolerability, and OS. **Results:** Overall, 98 patients (median age 67.6y) were randomized, with 92 pts treated and evaluable for the primary endpoint (70% OS-evaluable; 89 PFS50%-evaluable; 55 CTC-evaluable). All had progressed on ADT; 99% were post-docetaxel, 90% post-abiraterone/enalectamide, 38% post-cabazitaxel. The overall RR was 54% (95%CI 39-69%, meeting threshold for primary endpoint) in the 400mg cohort and 37% (95%CI 23-53%) in the 300mg cohort. With a median follow-up of 30.5 months, the median PFS of APA was 5.4 mo. Subgroup analyses per altered gene indicated indicated response rates for: BRCA1/2 of 80% (24/30; mPFS 8.1mo); PALB2 57% (4/7; mPFS 5.3mo); ATM 37% (7/19; mPFS 6.1mo); CDK12 25% (5/20; mPFS 2.9mo); others [ATRX, CHEK1, CHEK2, FANC, FANCF, FANCG, FANCD2, FANCM, RAD50, WRN] 50% (4/8; mPFS 2.8mo). The highest mPFS50% response rates were observed in the BRCA1/2 (22/30; 73%) and PALB2 (4/6; 67%) subgroups. **Conclusions:** Olaparib has antitumor activity against heavily pre-treated mCPRC with DDR gene defects, with BRCA1/2 aberrant tumors being most sensitive but with confirmed responses in patients with other DDR alterations. Clinical trial information: NCT01682772.

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**5007 Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

**Decreased fracture rate by mandating bone-protecting agents in the EORTC 1333-03 trial comparing enzalutamide and Ra223 versus enzalutamide alone: An interim safety analysis.**

*First Author: Bertrand F. Tombal, Université Catholique de Louvain, Brussels, Belgium*

**Background:** Skeletal fractures, pathological or not, are a frequent and underestimated side-effect of systemic treatment of metastatic castration resistant prostate cancer (mCPRC). The ERA223 trial (NCT02043678) was recently unblinded following the report of a significant increase in the fracture rates when abiraterone is combined with Ra223. Hence, FDA and EMA advised against this combination. The question whether mandated use of bone protecting agents (BPA), zoledronic acid or denosumab, would have mitigated the fracture risk and whether this risk also exists in the enzalutamide/Ra223 combination is presently unknown. **Methods:** The phase III EORTC-1333-GUCG/PEACEIII (NCT02194842) trial compared enzalutamide vs. a combination of Ra223 and enzalutamide in asymptomatic or mildly symptomatic mCPRC patients (https://www.eortc.org/research_field/clinical-detail/1333). After the unblinding of ERA223, the trial was amended (v4.0, April 19, 2018) to mandate that all patients must start a BPA. We report the fracture rate in the safety population of 146 treated patients as of 2801/2019. **Results:** Overall, 54.2% of the patients in the enza/Ra223 arm and 51.4% of the enza arm did not receive BPA: 18.0% in the enza/Ra223 arm and 27.0% in the enza arm did not use BPA at randomization, but started during protocol treatment according to the v4.0 amendment. 27.8% and 21.6% respectively, received BPA as of randomization. **Conclusions:** There is a 13% risk of fracture with enzalutamide in asymptomatic mCPRC, in line with previous reports. This risk is significantly increased to 33% when Ra223 is added to enzalutamide. Strikingly, the risk is almost abolished by mandatory continuous administration of BPA starting at least 6 weeks before the first injection of Ra223, thus emphasizing the importance of treating mCPRC patients with BPA. Clinical trial information: NCT02194842.
Background: Androgen receptor (AR) signaling is an important growth mechanism in mCRPC, providing the rationale for treatment with AR axis inhibitors such as ENZ and AAP. Targeting AR with anti-androgens such as ENZ can result in compensatory autocrine and paracrine androgenic stimulation. Therefore, using ENZ with the androgen biosynthesis inhibitor AAP AAP could improve clinical outcomes relative to using ENZ alone.

Methods: Men with progressive mCRPC by Prostate Cancer Working Group 2 criteria were eligible. Prior treatment with taxanes for mCRPC and any prior treatment with ENZ or AAP was exclusionary. (pts) were randomized 1:1 to ENZ or ENZ/AAP at standard FDA-approved doses. Randomization was stratified by prior chemotherapy and Halabi prognostic risk groups. Treatment therapy was maintained. The primary endpoint was overall survival (OS) defined as the date of randomization from date of death or last follow-up. The log-rank test had 90% power to detect a hazard ratio (HR) of 0.7 with a one-sided type-1 error rate of 0.025. Secondary endpoints included radiographic progression free survival (rPFS) and on-treatment PSA declines. Exploratory end-points included imaging changes, and changes in serum biomarkers such as androgens, angiokines, and circulating microRNA and RNA. The primary analysis was based on the stratified log-rank test adjusting on the stratification factors. Results: Between January 2014 and August 2016, 1311 men were randomized; 657 to ENZ and 654 to ENZ/AAP balanced between arms, including stratification variables. 15.6% of pts were of high risk, 35.3% intermediate, and 48.1% low. Median OS was 33.6 mo (95% CI 30.5-36.4) and 32.7 mo (95% CI 29.9-35.4) respectively, two-sided p = 0.53. Fifty percent PSA decline rate was 80% vs. 76.5%. Grade 3-4 adverse events (AE) (all attributable factors) were 55.6% and 68.8% respectively. Treatment discontinuation due to AEs occurred in 5% and 12%, pt withdrawal in 5% and 13%, and progression or death in 57% and 48% of pts respectively. Conclusions: Addition of abiraterone acetate to enzalutamide did not prolong survival in men with mCRPC. The combination resulted in more AEs than enzalutamide alone. Support: U10CA180821, U10CA180882, U24CA196171; https://acknowledgments.alliancefound.org. Clinical trial information: NCT01949337.

5011 Poster Discussion Session: Displayed in Poster Session (Board #123), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Copy number analysis to identify tumor suppressor genes associated with enzalutamide (Enza) resistance and poor prognosis in metastatic castration-resistant prostate cancer (mCRPC) patients. First Author: Xiangnan Guan, Knight Cancer Institute, Oregon Health & Science University, Portland, OR

Background: Although enzal prolines long in mCRPC pts, the development of drug resistance and subsequent disease progression is nearly universal. Seeking to identify a potentially actionable molecular mechanism that underlie enza resistance, we analyzed whole genome sequencing (WGS) and RNA sequencing (seq) of tumors obtained from patients with enza-naive or -resistant mCRPC. Methods: One hundred and one men with mCRPC who underwent image-guided biopsy and subsequent WGS were included (n = 64 with enza-naive and n = 37 with enza-resistant mCRPC). The differential copy number alteration (CNA) events enriched in enza-resistant vs. naive samples were determined, and the prognostic significance of differential CNAs was assessed. RNA-seq data were evaluated to confirm that CNAs correlated with changes in gene expression of relevant loci and to identify potentially druggable targets selectively activated in tumors with specific CNAs. Results: Copy number loss was more common than gain in enza-resistant tumors. Specifically, we identified 123 protein-coding genes that were more commonly lost in enza-resistant samples—eight of which were previously described tumor suppressor genes. There was a strong concordance of copy number loss and reduced RNA expression of these genes. We identified one gene from this list of eight genes whose copy number loss was associated with poor overall survival (median overall survival from date of CRPC was 19.1 months in tumors with gene loss vs. 42.0 months in intact tumors, hazard ratio 3.8 [1.46-9.8], log-rank p = 0.003). Finally, Master Regulator analysis determined that tumors with copy number loss of this poor prognosis gene had activation of several potential-targetable factors, including the kinases Akt and PLK1. Conclusions: Copy number loss of specific tumor suppressor genes is associated with enza resistance in mCRPC patients. Previously unappreciated molecular subsets of enza-resistant CRPC were identified, including one subset associated with poor clinical outcome.
Diagnostic performance of 18F-DCFPyL in the OSPREY Trial: A prospective phase 2/3 multicenter study of 18F-DCFPyL PET/CT imaging in patients (Pts) with known or suspected metastatic prostate cancer (mPC). First Author: Michael J. Morris, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Accurate detection of prostate cancer is imperative to patient management, yet standard imaging methods perform poorly in accurately detecting mPC. 18F-DCFPyL is a novel PET imaging agent that selectively binds to prostate-specific membrane antigen, a recognized target for prostate cancer. OSPREY was a prospective, multicenter study in pts with either newly diagnosed high-risk prostate cancer (cohort A), or known or suspected mPC (cohort B). Here we focus on cohort B. Methods: 117 pts planned for biopsy of recurrent or mPC received 18F-DCFPyL. Pts underwent image-guided biopsy. Sensitivity, positive predictive value (PPV), and safety of 18F-DCFPyL PET/CT were the key endpoints for cohort B. 18F-DCFPyL PET/CT scans were evaluated by three independent, blinded central readers; and results were compared to histopathology as the truth standard. Results: The sensitivity and PPV of 18F-DCFPyL PET/CT as compared to histopathology ranged from 92.9-98.6% (lower bound of 95% CI: 84.0-91.6%) and 81.2-87.8%, respectively. Diagnostic performance by anatomic location showed high sensitivity and high PPV in all sites of disease (Table). Only two (1.7%) cohort B pts experienced ≥1 drug-related AE (dysgeusa and generalized rash), both were mild (Grade 1) in severity.

Conclusions: 18F-DCFPyL PET/CT was well tolerated and demonstrated high sensitivity and PPV in accurately detecting nodal, bone, and visceral/soft tissue metastases. A positive 18F-DCFPyL PET/CT scan is highly likely to represent pathologically proven distant disease, demonstrating the potential of 18F-DCFPyL as a PET imaging agent to favorably influence treatment planning.

Clinical trial information: NCT02981368.

5014 Poster Discussion Session; Displayed in Poster Session (Board #126), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Prospective head-to-head comparative phase 3 study between 18F-fluciclovine and 68Ga-PSMA-11 PET/CT in patients with early biochemical recurrence of prostate cancer. First Author: Jerome Calais, UCLA, Los Angeles, CA

Background: This is a prospective single-center, single-arm, head-to-head phase 3 study of paired 18F-fluciclovine (FACBC) and 68Ga-PSMA-11 (PSMA) PET/CT scans for localizing early biochemical recurrence (BCR) of prostate cancer (PCa) after radical prostatectomy (RP) (NCT02940262). Methods: Fifty consecutive patients with BCR and prostate specific antigen (PSA) levels ranging from ≤0.2 to ≤2.0 ng/mL without any prior salvage therapy were included. All patients underwent FACBC and PSMA PET/CT scans within ≤15 days. PET/CT scans were each interpreted by 3 independent blinded expert readers not involved in study design and data acquisition. Region consensus interpretation (T,N,M,1A,1B,1C) was generated based on majority rule in cases of reader disagreement (≥2 vs 1). PET/CT scans were considered as positive if any region was rated as positive. Detection rates per patient and per-region served as primary study endpoint. Results: Median time interval between the 2 scans was 6 days (range 1-15). Median PSA level at the time of imaging was 0.50 ng/mL (mean 0.63; range 0.2-2.0 ng/mL). The detection rates were significantly lower with FACBC than with PSMA PET/CT per-patient (26% vs 56%; p = 0.003) and per-region for pelvic nodes (N) (8% vs 30%; p = 0.003) or any extra-pelvic lesions (M) (0% vs 16%; p = 0.008). Reader agreement for PSMA PET/CT image interpretations was significantly higher than for FACBC PET/CT (0.67 vs 0.20; p = 0.015). Conclusions: In patients with BCR and low serum PSA levels after RP, PSMA PET/CT demonstrates higher detection rates and superior reader agreement when compared with FACBC PET/CT. Therefore, PSMA PET/CT should be the imaging modality of choice in patients with early BCR. Clinical trial information: NCT03515577.

5013 Poster Discussion Session; Displayed in Poster Session (Board #125), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Association of noninvasive, radiographic measurement of prostate-specific membrane antigen (PSMA) expression with response to PSMA-targeted radionuclide therapy (TRT). First Author: Panagiotis J. Vlachostergios, Division of Hematology & Medical Oncology, Weill Cornell Medical College & New York-Presbyterian Hospital, New York, NY

Background: Prostate surface membrane antigen (PSMA) is usually overexpressed in PC and is enriched in castration-resistant tumors. PSMA-TRT is of interest as a potential treatment for patients with mPC. In the field of theranostics there are accumulating reports demonstrating that PSMA uptake on imaging is a pre-requisite for response. We have conducted a number of trials which have incorporated PSMA imaging, but have not selected patients for treatment based upon imaging results and performed an analysis examining the relationship between imaging and response. Methods: Men with mCRPC had either planar radiolabeled J591 imaging (111In-J591 and/or 177Lu-J591) or 68Ga-PSMA-11 PET/CT. Visual scores were assigned based upon PSMA uptake in tumors compared to liver uptake and scored on a 0-4 scale. Imaging scores were associated with PSA decline (≥30%, ≥50%) using Cox regression analysis. As several studies were dose-escalation in nature with prior demonstration of dose-response, we controlled for dose administered. Results: 216 men with metastatic CRPC, median PSA 72.45ng/dl, were treated with PSMA-TRT as follows: 177Lu-J591 (n=136), 177Lu-J591-617 combination (n=6), 225Ac-J591 (n=7), 90Y-J591 (n=29). 116 (53.7%) pts received low dose and 100 (46.3%) high dose as previously defined in the individual studies. 25 (52.6%) pts had PSMA expression by imaging (VS 0-1) whereas 161 (74.5%) had high PSMA expression (VS 2-4). High PSMA expression was associated with more frequent PSA decline (≥30%: 39.2 vs 17.9% p=0.003; ≥50%: 27.5 vs 8.9% p=0.004). For controlling dose for control, this association remained significant for low (≥30%: 35% vs 8.6% p=0.04) and high doses of radionuclide therapy (≥50%: 34.9 vs 9.5% p=0.02). 13 (6%) pts with no PSMA uptake (VS=0) had PSA declines. Conclusions: This is the first study to formally analyze response to PSMA-TRT by PSMA imaging expression in an unselected patient population. The level of PSMA expression measured by imaging is associated with the chance of responders. However, a subset of patients without any significant PSMA uptake on imaging did demonstrate response to PSMA-TRT, indicating that imaging cannot exclude all patients that might benefit. Clinical trial information: NCT03545165, NCT03276572, NCT03042468, NCT02552394.

5015 Poster Discussion Session; Displayed in Poster Session (Board #127), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Cardiovascular morbidity in a randomized trial comparing GnRH-agonist and antagonist among patients with advanced prostate cancer. First Author: David Margel, Rabin Medical Center, Petah Tikva, Israel

Background: Androgen-deprivation therapy (ADT) used in prostate-cancer may increase risk of cardiovascular disease (CVD). Limited preclinical and retrospective clinical data suggest that use of gonadotrophin-releasing hormone (GnRH)-agonist may be associated with lower risk of CVD compared to GnRH-antagonist. Methods: We conducted a randomized open-label study comparing the one year incidence of major cardiovascular and cerebrovascular event (MACCE) in prostate-cancer patients with pre-existing CVD commencing on GnRH-agonists or antagonists. Patients were followed every 3 months for the development of MACCE defined as either death, myocardial infarction (MI), cerebrovascular event (CVA), or percutaneous-coronary intervention (PCI). Serum levels of N-terminal pro-B-type natriuretic peptide (NTproBNP) were analyzed at baseline, 3, 6 and 12-months. Results: Eighty patients were enrolled (41 randomized to GnRH-antagonist, 39 to GnRH-agonist). Patients in both arms had similar age, baseline cardiovascular and prostate-cancer characteristics. During follow-up 15 patients developed a new cardiovascular event. Of these, nine patients developed MACCE (two deaths, one MI, two CAVs, and four PCI). Twenty percent (n = 8) of patients randomized to GnRH-agonists had a MACCE compared to 3% (n = 1) randomized to antagonists (log-rank p = 0.013). The absolute risk reduction for MACCE at 12 months using GnRH-antagonist was 18% (95%CI 5-31). Baseline levels of NTproBNP predicted events (AUC = 0.73 95%CI 0.54-0.91 p = 0.03) and increased over time only among patients with CV events. Conclusions: This is the first prospective study to test cardiovascular outcome among prostate-cancer patients receiving ADT. We demonstrated that in patients with pre-existing CVD, GnRH-antagonists was associated with development of fewer cardiovascular events compared to GnRH-agonists. Clinical trial information: NCT02475057.
Outcomes of men with recurrent MO prostate cancer who defer androgen deprivation therapy until metastasis. First Author: Catherine Handy Marshall, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD

Background: Optimal timing and criteria for implementation of androgen deprivation therapy (ADT) in men with relapsed MO prostate cancer (PCa) remains undefined. Early ADT induces the non-metastatic castration resistant PCa (nmCRPC) clinical state; FDA approved apalatin, abiraterone acetate (APA) and enzalutamide (PROSPER) for nmCRPC based on prolongation of metastasis free survival (MFS) which is now considered a valid endpoint for drug approval. Because overall survival (OS) in PCa is usually long and long-term ADT is associated with irreversible adverse events and high costs, we sought to evaluate OS and other outcomes of men with relapsed PCa and ADT deferred until metastasis. Methods: Retrospective review of 2,636 men who had radical prostatectomy (RP) between 1981-2017 and developed biochemically recurrent PCa from a single-institution. Patients who received ADT prior to metastasis were excluded. Kaplan-Meier survival estimates of MFS and OS were derived from RP to event or censor. Multivariable Cox proportional hazards regression was used to identify prognostic factors. Results: 1,866 men treated with deferred ADT until metastasis or censored metastasis-free were eligible. Median follow-up 10 years (IQR=5-16), age 60 years, PSA 33 months, Gleason <7 (24%), Gleason 7 (55%), Gleason >7 (21%), 688 (41%) received salvage radiotherapy, 646 (38%) had metastasis, and 277 (16%) received tams叛ad tamoxifen (Table). In multivariable models, age (HR 1.06, 95% CI 1.04-1.1), Gleason <8 vs ≥8 (HR 0.4, 0.3-0.5), RP stage (organ confined vs not 0.6, 0.5-0.8), PSADT (0.995, 0.993-0.997) and salvage RT (0.88, 0.81, 0.96) were associated with OS. Conclusions: Deferred ADT in relapsing MO patients is associated with long OS measured from time of local treatment, comparable to OS with salvage ADT in contemporary experience. Drug approval trials in nmCRPC should focus on patients at high risk for metastasis and death prior to ADT, and determine standardized criteria for initiation of ADT. Prolongation of MFS in nmCRPC requires further validation and may not necessarily reflect a net OS benefit.

5016 Poster Discussion Session; Displayed in Poster Session (Board #128), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

5017 Poster Discussion Session; Displayed in Poster Session (Board #129), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Final results from the randomized CABADO trial: Patient preference between cabazitaxel and docetaxel for first-line chemotherapy in metastatic castrate-resistant prostate cancer (mCRPC). First Author: Giulia Bacicarello, Department of Cancer Medicine, Gustave Roussy Cancer Campus, Paris-Sud University, France, Villejuif, France

Background: Docetaxel and cabazitaxel represent now the standard of care in men with mCRPC with similar efficacy reported in metastatic first-line setting in the First GENERA phase 3 trial. We assessed patients’ preference between the two taxanes. Methods: Patients with taxane-naïve mCRPC were randomized in a 1:1 ratio to receive either docetaxel 75mg/m2q3w or x 4 followed by cabazitaxel 25mg/m2q3w (DO-CA), or the reverse sequence (CA-DO). Randomization was stratified based on prior next generation AR axis inhibitors use. The primary endpoint was patient preference between taxanes, as assessed by questionnaires in patients who had received at least one cycle of each taxane and who had not experienced a progression while on the first taxane. Results: From June 2014 to October 2016, 195 men were randomized in 17 centers. After adjusting for the treatment period effect, more patients preferred cabazitaxel (43%) vs docetaxel (27%) (p = 0.004); 30% had no preference between taxanes. Fatigue, patient-defined quality of life, hair loss, and pain were the most common factors influencing patient preference. Febrile neutropenia was experienced by 5 (7.1%) men treated with cabazitaxel during the first period who received G-CSF and by 2 (7.1%) of those who did not. No febrile neutropenia was reported with docetaxel in both arms and with cabazitaxel during the 2nd period, irrespective of the use of G-CSF. The incidence of diarrhea during the first 3-month period was slightly reduced with G-CSF use in men receiving cabazitaxel (32.1% vs 24.3%) but not in those receiving docetaxel (23.8% vs 25%). The median progression-free survival was 9.81 in the DO-CA arm and 9.33 months in the CA-DO arm. The median overall survival was also similar in the two groups (22.64 in the DO-CA arm and 20.73 months in the CA-DO arm. Conclusions: Although cabazitaxel and docetaxel have similar efficacy when used as first-line in mCRPC men, more patients prefer cabazitaxel. Clinical trial information: NCT02044354.

5018 Poster Discussion Session; Displayed in Poster Session (Board #130), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Predictive genomic biomarkers in mCRPC remain elusive. Prior studies suggest that tumor suppressor (TS) loss is prognostic, and may result in predictive, conferring significantly shorter TTTF on both NHT and D. A score based on presence of tumor suppressor deficiency (34%) due to copy-number loss (25%) or mutation (9%); signaling (16%), genes involved in DNA repair (14%), Wnt signaling (14%) and cell cycle control (6%). In total, these aberrations were observed in 76% of patients, with 35% harboring two or more. No androgen receptor (AR) mutations were detected. Conclusions: The prevalence of AR deficiency is comparable with that observed in mCRPC consistent with this being a feature of metastatic disease. In contrast, AR mutations are not observed in this treatment-naïve group. The prevalence of DNA repair deficiency is less than observed in mCRPC but more than reported in prostatectomy cohorts. Although it is possible to use FFPE biopsies for tNGS, the test failure-rate poses challenges to evaluating treatment in low prevalence biomarker-defined groups. These data will inform the design and conduct of future trials.

5019 Poster Discussion Session; Displayed in Poster Session (Board #131), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Targeted next-generation sequencing (tNGS) of metastatic castrate-sensitive prostate cancer (M1 CSPC): A pilot molecular analysis in the STAMPEDE multi-center clinical trial. First Author: Clare Gilson, MRC Clinical Trials Unit at UCL, London, United Kingdom

Background: The STAMPEDE trial recruits men with high risk prostate cancer commencing first line systemic therapy. In a pilot study to ascertain the feasibility of tNGS and the prevalence of common genomic aberrations, we tested a commercially clinically-accruald assay on tumor blocks and present data obtained in the largest cohort of treatment-naïve M1 CSPC to date. Methods: Archival FFPE blocks were retrieved from trial participants and a single block submitted for sequencing by a Foundation Medicine. Inc. tNGS assay that includes 395 genes. Results: We successfully obtained tNGS data on 115 (62%) of 186 patients enrolled between Nov-2011 and April-2017 at 15 UK participating centers. The median age was 70 years (IQR 44-85); 97% had de novo M1 disease and 83% Gleason score ≥8. We observed PTEN deficiency (34%) due to copy-number loss (25%) or mutation (9%); TP53 mutation or loss (33%) and aberrations in PI3K signaling (16%), genes involved in DNA repair (14%), Wnt signaling (14%) and cell cycle control (6%). In total, these aberrations were observed in 76% of patients, with 35% harboring two or more. No androgen receptor (AR) mutations were detected. Conclusions: The prevalence of PTEN deficiency is comparable with that observed in mCRPC consistent with this being a feature of metastatic disease. In contrast, AR mutations are not observed in this treatment-naïve group. The prevalence of DNA repair deficiency is less than observed in mCRPC but more than reported in prostatectomy cohorts. Although it is possible to use FFPE biopsies for tNGS, the test failure-rate poses challenges to evaluating treatments in low prevalence biomarker-defined groups. These data will inform the design and conduct of future trials.
HSDB31 and overall survival (OS) in men with low-volume (LV) metastatic prostate cancer (PCa) treated with androgen deprivation therapy (ADT) or chemohormonal therapy in the CHAARTED Randomized trial. First Author: Jason W.D. Hearn, University of Michigan, Ann Arbor, MI

Background: The HSDB31(1245A>C) variant allele, whose frequency varies by race, encodes a missense sequence that stabilizes the rate-limiting enzyme responsible for extragonadal androgen synthesis, thus enhancing intratumoral dihydrotestosterone (DHT) synthesis. Multiple retrospective studies have noted that men inheriting the HSDB31(1245C) variant allele exhibit early resistance to ADT. We sought to validate these findings with prospective data from the Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED).

Methods: Men with newly metastatic PCa were randomized to receive either ADT plus docetaxel at a dose of 75 mg/m2 every 3 weeks for 6 cycles (arm A) or ADT alone (arm B). We determined germline HSDB31 genotype in the subset of men with LV disease (<4 bone metastases, no visceral metastases). We analyzed freedom from castration-resistant prostate cancer (CRPC) and OS according to HSDB31 genotype using Cox and Kaplan-Meier methods.

Results: 197 patients with LV disease had blood samples available and were genotyped, including 97 in arm A and 100 in arm B. Docetaxel did not improve OS of LV men. Of the 197 men, 47% were homozygous wild-type (WT), 43% were heterozygous, and 10% were homozygous variant. When all 197 men were analyzed as one group, the median time to progression was 39.7 months in WT men vs. 25.0 mos. in men with one or more copies of the variant allele (HR 1.27, 95% CI 0.89 to 1.82; p = 0.187). Although OS data are still maturing, at 52 months OS was 83% (95% CI 75% to 91%) in homozygous WT men vs. 64% (95% CI 55% to 74%) in men with one or more alleles. There was a suggestion that docetaxel delayed development of CRPC among men with at least 1 variant allele (20.3 vs. 40.7 mos.; HR 0.66, 95% CI 0.40 to 1.04; p = 0.08). Benefit for men with high-volume disease was not evident.

Conclusions: Inheritance of the HSDB31(1245C) allele that augments DHT synthesis may be associated with lower OS in men treated with ADT with or without docetaxel for LV newly metastatic PCa. Additional study is warranted in patients with LV disease. Clinical trial information: NCT00309985.
5024 Poster Session (Board #136), Sat, 1:15 PM-4:15 PM
Age-related efficacy and safety of apalutamide (APA) plus ongoing androgen deprivation therapy (ADT) in subgroups of patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC): Post hoc analysis of SPARTAN. First Author: Julie Nicole Graff, Knight Cancer Institute, Oregon Health & Science University, Portland, OR

Background: SPARTAN, a randomized phase 3 placebo (PBO)-controlled study in pts with high-risk nmCRPC and PSA doubling time ≤ 10 mo, showed that, compared with PBO, addition of APA to ongoing ADT treatment (tx) prolonged metastasis-free survival (MFS) benefit. The current analysis assessed the impact of age on MFS in the APA and PBO arms. The incidence of grade 3/4 treatment-emergent adverse events (TEAE) with age in both tx arms was lessened with APA vs PBO for all age subgroups (Table). There was a similar risk of symptomatic progression with APA vs PBO was reduced by 59%; MFS risk was reduced by 86% and 76% for pts < 65 and 65-75 y, respectively. Risk of FFS with APA vs PBO was reduced across all age subgroups, FFS pts in pts < 65, 65-75, and > 75 yr; HR, 0.59 (p = 0.0092), respectively. Risk of symptomatic progression was lessened with APA vs PBO for all age subgroups (Table). There was a similar increase in incidence of tx-emergent adverse events (TEAE) with age in both tx arms that remained higher with APA. Incidence of grade 3/4 TEAE (increase in incidence of tx-emergent adverse events) with age in both tx arms was lessened with APA vs PBO for all age subgroups (Table). There was a similar

5025 Poster Session (Board #137), Sat, 1:15 PM-4:15 PM
Predictors of falls and fractures in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC) treated with apalutamide (APA) plus ongoing androgen deprivation therapy (ADT). First Author: TAN, Guay Gu, Pollock, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA

Background: SPARTAN, a phase 3 study of APA vs placebo (PBO) added to ongoing ADT in pts with nmCRPC, demonstrated that APA significantly prolongs metastasis-free survival, time to symptomatic progression, and second progression free survival (Smith et al. NEJM 2018), with no decline in health-related quality of life (Saad et al. Lancet Oncol 2018). SPARTAN pts who received APA vs PBO, with ongoing ADT had higher rates of falls (15.6% vs 9.0%) and fractures (11.7% vs 6.5%). An analysis was performed to identify clinical characteristics associated with falls and fractures in APA-treated SPARTAN pts. Methods: Of 1207 pts enrolled, 806 were randomized to APA, Univariable Cox proportional hazards model (UVA) assessed the association of 47 baseline clinical characteristics (demographics, comorbidities, and medication use, including bone-sparing agents) with time to fall or time to fracture. Characteristics with p values < 0.10 were included in a multivariate Cox proportional hazards model (MVA) to determine independent factors associated with these outcomes (p < 0.05). Results: Factors associated with time to both fall and fracture on UVA (p < 0.10) included older age, low serum albumin, and poor ECOG performance status (PS). Additional factors associated with time to fall were cerebrovascular accidents/transient ischemic attacks, neuropathy, depression, α-blocker use, and antidepressant use. On MVA, older age, poor PS, and low serum albumin were independently associated with falls; older age and low serum albumin were independently associated with fractures (Table). Conclusions: At initiation of APA added to ongoing ADT, nmCRPC pts with higher risk of falls and fractures can be identified and are candidates for intervention to reduce the risk for these events. Clinical trial information: NCT01946204.
**5028**  
Poster Session (Board #140), Sat, 1:15 PM-4:15 PM  
RESIST-PC phase 2 trial: 177Lu-PsMA-617 radionuclide therapy for metastatic castration-resistant prostate cancer.  
First Author: Jeremie Calais, UCLA, Los Angeles, CA, USA  
Background: This is an investigator-initiated open-label prospective bi-centric single-arm phase 2 clinical trial (NCT03043212) of 177Lu-PsMA-617 radionuclide therapy in patients with progressive metastatic castration-resistant prostate cancer (mCRPC). **Methods:** Patients with progressive mCRPC (biochemical, radiographic, or clinical) after ≥1 novel androgen axis drug (NAAD), either chemotherapy (CTX) naïve or post-CTX, with sufficient bone marrow reserve and normal kidney function were eligible. All patients underwent a screening PSMA PET/CT to confirm target expression. Patients received up to 4 cycles of 177Lu-PsMA-617 every 8-12 weeks and were randomized into 2 treatment activities groups (6.0 or 7.4 GBq). Kidney dosimetry was performed for the first cycle. Efficacy was defined as serum PSA decline of ≥50% from baseline at 12 weeks and served as primary endpoint. **Results:** 64 patients (median PSA 75 ng/ml; range 0.5-2425) were included in the study. 20% were CTX naïve while 80% were post-CTX (1.9 CTX regimens on average, range 1-4). 45% completed 4 cycles of 177Lu-PsMA-617. Androgen deprivation therapy was given concomitantly in 83%, NAAD in 23% and immunotherapy in 6%. PSA decline of ≥50% was observed in 23% of patients at 12 weeks and 38% of patients at any time (best PSA response). The median time to best PSA response was 22 weeks (range 6-49 weeks). 16% had a PSA decline of ≥90% and 59% had any PSA decline (> 0%). Mild and transient (CTCAE grade 1-2) side effects included xerostomia (72%), nausea/vomiting (69%) and bowel movement disorders (45%). CTCAE grade 3 toxicity included nausea/vomiting (6%), anemia (8%), leukopenia (5%), kidney failure (3%), thrombocytopenia (3%) and neutropenia (3%). The mean kidney dose was 2.7 Gy for the first cycle (range 0.9-5.9) i.e. 0.4 Gy/GBq (range 0.15-0.9). There was no difference between the efficacy and toxicity for the 6.0 GBq (n = 23) and 7.4 GBq (n = 41) treatment arms. Conclusion: 177Lu-PsMA-617 radionuclide therapy is well tolerated in patients with progressive mCRPC. PSA decline by ≥50% was observed in 38% of patients. The best PSA response rate occurred after 3 cycles. Updated data will be provided at the time of the conference. Clinical trial information: NCT03043212.
5032 Poster Session (Board #144), Sat, 1:15 PM-4:15 PM
Profiling of genomic alterations in MAPK/ERK signaling in a large cohort of metastatic prostate cancer (mPC) patients. First Author: Edwin Lin, University of Utah, Huntsman Cancer Institute, Salt Lake City, UT

Background: All mPC patients eventually progress on current treatments and progression remains poor. In vitro models and small patient cohorts have shown that mPC progression is associated with increased MAPK/ERK signaling. However, in clinical mPC, the genomic alterations that cause aberrant MAPK/ERK signaling and their frequency are poorly defined. We hypothesize that profiling of genomic alterations in MAPK/ERK in a large cohort of heavily pretreated progressive mPC patients will provide a robust measure of importance, and reveal recurrent patterns of alteration. Given the large number of drugs that target MAPK/ERK, these may be incorporated into novel combinational treatments for mPC.

Methods: 2,679 plasma samples from 2,309 men with mPC were assessed by a validated ctDNA NGS panel that sequences 73 clinically relevant cancer genes (Guardant360, Redwood City, CA) and profiles indels, amplifications, and fusions with high sensitivity and specificity. Genes were assigned to gene sets corresponding to biological pathways and molecular functional classes using the REACTOME database, followed by calculation of summary statistics. Interdependencies between genetic alterations at inter- and intragene set levels were discovered by a Bayesian network approach. Results: 56% of mPC samples harbored alterations in MAPK/ERK signaling genes. These included receptor tyrosine kinases (RTKs), MAP kinase cascade, and cell cycle control genes. Gene amplifications were the most frequent alterations in RTK, RAF, and cell cycle control genes, a novel finding. Bayesian network analysis revealed increased positive interdependencies between alterations of RTKs and MAPK/ERK genes. In RTK genes, co-amplifications were especially frequent between MET & EGFR and PDGFRA & KIT. Conclusions: In a large cohort of mPC patients, we show that MAPK/ERK gene alterations are present in over half of mPC patients. RTKs, RAF, and CDK4/6 amplifications are among the most frequent events, display recurrent patterns of co-alteration, and are targetable by existing drugs. Future work to assess the biological and clinical significance of these recurrent patterns of alteration will pave the way for novel combinational treatments.

5034 Poster Session (Board #146), Sat, 1:15 PM-4:15 PM
Phase 1 study of pasotuxizumab (BAY 2010112), a PSMA-targeting Bispecific T Cell Engager (BiTE) immunotherapy for metastatic castration-resistant prostate cancer (mCRPC). First Author: Horst-Dieter Hummel, Comprehensive Cancer Center Mainfranken, University Hospital Würzburg, Würzburg, Germany

Background: mCRPC has a poor prognosis and immunotherapies are largely ineffective. PSMA is a promising therapeutic target in mCRPC, and pasotuxizumab is a PSMA x CD3 BiTE that mediates tumor cell killing. Methods: NCT01723475 was a first-in-human, multicenter, dose-escalation study in patients (pts) with mCRPC refractory to standard therapy. Pts received pasotuxizumab as a continuous intravenous infusion in cohorts of 3–4 pts. Dose-escalation followed a continuous reassessment methodology design. The primary objective was to determine safety and maximum tolerated dose (MTD); secondary objectives included pharmacokinetics, biomarkers, and tumor response. Results: 16 pts were enrolled into 5 dosing cohorts (5 μg/d, n = 3; 10 μg/d, n = 4; 20 μg/d, n = 3; 40 μg/d, n = 4; 80 μg/d, n = 2). All pts had ≥1 AE of any grade; most common were fever (94%), chills (69%), and fatigue (50%). 13 pts (81%) had ≥1 AE of grade ≥3; most common were decreased lymphocytes and infections (both 44%). No grade 5 AE occurred. A serious AE related to study drug was reported for 1 pt (fatigue, 20 μg/d). No anti-drug antibodies were observed. Recruitment was stopped before MTD was reached to facilitate initiation of a new study sponsored by Amgen. Antitumor activity as indicated by PSA serum level decline was dose-dependent, with a mean best PSA change per dosing cohort versus baseline of +0.74% (5 μg/d), −17.9% (10 μg/d), −37.4% (20 μg/d), −42.5% (40 μg/d) and −54.9% (80 μg/d). PSA decreases of ≥50% occurred in 3 pts (n = 1 each in 20 μg/d, 40 μg/d, and 80 μg/d cohorts). One long-term PSA responder was treated for 14 months (40 μg/d) and one for 19.4 months (80 μg/d). The latter pt showed a complete regression of soft-tissue metastases and marked regression of bone metastases as assessed by PSMA-PET/CT, > 90% reduction in PSA and alkaline phosphatase, and a significant and durable improvement in disease-related symptoms. Conclusions: Pasotuxizumab had an acceptable safety profile and dose-dependent clinical activity in mCRPC pts. There were two long term responders in the dose escalation. This is the first clinical study showing a BiTE immunotherapy can be efficacious in solid tumors.

5033 Poster Session (Board #145), Sat, 1:15 PM-4:15 PM
Personalized peptide vaccination for castration-resistant prostate cancer progressing after docetaxel chemotherapy. A randomized, double-blind, placebo-controlled, phase III trial. First Author: Masanori Naguchi, Kurume University School of Medicine, Kurume, Japan

Background: To develop a new treatment modality, we conducted a phase III randomized trial of personalized peptide vaccination (PPV) for human leukocyte antigen (HLA)-A24 positive patients with castration-resistant prostate cancer (CRPC) who failed docetaxel chemotherapy. Methods: Patients were randomly assigned in a 2:1 ratio to receive PPV or placebo. Four of 12 warehouse peptides selected based on prevailing peptide-specific immunoglobulin G levels or the corresponding placebo were subcutaneously injected 6 doses weekly followed the maximum of 30 doses bi-weekly until disease progression. The primary end point was overall survival (OS), and secondary end points were progression-free survival (PFS) and immune responses. Results: From August 2013 to April 2016, 310 patients were randomly assigned (207 to PPV and 103 to placebo), and 306 patients were analyzed by the full analysis set (204 to PPV and 102 to placebo). Baseline characteristics were balanced between groups. Estimated median OS was 16.1 months (95% CI, 13.0 to 18.2) with PPV and 16.9 months (95% CI, 13.1 to 20.4) with placebo. Median PFS was also not significantly different among them. Median Grade ≥ 3 adverse events were observed in 41% in both groups. The analysis of treatment arm effects among various subgroups revealed a lower HR for OS in favor of the PPV arm in patients with a < 64% neutrophil proportion (HR, 0.55; 95%CI, 0.33 to 0.93) with a significance of p = 0.03. In the subgroup of patients not progressing after docetaxel chemotherapy, PPV did not prolong either OS or PFS in HLA-A24 positive patients with CRPC progressing after docetaxel chemotherapy. Clinical trial information: 0000113088.

5035 Poster Session (Board #147), Sat, 1:15 PM-4:15 PM
Overall survival (OS) of African-American (AA) and Caucasian (CAU) men who received sipuleucel-T for metastatic castration-resistant prostate cancer (mCRPC): Final PROCEED analysis. First Author: A. Oliver Sarrot, Tulane Medical School, New Orleans, LA

Background: Prostate cancer risk and mortality are higher in AAs versus CAUs. Post-hoc analyses of pooled Phase 3 data (n = 737) suggested substantial OS benefit for AA men receiving sipuleucel-T (n = 33) vs placebo (n = 10) (McLeod 2012). Compared with pooled placebo patients (n = 249), number needed to treat for OS benefit at 3 years was 3 for AAs and 8 for all sipuleucel-T-treated patients (n = 488) (Moses 2019). Herein we analyzed PROCEED (NCT01306890), a large real-world registry, in which all patients received sipuleucel-T. Methods: In PROCEED, 1902 mCRPC patients received ≥1 sipuleucel-T infusion. OS of all AA (n = 221) and CAU (n = 1649) men were compared. Baseline prostate-specific antigen (PSA), the most important prognostic variable for OS after sipuleucel-T (Schellhammer 2013), substantially differed by race. Thus, OS for a PSA-matched cohort (n = 219 AA; n = 438 CAU) was compared and univariable/multivariable analyses were performed. Post-sipuleucel-T use of OS-prolonging anticancer interventions was also assessed. Results: After a median follow-up of 44.6 mo, median OS was 35.2 (all sipuleucel-T-treated AAs) and 29.9 mo (all sipuleucel-T-treated CAUs): HR 0.81, 95% CI 0.68–0.97; P = 0.03. In the PSA-matched cohort, median OS was 35.3 and 25.8 mo, respectively (HR 0.70, 95% CI 0.57–0.86; P < 0.001). Sipuleucel-T-treated AAs with lower baseline PSA had markedly longer median OS vs sipuleucel-T-treated CAUs. Among those with ≤ median baseline PSA (29.48 ng/ml), median OS was 54.3 mo (AA) vs. 33.4 (CAUs); HR 0.52, 95% CI 0.37–0.72; p < 0.001. Along with other known prognostic factors, AA race was independently associated with prolonged OS on detailed multivariable analyses (HR 0.60, 95% CI 0.40–0.74; p < 0.001) and confirmed on sensitivity analyses. Post-sipuleucel-T life-prolonging anti-cancer therapies were balanced between groups. Conclusions: Sipuleucel-T-treated AAs had significantly improved OS vs sipuleucel-T-treated CAUs. This analysis marks the largest known racial difference in OS in response to any therapy for mCRPC, a finding with implications for both prostate cancer pathophysiology and cancer immunotherapy. Clinical trial information: NCT01306890.
We sought to evaluate the efficacy of platinum-based chemotherapy in metastatic castration-resistant prostate cancer (mCRPC). Pre-treatment high levels of ctDNA reflect poor prognosis (Romanel et al, Sci Transl Med 2015; Annala et al, Cancer Discov 2018). However, the role of plasma ctDNA in prostate tumour monitoring is largely unexplored. We aimed to determine if monitoring tumour response by quantifying ctDNA levels in plasma could enable early assessment of therapy efficacy for mCRPC. Methods: Between January 2011 and June 2016, 132 sequential plasma samples from 54 mCRPC patients (pts) (30 pre- and 24 post-chemotherapy) treated with abiraterone (abi) were collected. Targeted next-generation sequencing was performed on the PGM Ion Torrent using a 316 or 318 Chip to account for 1000X expected coverage per target. We estimated the global tumour content for each sequential plasma sample from study patients by using the approach developed in (Carreira et al, Sci Transl Med 2014; Romanelli et al, Sci Transl Med 2015), which extends the CLONET framework (Prami et al, Genome Biol 2014). Prostate Cancer Working Group-3 (PCWG3) criteria were used to assess clinical, biochemical (PSA) and radiographic (RAD) progression disease (PD). We considered ctDNA PD any increase of ctDNA from baseline value. Results: In our cohort of 54 pts (median age: 75 years, range 70-78), we observed 17 (31.5%) PD, 14 (25.9%) stable disease, and 23 (42.6%) partial/complete response after the first 3 months (mo) abi treatment. The odds ratio (OR) for PD having any increase in ctDNA and a PSA decline < 50% at ~3-mo therapy was 10.83, 95% CI 2.55-45.95, P = 0.001, and 3.27, 95% CI 0.89-12.3, P = 0.074, respectively. In addition, we assessed all 3 types of median PD time from starting abi treatment, suggesting the ability of ctDNA variation to predict early PD (rad PD = 0.8, P = 0.04), and that PD was not associated with ctDNA PD > 3 mo, P = 0.008). An increase of ctDNA levels during the first 3-mo abi treatment was significantly associated with a long-term androgen deprivation therapy (ADT) before plasma sample collection (previous ADT > 24 mo vs > previous ADT =23 mo vs < 12 mo: P = 0.036). Conclusions: In mCRPC, an early change in ctDNA fraction may be considered as a predictive biomarker playing a key role in individualized disease monitoring. Prospective validation of treatment decisions based on ctDNA is now required.
Background: NCT02288936.  

Impact of enzalutamide and sequential flutamide and enzalutamide therapy for metastatic castrate-resistant prostate cancer (mCRPC) combined with adaptive blockade therapy overall survival: A follow-up study of randomized phase 2 trial (OCCU-CRPC study). First Author: Taro Igochi, Department of Urology, Osaka City University Graduate School of Medicine, Osaka, Japan

Background: In Asia, bicalutamide-combined androgen blockade (CAB) is widely used to treat metastatic or locally advanced prostate cancer. Enzalutamide (ENZA) shows benefits in men with metastatic and nonmetastatic castration-resistant prostate cancer (mCRPC or nMCRPC). The interpretation of the results is limited by the use of androgen-independent anti-enzalutamide therapy after bicalutamide-CAB. Methods: The multicenter open-label phase 2 trial OCCU-CRPC (NCT02346578) randomized patients (1:1) with CRPC after bicalutamide-CAB to ENZA (160 mg/d) or FLU (375 mg/day). Patients were stratified according to distant metastases. The primary endpoint was the prostate-specific antigen (PSA) response rate (≥50% decrease) at 3 months. The endpoints of this follow-up observational study include PSA progression-free survival of ENZA therapy (PSA-ENZA), time to treatment failure of ENZA therapy (TTF-ENZA), and overall survival (OS). Results: In total, 103 patients were randomized to ENZA (n = 52) and FLU (n = 51). Overall, 67% had distant metastases and 10% had prior radical therapy. Twenty-five (48%) and 38 (75%) patients, respectively, discontinued their assigned treatment because of progressive disease or adverse events (AEs) and were treated by standard of care. Of the 38 patients that discontinued FLU, 34 (89%) received ENZA as subsequent therapy. The median follow-up time was 14 months (ENZA), interquartile range (IQR): 9.5-24.8) and 17.2 months (FLU, IQR: 9.8-24.9). PSA-ENZA was longer in patients not treated with FLU (hazard ratio (HR), 0.29; 95% confidence interval (CI): 0.10-0.83; p < 0.001), but there was no significant difference in TTF-ENZA (HR, 1.27; 95% CI: 0.73 to 2.21, p = 0.397) and OS (HR, 1.07; 95% CI, 0.31 to 1.89; p = 0.567) between the two groups. The AEAs of ENZA were consistent with those observed in prior phase 3 trials. Conclusions: ENZA after bicalutamide-CAB resulted in greater PSA-ENZA than sequential FLU and ENZA therapy. No differences were observed in TTF-ENZA and OS between ENZA after bicalutamide-CAB and sequential FLU and ENZA therapy. Clinical trial in formation: NCT02346578.
Health-related quality of life (HRQoL) and pain progression with enzalutamide (ENZ) in metastatic hormone-sensitive prostate cancer (mHSPC) from the ARCHES study. First Author: Aurko Sen. Stellenbosch University, Tygerberg Hospital, Stellenbosch, South Africa

Background: The Phase 3 ARCHES trial (NCT02677896) evaluated the efficacy and safety of ENZ + androgen deprivation therapy (ADT) vs placebo (PBO) + ADT in 1150 men with mHSPC. Here we report patient-reported outcome (PRO) data using Functional Assessment of Cancer Therapy-Prostate (FACT-P) and Brief Pain Inventory Short Form (BPI-SF). Methods: FACT-P and BPI-SF were assessed at baseline (BL), week (wk) 13, and therapy every 12 wks until disease progression. Longitudinal changes were assessed using mean scores and mixed-model repeated measures; lower BPI-SF scores represent less pain/interference; higher FACT-P scores represent better HRQoL. Time from BL to first deterioration in PRO score was assessed by Kaplan-Meier estimates and Cox proportional hazards models. Clinically meaningful difference was defined by change from baseline ≥10 for FACT-P total and ≥2 for worst pain/severity. Results: PRO instrument completion rates were high (88–96%) up to wk 73. At BL, men in both arms were generally asymptomatic and reported good HRQoL (FACT-P total: ENZ + ADT, 113.9; PBO + ADT, 111.8; HRQoL and pain scores remained stable over time and there were no clinically meaningful differences between groups in change from BL to wk 73. The proportion of men with no change or improvement in PRO scores (67–88%) was similar in both groups at all time points up to wk 73. There was no significant difference between study arms for FACT-P total at wk 73 (HR 0.90 [95% CI (0.74, 1.09); p = 0.2998]. ENZ + ADT significantly delayed time to pain progression for worst pain (HR 0.82 [0.69, 0.98]; p = 0.0322) and pain severity (HR 0.79 [0.65, 0.97]; p = 0.0209) vs PBO + ADT. Conclusions: Men with mHSPC were generally asymptomatic and had high levels of HRQoL and low levels of pain at BL, likely due to most men initiating ADT several months prior to study entry. No clinically meaningful differences in HRQoL were observed between ENZ and PBO. The prolongation in radiographic progression-free survival observed with ENZ + ADT was accompanied by a significantly prolonged time to progression of worst pain and pain severity vs PBO + ADT. Clinical trial information: NCT02677896.

LHRHaAA+ (Arm A) vs. AA+ (Arm B)

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Enrolled</th>
<th>34</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>74 (60-86) years</td>
<td>76 (60-86) years</td>
<td></td>
</tr>
<tr>
<td>Median baseline PSA (ng/ml)</td>
<td>26.0 (1.2-762)</td>
<td>30.5 (3.1-1,680)</td>
<td></td>
</tr>
<tr>
<td>PSA-decline ≥50%</td>
<td>23/34 (67.6%)</td>
<td>24/33 (72.7%)</td>
<td></td>
</tr>
<tr>
<td>Median serum testosterone level at baseline (ng/ml)</td>
<td>0.08 (0.020-2.101)</td>
<td>0.060 (0.023-4.292)</td>
<td></td>
</tr>
<tr>
<td>Median serum testosterone level at end-of-treatment visit (ng/ml)</td>
<td>0.062 (0.016-2.130)</td>
<td>0.059 (0.021-6.439)</td>
<td></td>
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<tr>
<td>Time from PSA progression (60)</td>
<td>288 (26-989)</td>
<td>336 (0-1,181)</td>
<td></td>
</tr>
<tr>
<td>Rate of PFS at month 12</td>
<td>0.90</td>
<td>0.78</td>
<td></td>
</tr>
</tbody>
</table>

*One patient was included by investigator despite non-castrate levels of testosterone. Study was not powered for a direct comparison between treatment arms.
ARCHES: Efficacy of androgen deprivation therapy (ADT) with enzalutamide (ENZA) or placebo (PBO) in metastatic hormone-sensitive prostate cancer (mHSPC)

Background: ENZA has demonstrated benefit in men with metastatic and nonmetastatic castration-resistant prostate cancer (CRPC). ARCHES assessed the efficacy of ENZA with ADT in men with mHSPC, including pre-specified subgroups based on prior therapy. Methods: ARCHES, a multinational, double-blind, Phase 3 study (NCT02677896), randomized patients (pts) with mHSPC to ENZA (160 mg/d) + ADT or PBO + ADT, stratified by disease volume (CHAARTED criteria) and prior docetaxel (doco) use. Primary endpoint was radiographic progression-free survival (rPFS; centrally assessed radiographic progression or death within 24 weeks of treatment discontinuation). Secondary endpoints included time to initiation of new antineoplastic therapy and overall survival (OS). Treatment continued until disease progression or unacceptable toxicity. Results: 1150 men were randomized to ENZA (n = 574) or PBO (n = 576). Overall, 63% had high-volume disease, 18% had prior docetaxel, and 91% had prior ADT or orchitectomy (orch). Median follow-up was 14.4 mo. ENZA + ADT significantly improved rPFS (Table); significant improvements in rPFS were also reported in prior treatment subgroups. Severe disease progression was improved with ENZA + ADT (Table), with no significant impact in time to deterioration in urinary symptoms. OS data are immature. Grade 3-4 adverse events (AEs) were reported in 23.6% of ENZA pts vs. 24.7% of PBO pts with no unexpected AEs. Conclusions: ENZA + ADT significantly improved rPFS and other efficacy endpoints. PBO + ADT in men with mHSPC. Preliminary safety analysis appears consistent with the safety profile of ENZA in previous CRPC clinical trials. Clinical trial information: NCT02677896.

ARCHES: Efficacy of androgen deprivation therapy (ADT) with enzalutamide (ENZA) or placebo (PBO) in metastatic hormone-sensitive prostate cancer (mHSPC)

Background: ENZA has demonstrated benefit in men with metastatic and nonmetastatic castration-resistant prostate cancer (CRPC). ARCHES assessed the efficacy of ENZA with ADT in men with mHSPC, including pre-specified subgroups based on prior therapy. Methods: ARCHES, a multinational, double-blind, Phase 3 study (NCT02677896), randomized patients (pts) with mHSPC to ENZA (160 mg/d) + ADT or PBO + ADT, stratified by disease volume (CHAARTED criteria) and prior docetaxel (doco) use. Primary endpoint was radiographic progression-free survival (rPFS; centrally assessed radiographic progression or death within 24 weeks of treatment discontinuation). Secondary endpoints included time to initiation of new antineoplastic therapy and overall survival (OS). Treatment continued until disease progression or unacceptable toxicity. Results: 1150 men were randomized to ENZA (n = 574) or PBO (n = 576). Overall, 63% had high-volume disease, 18% had prior docetaxel, and 91% had prior ADT or orchitectomy (orch). Median follow-up was 14.4 mo. ENZA + ADT significantly improved rPFS (Table); significant improvements in rPFS were also reported in prior treatment subgroups. Severe disease progression was improved with ENZA + ADT (Table), with no significant impact in time to deterioration in urinary symptoms. OS data are immature. Grade 3-4 adverse events (AEs) were reported in 23.6% of ENZA pts vs. 24.7% of PBO pts with no unexpected AEs. Conclusions: ENZA + ADT significantly improved rPFS and other efficacy endpoints. PBO + ADT in men with mHSPC. Preliminary safety analysis appears consistent with the safety profile of ENZA in previous CRPC clinical trials. Clinical trial information: NCT02677896.

LATITUDE

Background: Patients with metastatic prostate cancer (mPC) are treated with lifelong ADT even after progression and every treatment for mPC has been tested only in the setting of androgen deprivation. Androgen synthesis inhibitor AA which inhibits synthesis of androgen that later get converted to testosterone has been studied and approved only alongside ADT similar to all other treatments that have no or limited activity on testosterone suppression. We reviewed the ability of AA to sufficiently suppress testosterone levels as compared to AA plus ADT and its potential impact on cost savings. Methods: This retrospective study included consecutive patients with mCRC treated with AA alone or in combination with ADT (in absence of orchietomy) who had been followed with serial testosterone values on therapy. A cost analysis was performed to determine the cost avoidance by omitting leuprolide injections while on AA. The cost avoidance was calculated by multiplying the total number of injections by the wholesale acquisition cost of $5225.86 for a three month leuprolide injection. Results: 457 patients included in the final analysis, 36 received AA plus ADT, 10 received AA alone, and 11 started off with AA plus ADT before transitioning to AA alone. Testosterone levels were drawn 235 times. Testosterone was undetectable (below < 2 ng/dL) in both arms, 134 of 152 in combination arm and 86 of 99 in the AA alone arm. The median testosterone concentration when detectable was 3 ng/dL in AA alone and 3.5 ng/dL. A plus ADT alone in the combination arm and only one testosterone value in AA arm had testosterone > 30 ng/dL. The mean duration of AA use in this study was close to one year, and the total duration of therapy was approximately 61 years which could result in elimination of 244 leuprolide administrations and approximately $1,29 million in total cost. Conclusions: AA alone is able to effectively suppress testosterone synthesis in patients with prostate cancer. ADT with GnRH agonist or antagonist can be safely withheld while on therapy with AA and testosterone values followed to confirm adequate androgen suppression. This has acquired new significance after studies in patients with hormone sensitive disease where the duration of treatment was 3-4 years which could translate to an avoidable expense of $55.5 million for 960 patients in ‘STAMPEDE’ study and $34.5 million in ‘LATITUDE’ study from leuprolide administration in combination arm.

5050 Poster Session (Board #162), Sat, 1:15 PM-4:15 PM

A multicentric phase II randomized trial of docetaxel (D) plus enzalutamide (E) versus E (D-E) as first-line chemotherapy for metastatic castration-resistant prostate cancer (mCRPC)

Background: D and E demonstrated to be efficacious in the treatment of mCRPC pts. Due to different antitumor mechanism of action of these agents, it could be postulated that their combination can improve disease control. CHEIRON study tried to demonstrate the candidate efficacy of chemo-hormonal combination D-E versus D in mCRPC first-line. Methods: Eligibility criteria included mCRPC diagnosis, ECSG PS ≤ 2, adequate renal, hepatic and hematological functions, no prior treatment for mCRPC. Pts were randomized to receive D 75 mg/m² IV q4weeks plus prednisone 5 mg PO BID for 8 courses alone or plus E 160 mg PO daily for 24 weeks. Stratification criteria were presence of pain and visceral metastases. The primary endpoint of the study was the rate of pts without disease progression (according to PCWG2) at 6 mos after randomization. Results: Between 09/2014 and 10/2017, 246 pts (median age 70 years, range 44-88, pain reported by 54 pts, visceral metastases present in 50 pts) were randomized to DE (120) or D (126). The rate of pts without disease progression at 6 mos was significantly higher in DE arm compared to D arm (89.1% vs 72.8%; p = 0.002). Similarly, a higher proportion of DE pts achieved a PSA reduction ≥ 50% compared to the baseline values compared to the D pts (92% vs 69%; p < 0.0001). No differences were observed in terms of objective response rate. Major haematological toxicities consisted of grade 3-4 neutropenia (13 pts DE – 11 pts D), febrile neutropenia was observed in 10 DE pts and in 6 D pts. At a median follow-up of 24 mos, the median progression free survival was 10.1 mos and 9.1 mos in DE and D arm, respectively (p = 0.01). In DE arm the median overall survival was 33.7 mos compared to 29.6 mos of the standard arm (p NS). Conclusions: The present study was the first phase II randomized trial, which tested the addition of a new generation hormone agent to D compared to D alone. From this data, DE improved the 6-mo disease control with a prolongation of FFS compared to the standard chemotherapy. Clinical trial information: NCT02453009.

5051 Poster Session (Board #163), Sat, 1:15 PM-4:15 PM

Clinical and genomic hallmarks of low PSA secretors in metastatic castration-resistant prostate cancer (mCRPC)

Background: Patients with metastatic prostate cancer (mPC) are treated with lifelong ADT even after progression and every treatment for mPC has been tested only in the setting of androgen deprivation. Androgen synthesis inhibitor AA which inhibits synthesis of androgen that later get converted to testosterone has been studied and approved only alongside ADT similar to all other treatments that have no or limited activity on testosterone suppression. We reviewed the ability of AA to sufficiently suppress testosterone levels as compared to AA plus ADT and its potential impact on cost savings. Methods: This retrospective study included consecutive patients with mCRC treated with AA alone or in combination with ADT (in absence of orchietomy) who had been followed with serial testosterone values on therapy. A cost analysis was performed to determine the cost avoidance by omitting leuprolide injections while on AA. The cost avoidance was calculated by multiplying the total number of injections by the wholesale acquisition cost of $5225.86 for a three month leuprolide injection. Results: 457 patients included in the final analysis, 36 received AA plus ADT, 10 received AA alone, and 11 started off with AA plus ADT before transitioning to AA alone. Testosterone levels were drawn 235 times. Testosterone was undetectable (below < 2 ng/dL) in both arms, 134 of 152 in combination arm and 86 of 99 in the AA alone arm. The median testosterone concentration when detectable was 3 ng/dL in AA alone and 3.5 ng/dL. A plus ADT alone in the combination arm and only one testosterone value in AA arm had testosterone > 30 ng/dL. The mean duration of AA use in this study was close to one year, and the total duration of therapy was approximately 61 years which could result in elimination of 244 leuprolide administrations and approximately $1,29 million in total cost. Conclusions: AA alone is able to effectively suppress testosterone synthesis in patients with prostate cancer. ADT with GnRH agonist or antagonist can be safely withheld while on therapy with AA and testosterone values followed to confirm adequate androgen suppression. This has acquired new significance after studies in patients with hormone sensitive disease where the duration of treatment was 3-4 years which could translate to an avoidable expense of $55.5 million for 960 patients in ‘STAMPEDE’ study and $34.5 million in ‘LATITUDE’ study from leuprolide administration in combination arm.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Aggressive variant prostate cancer (AVPC) molecular signature in castration-sensitive, de novo metastatic prostate cancer (mPCa).

**Background:** AVPC are a subset of prostate cancers (PC) that share clinical features with the small-cell prostate carcinomas, a rare morphological variant with atypical and virulent behavior. They are estimated to represent 30% of lethal PC and are characterized by a molecular signature of combined defects (≥2) in TP53, RB1 and APCC (AVPC_MS). The AVPC_MS is associated with androgen independence in preclinical models and predicts benefit from the addition of carboplatin to cabazitaxel in men with castration resistant prostate cancer (CRPC). The prevalence and significance of the AVPC_MS in castration sensitive mPCa is unknown.

**Methods:** In a Phase II trial 119 men with mPCa treated with 6 months of standard systemic therapy (SST) were randomized to the addition of local therapy. PCa samples obtained at diagnosis and after 6 months of SST were stained for markers including TP53, RB1 and PTEN, and subject to whole genome sequencing. TP53 was considered defective if expressed in ≥10% of tumor cells, and RB1 and PTEN if in ≤10%. Progression free survival (PFS) was estimated from SST start.

**Results:** To date specimens from 38 men have been evaluated. Immunohistochemistry (IHC) results are shown below. The median PFS of men with AVPC_MS POSITIVE vs baseline was 11 (34.4%) vs 17 (63.0%) and lower rates of visceral metastases (n=9). Pts treated with 1L-Doc had higher rates of visceral metastases (22.9% vs 5.7%; p=0.003), high ALP (68.8% vs 43.2%; p=0.004) and low Hb (12.5% vs 3.4%). FPS to 1L-therapy was longer for Avi/Enza than for Doc (9.6 vs 8.3m; HR: 0.52; p=0.001). The pattern of disease progression (PSA, radiographic, clinical) was similar in Doc and Avi/Enza treated pts.

**Conclusions:** No difference between pts treated with initial Avi/Enza vs Doc was observed in OS (28.2 vs 24.8m; HR: 1.18; p=0.474). No significant OS differences were observed in the MV model. Conclusions: No differences in OS were observed between treatment sequence starting with Doc vs Avi/Enza in pts ≤75 yrs. Pts treated with 1L-Doc had worse baseline prognostic features. Age should not be considered as a factor for treatment choice overall in men with mPCa.

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**5052 Poster Session (Board #164), Sat, 1:15 PM-4:15 PM**

**Prostate Cancer**

**5052 Poster Session (Board #164), Sat, 1:15 PM-4:15 PM**

**5053 Poster Session (Board #165), Sat, 1:15 PM-4:15 PM**

**Treatment sequence in elderly metastatic castration-resistant prostate cancer (mCRPC) patients (pts) in a prospective cohort study.**

**First Author:** Maria Jose Madrid-Vidal, Reina Sofia Univerist Hospital, Cordoba, Spain.

**Background:** Abiraterone (Abi), enzalutamide (Enza) and docetaxel (Doc) are all valid first-line (1L) mCRPC treatment options, SIOL guidelines (Droz, Eur Urol 2017) recommend that fit elderly pts should receive the same treatment as younger patients. Evidence of the optimal treatment sequence in this patient subpopulation is lacking.

**Methods:** We evaluated the outcome of elderly (≥ 75 yrs) pts treated in the prospective PROREPAIR-B cohort study (NCT03075735). We assessed the impact of 1L treatment option (Doc vs Abi/Enza) on overall survival (OS) and progression-free survival (PFS) to 1L-therapy following PCWG2 criteria. Uni- (UV) and multivariable (MV) cox regression models were used. MV model covariates included local therapy, Gleason Score, stage IV at diagnosis, visceral metastases, ALP (< ULN), LDH (< ULN), haemoglobin (Hb; < ULN), albumin (< ULN), and ECOG PS.

**Results:** 419 pts were included in the study. Of these, 137 (32.7%) had age ≥ 75 yrs. 48 (35%) received docetaxel and 88 (64.2%) had Abi/Enza as first-line therapy. Of the 121 pts that progressed on 1L-therapy, 30 (24.8%) did not receive 2L therapy. Choice of 2L-therapy was: Doc in 37 (30.6%), Abi/Enza in 38 (31.4%), Cabazitaxel in 9 (7.4%) and Radiosurgery in 23 (5.8%) pts. Pts treated with 1L-Doc had higher rates of visceral metastases (22.9% vs 5.7%; p=0.003), high ALP (68.8% vs 43.2%; p=0.004) and low Hb (12.5% vs 3.4%). FPS to 1L-therapy was longer for Abi/Enza than for Doc (9.6 vs 8.3m; HR: 0.52; p=0.001). The pattern of disease progression (PSA, radiographic, clinical) was similar in Doc and Abi/Enza treated pts.

**Conclusions:** No difference between pts treated with initial Abi/Enza vs Doc was observed in OS (28.2 vs 24.8m; HR: 1.18; p=0.474). No significant OS differences were observed in the MV model. Conclusions: No differences in OS were observed between treatment sequence starting with Doc vs Abi/Enza in pts ≥ 75 yrs. Pts treated with 1L-Doc had worse baseline prognostic features. Age should not be considered as a factor for treatment choice overall in elderly mCRPC pts based on treatment outcome.
Background: Germline mutations in DNA repair genes are common in patients with metastatic hormone-naïve prostate cancer (mPCa). Methods: A total of 76 patients with hormone-naïve mPCa treated with first-line ADT by luteinizing hormone-releasing hormone analogue (LHRHa) between 2014 and 2017 were recruited. Median follow-up was 34.8 mo. We focused on age, volume of metastatic spread, histologic grade, family history. All patients were genotyped for germline mutations in the BRCA1, BRCA2 and CHEK2 genes by polymerase chain reaction real-time and the Sanger sequencing. We used the standard definition of castration-resistance PCa (CRPC). Median time to CRPC were estimated using the Kaplan-Meier method, generated curves were compared using the log-rank test. Cox regression analyses were used to assess the prognostic value of BRCA1/2 and CHEK2 mutations.

Results: Pathogenic and likely pathogenic germline mutations in the BRCA2 and CHEK2 gene were identified in 19 (25 %) patients. No cases of BRCA1 mutations were detected. Median time to CRPC in BRCA2 and CHEK2 mutation carriers (7.9 mo, 95 % confidence interval (CI) 2.6 – 13.3), than in non-carriers (48.7 mo, 95 % CI 31.1 – 68.3, p < 0.001). There was no significant difference in median time to CRPC in BRCA2 (7.9 mo, 95 % CI 0.0-16.3) and CHEK2 mutation carriers (6.1 mo, 95 CI 5.0 – 7.2, p = 0.448) both were significantly shorter than in non-carriers (90.0 mo, p < 0.001). Multivariable analysis confirmed both BRCA2 (hazard ratio (HR): 2.63; 95 CI 1.32-5.26, p = 0.006) and CHEK2 (HR: 6.66, 95 CI 2.35-18.89, p < 0.001) mutations as an independent prognostic factor for time to CRPC, particularly in mPCa with low-volume metastasis spread (HR 3.09, 95 % CI 1.36-7.05, p = 0.001)

Conclusions: BRCA2 and CHEK2 carriers had worse outcomes (shortened time to CRPC) than noncarriers when conventionally treated for metastatic PCa by standard first-line hormone treatment with LHRHAs.

5056 Poster Session (Board #168), Sat, 1:15 PM-4:15 PM
Impact of germline DNA-repair gene BRCA2 and CHEK2 mutations on time to castration resistance in patients with metastatic hormone-naïve prostate cancer (mPCa).
First Author: Kseniya Skocir, MD, PhD; Sydney M. Turcsanyi, MD, PhD; Benjamin K. Finberg, MD; Philip S. Charkes, MD; Bouchard Center for Cancer Research, Providence Hospital, Providence, RI

Background: Genitourinary (Prostate) Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA

Methods: We developed the NanoVelcro CTC purification system with NanoString nCounter platform for CTC purification and RNA analysis. Based on the well-validated, tissue-based Prostate Cancer Classification System (PCSS), we selected the most aggressive and ARSI-resistant subtype- the PCS1, for CTC analysis. We applied a rigorous bioinformatic procedure to develop a CTC-PCS1 panel that is specific to PC CTCs. We validated NanoVelcro CTC-RNA Assay and CTC-PCS1 panel with PC cell lines to demonstrate sensitivity and specificity of the PCS1 Z score (the likelihood estimate of the PCS1 subtype) for identifying PCS1 subtype and ARSI resistance. We then selected 31 blood samples from 23 PC patients receiving ARSI to test in our assay. The PCS1 Z score of each sample was computed and compared with ARSI treatment sensitivity.

Results: We established a 16-gene CTC-PCS1 panel that consists of CTC-specific RNA signatures. The validation studies using PC cell lines showed that the assay can detect the RNA transcripts with high sensitivity and scalability in the range of 1-100 cells. We also showed that the genes in the CTC-PCS1 panel is highly expressed in PC cells. We further demonstrated that the CTC-PCS1 panel is highly specific in identifying PCS1-like samples, and the high PCS1 Z score is associated with ARSI resistance. In patient bloods, ARSI-resistant samples (ARSI-R, n=14) had significantly higher PCS1 Z scores compared with ARSI-sensitivity (ARSI-S, n=17) (Rank-sum test, P=0.003). In 8 patients who were initially sensitive to ARSI (ARSI-S) and later developed resistance (ARSI-R), we found that the PCS1 Z score increased from the time of ARSI-S to the time of ARSI-R (Parwise T-test, P=0.016).

Conclusions: Using our new methodology, we developed a first-in-human CTC-RNA assay to assess the prognostic value of clinically-relevant tissue-based RNA profiling into CTC tests. This approach allows for detecting RNA expression relevant to clinical drug resistance in a non-invasive fashion, which can facilitate patient-specific treatment selection and early detection of drug resistance- a goal in precision oncology.

5058 Poster Session (Board #170), Sat, 1:15 PM-4:15 PM
AR changes in circulating-tumor DNA (ctDNA) in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with high-dose testosterone.
5061  Poster Session (Board #173), Sat, 1:15 PM-4:15 PM
Risk of depression following prostate cancer work-up: A nationwide study. First Author: Anne Sofie Frobbérg, Danish Cancer Society Research Center, Copenhagen, Denmark

Background: Little is known about the psychological impact of undergoing evaluation for prostate cancer (PCa). We investigated the risk of developing a depression following PCa work-up with benign and malignant findings, respectively, compared with cancer-free men. Methods: A nationwide cohort of men who underwent prostate needle biopsies in Denmark from 1997–2011 was identified through the Danish Prostate Cancer Registry. Primary outcome was indication of moderate to severe depression defined as hospital contact for depression or first redemption of a prescribed antidepressant. For comparison, we selected a minimum of five age-matched cancer-free men per man who had undergone PCa specific diagnostic work-up. We excluded men with other cancer, major psychiatric disorder or use of antidepressants up to three years before study entry. Information on outcome and covariates (age, period, co-habitation status, income quintile and comorbidity) were retrieved from National Danish registries. We illustrated the risk of depression by cumulative incidence functions. Data were analyzed using Cox models adjusted for possible confounders. Results: We identified 54,766 men who underwent work-up including transrectal biopsies of the prostate, among these, 21,419 biopsy sets were benign and 33,347 men were diagnosed with PCa. We found an increasing cumulative incidence of depression in all groups. However, men diagnosed with PCa had a significantly higher risk throughout up to 18 years of follow-up. The adjusted hazard ratio (HR) of depression in men diagnosed with PCa was increased throughout the follow-up compared with BRCa1 alterations (A1 3.3% vs CA 0.9% and AA 2.1% vs AA 1.4% and AA 2% vs AA 0.8% vs AA 1.7%, p = 0.0034) and CHEK2 alterations (A1 4.3% vs CA 2.8% vs AA 0.4%, p = 0.02). There were no significant differences in the prevalence of individual or specific classes of GVs between those with or without a self-reported FH of prostate or breast/cancer. There was also no association between prevalent FH and other risk factors and age at germline testing (p = 0.40).

Conclusions: This national study found that the overall prevalence of pathogenic GVs in MM and HR GVs do not differ by race, ethnicity, or age at the time of testing, and suggests that all men with advanced prostate cancer should be offered germline testing.

5063  Poster Session (Board #175), Sat, 1:15 PM-4:15 PM
Evolving natural history of metastatic prostate cancer. First Author: Nellie Nafissi, Mayo Clinic Arizona, Phoenix, AZ

Background: The systemic therapies available to patients with metastatic prostate cancer (mPC) have improved dramatically over the past decade. Prior to 2010, the only agents with a proven survival benefit for patients with metastatic disease were androgen deprivation therapy and docetaxel. Since then, five new agents have been FDA approved and have proven survival benefit in phase III trials. Anecdotal experience suggests that the increased available options has resulted in increased overall survival benefit in mPC patients compared to 2009 (40.0% and 21.1%, respectively, p = 0.05).

Methods: In this study, we evaluated the impact of stage and treatment modalities. The age, GA per tumor and TMB were queried whether these subsets would share similar genomic alterations (GA) reflecting their disease biology and clinical features. Methods: CCG was performed using a hybrid capture-based assay on 61 PDC, 4,132 PAC and 217 PNC. Tumor mutational burden (TMB) was determined on 1.1 Mbp of sequenced DNA and microsatellite instability (MSI) was determined on 114 loci. Results: The age, GA per tumor and TPS of GA of PDC, PAC and PNC were similar (Table). Rb1 GA were predominant in PNC. TMB was most frequent in PNC, intermediate in PAC and lowest in PDC. AR GA were more common in PAC and PNC than PTEN GA which were most frequent in PDC. Targetable GA were identified in all 3 groups when focused on BRCA1/2 (PARP inhibitors) and PIK3CA (MDT inhibitors). There were no significant differences in the overall prevalence of MMR (MSH2/6, MLH1, PMS2, and MUTHY) and HR genes (BRCA1/2, ATM, CHEK2, RAD51D, and PALB2). Results: 3057 men were included in the final analysis: 2248 (74%) men were CA, 229 (7%) were AA, and 210 (7%) were AJ. Of these, 2665 (87%) men had a FH of CA and 463 (15%) had a PDC. In addition, 1068 (35%) were found to have a variant of uncertain significance, and 35 (1.6%) had the HOBXS1 G34E variant. There were no significant differences in the overall prevalence of MMR (CA 1.5% vs AA 0.9% vs AJ 1.4%, p = 0.89) and HR genes (CA 7.8% vs AA 7.9% vs AJ 10.5%, p = 0.37) by race/ethnicity. With respect to individual genes, AJ had a higher prevalence of HR genes (CA 3.3% vs AA 0.8% vs AJ 1.7%, p = 0.0034) and CHEK2 alterations (A1 4.3% vs CA 2.8% vs AA 0.4%, p = 0.02). There were no significant differences in the prevalence of individual or specific classes of GVs between those with or without a self-reported FH of prostate or breast/cancer. There was also no association between prevalent FH and other risk factors and age at germline testing (p = 0.40).

Conclusions: This national study found that the overall prevalence of pathogenic GVs in MM and HR GVs do not differ by race, ethnicity, or age at the time of testing, and suggests that all men with advanced prostate cancer should be offered germline testing.
SLFN11 expression (exp) in castration-resistant prostate cancer (CRPC) patients (pts) to predict response to platinum-based chemotherapy (PLT).

Methods: First, we identified 52 pts with CRPC, using various criteria. 27 pts had somatic sequencing data, obtained via exome sequencing (N=27) and/or CTCs (N=20) (via the Epic Sciences platform). In addition, tumor morphology for neuroendocrine (NE) features and genomic status of select genes (ie, AR, TP53, RB1, BRCA2, BRCA1, ATM) by whole exome sequencing were evaluated. Statistical comparisons used Cox re-
5069 Poster Session (Board #181), Sat, 1:15 PM-4:15 PM
ATM loss in primary prostate cancer: Analysis of > 1000 cases using a validated clinical-grade immunohistochemistry (IHC) assay. First Author: Emmanuel S. Antonescu. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD

Background: ATM is a protein kinase acting as the main signal transducer of double-strand DNA break repair, in addition to mediating other cellular functions. Germline and somatic pathogenic mutations in ATM occur in a significant fraction of prostate cancers, and targeted therapies for ATM-deficient tumors (e.g. ATR inhibitors) appear promising. Because DNA sequencing assays frequently cannot distinguish mono-allelic from bi-allelic ATM alterations, a clinical-grade protein IHC assay for ATM loss is needed to select men for these trials and better characterize ATM-deficient tumors. Methods: We validated an automated dichotomously-scored IHC assay to detect ATM protein loss in primary prostate cancer using prostate cancer cell lines with and without bi-allelic ATM inactivation and 49 high-grade (primary Gleason pattern 5) prostate tumors with known ATM genotypic status. We then examined the frequency of ATM loss among 23 tumors with pathogenic germline ATM mutations, as well as > 1000 additional primary prostate carcinomas using tissue microarrays (TMA). Results: ATM loss by IHC was found in 1.7% (7/49) of primary Gleason pattern 5 tumors with known ATM genotypic status. Of these, all cases with adequate tumor content and DNA yield had underlying pathogenic ATM alterations. Of the remaining 42 cases without ATM protein loss, none had ATM alterations. Among men with pathogenic germline ATM mutations, 74% (17/23) had ATM loss by IHC. Of these, 76% (13/17) had heterogeneous ATM loss of ATM protein in all tumor cells within a dominant tumor nodule, suggesting that ATM loss was an early clonal event. On TMA analysis, 90% (944/1044) of tumors were evaluable for ATM status by IHC. Among these, ATM loss was seen in 3.3% (31/944), and was significantly more common in tumors with Gleason scores 9-10 (20/198; 10.1%) than in those of all other Gleason grades (11/774; 1.5%) (p < 0.0001). Conclusions: Validated ATM IHC is a sensitive assay for detecting underlying genomic ATM alterations. ATM protein loss appears to be an early event occurring in the majority of tumors with underlying germline pathogenic ATM mutations, and is significantly enriched in high-grade prostate cancers (especially Gleason grades 9-10).

5070 Poster Session (Board #182), Sat, 1:15 PM-4:15 PM
Cell-free DNA as a biomarker for taxane treatment in advanced prostate cancer. First Author: Semini Sunamasanuya. Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom.

Background: Antitumor efficacy of chemotherapeutic drugs docetaxel and cabazitaxel against hormone-sensitive and castration-resistant prostate cancer (CRPC) is well recognized. The identification and validation of minimally invasive biomarkers of taxane response remain of paramount importance. Methods: Serial pre-, during and post-treatment plasma samples were collected prospectively from two large Phase III clinical trials, FIRSTANA (NCT01308567) and PROSELICA (NCT01308580). Chemotherapy-naïve patients (pts) were treated with docetaxel (75 mg/m^2) or cabazitaxel (20 or 25 mg/m^2) in FIRSTANA, and pts previously treated with docetaxel received cabazitaxel (20 or 25 mg/m^2) as second-line chemotherapy in PROSELICA. Plasma cell-free DNA (cfDNA) libraries were extracted, low-pass whole genome sequencing (Ip-WGS) libraries were prepared using the IGIEN SiaSeq FX DNA library kit, and samples sequenced on the Illumina NovaSeq 6000. Targeted next-generation sequencing (NGS) on a custom-made AmpliSeq panel of 30 genes, pre-selected for putative roles in taxane resistance, was also performed. Ip-WGS copy number (CN) profiles were generated using ichorCNV (v0.1.0) and CNV variants called using Ion Reporter software. Results: Overall, Ip-WGS data was generated from 265 samples (99 pts; 51 treated on the FIRSTANA study, 48 treated on the PROSELICA study), acquired at three time-points (pre-, during and at progression). Average cfDNA input was 10 ng and mean coverage achieved was 2X (SD 1.2X). We observed changes in Ip-WGS tumor purity over time as a result of therapy; samples from non-responding pts exhibited significantly higher tumor purity values post-treatment compared with samples from responding pts (p = 0.02). Targeted NGS results were available from 294 pts (153 from FIRSTANA, 141 from PROSELICA), and changes in tumor purity were also associated with treatment response (p = 0.04). CN frequency of key CRPC genes was similar to previously reported datasets; several aberrant loci associated with response to taxane therapy. Conclusions: cfDNA Ip-WGS may have clinical utility in the management of lethal prostate cancer. Funding: Sanofi. Clinical trial information: NCT01308580, NCT01308567.

5071 Poster Session (Board #183), Sat, 1:15 PM-4:15 PM
Implications of the United States Preventive Services Task Force (USPSTF) recommendations on prostate cancer (PCA) stage migration. First Author: Iris Yeong- Fung Sheng. Cleveland Clinic, Cleveland, OH

Background: Prostate specific antigen (PSA) screening has been controversial, given unrefined screening guidelines leading to overdiagnosis and overtreatment of “indolent” PCs. In 2008, the USPSTF recommended against PSA screening for men aged ≥75 and in 2012 broadened this recommendation to include all men. The impact of these changes is unstudied. We hypothesize that these screening changes could delay the diagnosis of advanced PCa. Methods: The Surveillance, Epidemiology and End Results Program (SEER) was used to identify men (age 55-69) diagnosed with PCa between 2004-2015. PCA stage was categorized as nodal (N1M0) and metastatic (NxM1). Trend analysis was stratified based on year 2004-2008 (group 1), 2009-2012 (group 2), and 2012-2015 (group 3). Using group 2 as a reference, multivariable logistic regression was used to identify predictors for N1M0 and NxM1 in each group. Results: From 2004-2015, there were 603,323 eligible men diagnosed with PCA (group 1: 262,240 men; group 2: 210,045 men; group 3: 131,038 men). In group 1, 1.4% had N1M0 and 2.8% had NxM1. In group 2, 2.1% had N1M0 and 3.7% had NxM1. In group 3, 1.4% had N1M0 and 6.1% had NxM1. The adjusted odds ratio (AOR) of N1M0 was 0.78 (95% CI: 0.74-0.82; p<0.0001) in group 1 and 1.71 (95%CI 1.63-1.80; p<0.0001) in group 3. Similar AOR trends were seen for NxM1 (group 1 0.68; 95% CI: 0.60 vs. 1.00 vs. 1.58, p<0.0001). Table: Subset analysis of non-eligible patients (age >70 and <55) showed a similar stage migration. Conclusions: With each USPSTF recommendation, there have been significantly more diagnoses of advanced PCs; suggesting stage migration. The sequence of having advanced PCA instead of more aggressive treatments, increased financial burden, and reduced quality of life. Future population studies are warranted to investigate whether the updated 2018 USPSTF recommendation now encapsulates the best target population.

Regression results for N1M0 and NxM1.

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<td>2013-2015</td>
<td>1.71 (1.63-1.80)</td>
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*Adjusted for age, race, income, and education.

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Multi-gene hereditary cancer testing, family history and prognosis in men with prostate cancer. First Author: Panagiotis J. Vlachostergios, Division of Hematology & Medical Oncology, Weill Cornell Medical College & New York-Presbyterian Hospital, New York, NY

Background: Multi-gene hereditary cancer testing is common in prostate cancer (PC). We assessed the frequency of pathogenic mutations (mt) and examined associations with family history (FH), cancer recurrence, and overall survival (OS). Methods: Men with clinically localized or metastatic PC consented to germline DNA testing using a validated panel of 30 genes associated with elevated risk for common cancers (Color Genomics). Chi-square test and Fisher's exact test were used to compare pathogenic mt and clinical characteristics. The Kaplan-Meier method was used to evaluate the associations of mt status with PSA recurrence and OS. Results: 315 men (median age 69, range 38-89) were included; 140 (44.4%) with localized and 175 (55.6%) with metastatic PC. FH was evaluated in one and 101 (32.1%) in ≥ 2 first-degree relatives. Genomic testing detected 12.1% of pts possessed a pathogenic mt (39 mt in 38 pts): BRC2 (n = 12, 3.8%), CHEK2 (n = 10, 3.2%), APC (n = 7, 2.2%), MUTYH (n = 3, 0.9%), ATM (n = 2, 0.6%), and 1 each (0.3%) with NBN, PALB2, RAD21, MSIG2, and mismatch repair gene variants. The prevalence of pathogenic mt was significantly higher with vesceral metastases (P = 0.001) but did not differ between localized and advanced PC pts (P = 0.602). In men with clinically localized PC at diagnosis (n = 226, 71.7%), pathogenic mt were associated with a shorter time to recurrence (30 vs 53 months, P = 0.004). Men with advanced PC (n = 175) and germline APC or MUTYH mt had worse median OS (44 vs 318 months, P = 0.004). Conclusions: Our findings confirm the incidence of men with non-PC FH associated with DNA repair gene mt and support testing in early stage pts. Further, our data support the prognostic significance of germline genetic alterations which deserves study in a larger cohort of pts.

Examination of the additive value of CTC biomarkers of heterogeneity (Het) and nuclear-localized (nl) AR-V7+ and CTCs in prediction of poor outcomes to androgen receptor signaling inhibitor (ARSI) in metastatic castration resistant prostate cancer (mCRPC). First Author: Howard I. Scher, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Prediction of ARSIs benefit in mCRPC is an unmet medical need. Recently, the Epic Sciences CTC based nAR-V7 test validated as a predictive biomarker in two multi-center validation studies and was approved by Medicare for use in mCRPC. While the nAR-V7 biomarker is highly specific to resistance and predictive of improved response with taxane Rx, it is a measure of just one mechanism of resistance to ARSI. CTC Het measured by the Shannon Index and CTC chromosomal instability measured by predicted number of Large Scale Transitions (pLST) have both been associated with poor OS to ARSIs in previous analysis. Here we investigate the relationship of Het and pLST to nAR-V7 in order to assess multi-clonal resistance and determine if these biomarkers can provide added sensitivity in the prediction of outcomes to ARSIs. Results: 275 blood samples from 347 line mCRPC patients prior to treatment with ARSI (n=148) or taxanes (n=137) were obtained between 2012 and 2017 from 3 clinical centers. Detectable CTCs in each blood sample were assayed for the nAR-V7 and Het using the Epic Sciences platform. Biomarkers were added in context of each other and outcomes including clinical co-variates. Results: 94% of samples had detectable CTCs, 84% were evaluable for Het analysis (> 2 CTCs), and 76% were evaluable for pLST (> 3 CTCs), respectively. Conclusions: Addition of CTC Het (Shannon Index) and CTC chromosomal instability (pLST) biomarkers to nAR-V7 identifies an additional 15% of mCRPC pts (38% of total) that are predicted to have poor survival to AR signaling inhibitors.

Clinical and safety outcomes of TALAPRO-2: A two-part phase III study of talazoparib (TALA) in combination with enzalutamide (ENZA) in metastatic castration-resistant prostate cancer (mCRPC). First Author: Neeraj Agarwal, University of Utah Huntsman Cancer Institute, Salt Lake City, UT

Background: TALA is a dual-mechanism PARP inhibitor that inhibits PARP catalytic activity and traps PARP on DNA. ENZA is a novel hormonal therapy approved to treat castration resistant prostate cancer. TALA + ENZA may improve clinical outcomes for men with mCRPC. However, TALA, is a substrate for efflux drug transporters P-gp and BCRP. Prior to the initiation of TALAPRO-2 part 1, the in vivo effect of ENZA on exposure of P-gp and BCRP substrates, such as TALA, had not been evaluated. Methods: TALAPRO-2 part 1 was designed to determine TALA starting dose based on safety and pharmacokinetics (PK) evaluation of TALA + ENZA. Pts were ≥ 18 yrs of age, had ECOG PS ≤ 1, with no prior systemic treatment for mCRPC. The starting dose of TALA in the first 13 pts was 1 mg once daily (QD) + ENZA 160 mg QD (1 mg QD cohort). Based on safety review of prespecified target safety events and PK data, TALA dose was reduced to 0.5 mg QD; additional pts were treated with a starting dose of TALA 0.5 mg QD + ENZA 160 mg QD (0.5 mg QD cohort). Results: 19 pts were enrolled in part 1 (1 mg QD cohort, 13; 0.5 mg QD cohort, 6). The median (range) age was 71 yrs (52-82). As of the analysis cutoff date, the median treatment duration was 25 and 11 wks for the 1 mg QD and 0.5 mg QD cohorts, respectively. Treatment-emergent adverse events (TEAEs) occurred in 19 pts. The most common TEAE, anemia, occurred in 76.9% and 33.3% of pts in the 1 mg QD and 0.5 mg QD cohorts, respectively. TEAEs that led to TALA dose reduction occurred in 6 pts (46.2%) and 0 pts in the 1 mg QD and 0.5 mg QD cohorts, respectively. In the 1 mg QD cohort, target safety events were reported for 7 pts (53.8%) vs 0 in the 0.5 mg QD cohort. 92% and 100% of pts had a 50% decline from baseline in PSA in the 1 mg QD and 0.5 mg QD cohorts, respectively, demonstrating preliminary anti-tumor activity. PK data showed that ENZA increased TALA exposure and that TALA 0.5 mg QD + ENZA maintained similar TALA exposure to that achieved with 1 mg QD monotherapy. Conclusions: TALA 0.5 mg QD + ENZA 160 mg QD had a manageable safety profile in pts with mCRPC and will be the starting dose for the randomized portion of TALAPRO-2 part 1. Clinical trial information: NCT03395197.
5077 Poster Session (Board #189), Sat, 1:15 PM–4:15 PM
Assessment of 2,000 patients presenting to a multidisciplinary prostate cancer clinic in the United Kingdom. First Author: Pandora Ruddi, St. Bartholomew’s Hospital, London, United Kingdom.

Background: Multidisciplinary clinics (MDCs) involving both oncologists and urologists are recommended for managing radical prostate cancer patients. The effectiveness of MDCs in arriving at best treatment decisions is unknown. We analysed patient characteristics and management decisions over 8 years in a MDC at Bart’s Hospital, London. Methods: Clinical data were collected in real time and analysed retrospectively, including demographics, tumour stage and grade, D’Amico risk group, treatment choice and first clinician seen. We compared variables in 1000 consecutive patients presenting between 2011-2015 (cohort A) to 1000 patients presenting 2016-18 (cohort B) to investigate trends over time. Results: 2000 patients were included, age 65.2 ± 8.6 years and 65.9 ± 9.1 years (p=0.08), with presenting PSA 9.0 (6.3-14.4) and 9.2 (6.4-15.0) ng/ml (p=0.36), in cohort A and B respectively. Disease severity and initial treatment decision are shown in the table. In low risk disease, 126 (75%) patients had active surveillance in cohort A, and 158 (90%) in cohort B (p=0.0003). In high risk disease, 202 (59%) patients had radiotherapy compared to 194 (50%) in cohort B (p=0.011). In cohort B, 127 (39%) patients seeing oncology first had radiotherapy compared to 143 (25%) patients who saw urology first (p<0.0001). 76 (23%) and 154 (27%) patients had surgery, that saw urology and oncology first, respectively (p=0.11).

Conclusions: In 2000 patients presenting to a prostate MDC over 8 years, active surveillance in low risk disease increased, radiotherapy in high risk disease reduced, and the proportion undergoing surgery was unchanged. The initial clinician seen influenced treatment choice; having both specialists in the same consultation may improve consistency of treatment decisions. Disease severity and treatment choice before and after 2016.

5078 Poster Session (Board #190), Sat, 1:15 PM–4:15 PM
Randomized phase II trial of presurgical androgen deprivation therapy (ADT) with or without axitinitib in prostate cancer (PCa) presenting with lymph node (LN) metastasis. First Author: Amadou J. Zuria, The University of Texas MD Anderson Cancer Center, Houston, TX.

Background: Strategies integrating androgen targeted and locoregional therapies are being increasingly used in PCa with regional spread, but are rarely curative. Angiogenesis inhibitors delay progression in castration resistant PCa and may synergize with ADT through endothelial cell apoptosis in hormone naïve patients (pts). We hypothesized that the frontline combination of ADT with the potent VEGF inhibitor Axi would improve PCa control relative to ADT alone and allow for meaningful time off systemic therapy after surgical consolidation.

Methods: Pts with either clinically detected LN+ (TnN1Mo or TnNxnA) or very high risk for LN PCa were treated with ADT for 2 mos and then randomized 2:1 to respectively add open label Axi (5 mg PO bid) vs. continue ADT alone for 4 mos until surgery. Those responding with PSA ≤ 5 ng/ml were offered prostatectomy and extended pelvic lymphadenectomy (RP). ADT +/- Axi was withheld post-operatively and PSA measured q3 mos until 1 y. Primary objective: proportion of pts progression free (FFP) 12 mos after ADT, defined as PSA ≤ 1.0 ng/ml and no radiation or ADT, aiming to detect a 35% difference faoeing ADT+R+Ax. Results: 72 pts completed accrual. We report on the 54 pts with LN+ disease: median age 62 y (range 42-76), pretreatment PSA 22.9 ng/ml (range 3.6 - 404.4), 38 N1 / 16 M1a. Table shows presurgical therapy outcomes. Path responses in the prostate were similar among bars, but in 5 ADT+Ax vs. 0 ADT LN+ pts there was no residual nodal disease. Testosterone recovery: 24/26 ADT+Ax and 9/19 ADT RP pts by mos. 21/56 ADT+Ax and 15/18 ADT pts had failed; 1 y FFP estimates 48.0% (SE 6.6%) and 16.7% (SE 3.8%), respectively (p = 0.02). 1 y undetectable PSA 9 pts (6 ADT+Ax). No grade 4 toxicities or unexpected side-effects were observed. Conclusions: 1 year after ADT, ADT+Ax resulted in proportionally greater number of LN+ PCa pts off treatment and prostatectomy-free than ADT alone. Tissue analysis is evaluating predictors of benefit to further develop angiogenesis inhibition as part of combination strategies for hormone naïve PCa. Clinical trial information: NCT01409200.

5079 Poster Session (Board #91), Sat, 1:15 PM–4:15 PM
CALGB 90203 (Alliance): Radical prostatectomy (RP) with or without neoadjuvant chemohormonal therapy (CHT) in men with clinically localized, high-risk prostate cancer (CLHRPC). First Author: James Andrew Eastham, Memorial Sloan Kettering Cancer Center, New York, NY.

Background: Neoadjuvant CHT followed by RP did not increase 3-year biochemical high-risk prostate cancer (CLHRPC). Disease at presentation and grade, D'Amico risk group, treatment choice and first clinician seen. We compared variables in 1000 consecutive patients presenting between 2011-2015 (cohort A) to 1000 patients presenting 2016-18 (cohort B) to investigate trends over time. Results: 2000 patients were included, age 65.2 ± 8.6 years and 65.9 ± 9.1 years (p=0.08), with presenting PSA 9.0 (6.3-14.4) and 9.2 (6.4-15.0) ng/ml (p=0.36), in cohort A and B respectively. Disease severity and initial treatment decision are shown in the table. In low risk disease, 126 (75%) patients had active surveillance in cohort A, and 158 (90%) in cohort B (p=0.0003). In high risk disease, 202 (59%) patients had radiotherapy compared to 194 (50%) in cohort B (p=0.011). In cohort B, 127 (39%) patients seeing oncology first had radiotherapy compared to 143 (25%) patients who saw urology first (p<0.0001). 76 (23%) and 154 (27%) patients had surgery, that saw urology and oncology first, respectively (p=0.11).

Conclusions: In 2000 patients presenting to a prostate MDC over 8 years, active surveillance in low risk disease increased, radiotherapy in high risk disease reduced, and the proportion undergoing surgery was unchanged. The initial clinician seen influenced treatment choice; having both specialists in the same consultation may improve consistency of treatment decisions. Disease severity and treatment choice before and after 2016.
5081 Poster Session (Board #193), Sat, 1:15 PM-4:15 PM
Targeting backdoor androgen synthesis through AKR1C3 inhibition: A presurgical hormonal ablative trial in high risk localized prostate cancer (PCa). First Author: Laura Graham, University of Washington, Seattle, WA

Background: Studies have shown that localized PCa may resist neoadjuvant androgen receptor (AR)-targeted therapies as a result of persistent intraprostatic androgens, likely arising through upregulation of steroidogenic enzymes. Therefore, we sought to evaluate clinical effects of combinational AR-targeted therapy, including indomethacin (Indo) to inhibit the steroidogenic enzyme AKR1C3, in men with high risk PC undergoing radical prostatectomy (RP). Methods: This was an open label, single-site, Phase II neoadjuvant trial in men with localized high to very-high risk PC, as defined by NCCN criteria. Patients received 12 weeks of neoadjuvant apalutamide (Apa), abiraterone (Abi) plus prednisone, degarelix, and Indo at their respective FDA-approved doses followed by RP. The primary objective was to determine the pathologic complete response (pCR) rate. Secondary objectives included assessing for minimal residual disease (MRD) (i.e. ≤0.25 cm³ tumor volume corrected for cellularity), measuring intraprostatic androgens and assessing molecular features associated with drug resistance. Twenty evaluable patients provided 91% power (one-sided alpha = 7.5%) to detect a difference in pCR rate of 5% (H0) vs. 25% (H1). Results: Twenty-two patients enrolled and 20 were evaluable for the primary endpoint (1 patient came off to pursue stereotactic radiosurgery; 1 was removed after developing grade 2 transaminisits). At baseline, the median PSA was 10.1 ng/mL (4.4-159.4), 4 (20%) patients had Gleason grade group (GG) 4 disease and 16 had GG 5 disease. At RP, 1 (5%) patient had a pCR, 6 (30%) had MRD, 18 (90%) had ypT4 disease and 7 (35%) had lymph node (LN) metastases. Treatment was generally well tolerated and adverse events were consistent with each individual drug’s known safety profile. Additional follow up data and correlative work will be presented at the meeting. Conclusions: In our cohort of men with high-risk PC, pCR rates remained low even with combinational AR-directed therapy. Ongoing pharmacodynamic studies aimed at determining if Indo effectively inhibited AKR1C3 will provide important insights regarding the utility of targeting this steroidogenic enzyme. Clinical trial information: NCT02849990.

5083 Poster Session (Board #195), Sat, 1:15 PM-4:15 PM
Human prostate cancer immune phenotypes after androgen deprivation therapy. First Author: Matthew Dallos, Columbia University, New York, NY

Background: The prostate tumor microenvironment (TME) is generally non-inflammatory. However, we previously showed in pre-clinical models that androgen deprivation therapy (ADT) induces a complex immune cell infiltrate. Whether ADT similarly promotes inflammation in patients remains unclear. Therefore, we collected specimens from patients with localized prostate cancer treated with neoadjuvant degarelix and hypothesized that we could decipher key changes in the immune TME after ADT utilizing a novel cancer systems biology approach. Methods: We identified a cohort of patients treated with neoadjuvant degarelix (240mg SQ) as part of two clinical trials (NCT01696877, NCT01542021). Patients were treated with degarelix either 4 days (N = 13), 7 days (N = 17) or 14 days (N = 8) prior to radical prostatectomy. RNA was extracted from FFPE tissue and analyzed by RNAseq. To deconvolute fractional contributions of different immune cell subsets we performed CIBERSORT and Uniform Manifold Approximation and Projection (UMAP) analysis. Treatment groups were compared to a cohort of untreated matched controls (N = 37). Results: Degarelix induced a complex immune cell infiltrate in human primary prostate tumors with an increase in both pro- and anti-inflammatory cell subsets and changes in expression of immune checkpoints compared to untreated matched controls. Degarelix therapy also significantly changed associated gene signatures within the lymphoid and myeloid compartments over time. Conclusions: ADT leads to profound immune remodeling within the prostate TME. Our analysis of human primary prostate tumors supports the hypothesis that the optimal time for immunologic intervention is the peri-castration period. These data also suggest that combinational immunotherapy strategies that target particular immune cell subsets will likely be required to successfully promote robust anti-tumor immune responses in prostate cancer.

5084 Poster Session (Board #196), Sat, 1:15 PM-4:15 PM
IMRT pelvic radiotherapy with simultaneous integrated boost in high-risk prostate cancer: Results after 10 years. First Author: Christian EKanger, Kreftavdelingen, Haukeland Universitetssjukehus, Bergen, Norway, Bergen, Norway

Background: To report 10 years results after image guided intensity-modulated radiotherapy (IMRT) with hypofractionated simultaneous integrated boost (SIB) in high-risk prostate cancer. Methods: Between 2007 and 2009, 97 patients with an estimated risk of lymph node metastases above 15% (Roach equation) were prospectively included in a phase II study. Patients were treated with 2.2 Gy to the prostate, vesica seminalis and elective pelvic field in 25 fractions over 5 weeks with androgen deprivation therapy for 2 years. Toxicity was scored according to RTOG criteria and biochemical free survival (BFS) using the Phoenix definition. Patients were divided into three groups; very high-risk patients (VHR) according to NCCN 2015 criteria (n=50), high-risk patients (HR) (n=32), and patients with N+ disease and/or pretreatment s-PSA ≥100 (n=15). Differences were examined using Kaplan Meier estimates with log rank test. Results: Ten year BFS in the entire cohort was 63%. Metastasis-free survival (MFS) was 77% and prostate-cancer-specific survival (PCSS) 88%. Overall survival (OS) was 69% and local failure rate was 11%. VHR vs. HR subgroups had significant different BFS, 58% vs 84% (p=0.01) respectively. MFS and PCSS in the VHR group compared to the HR group was 78% vs 91% (p=0.108) and 86% vs 97% (p=0.157) respectively. Patients with N+ and/or PSA>100 had worse outcome compared to the HR/VHR groups, but not all had treatment failure. BFS was 33% vs 68% (p=0.001). MFS 47% vs 83% (p=0.000) and PCSS 73 % vs 90% (p=0.04), respectively. Patients who reached a PSA nadir value below 0.1 (n=80) had significant better outcomes, with PCSS 93% vs 65% (p=0.001) and BFS 74% vs 12% (p=0.000), respectively. Acute grade 2 GI and GU toxicity was observed in 27% and 40%, grade 3 GI and GU toxicity in 1% and 3%, late grade 2 GI and GU toxicity at 3 years appeared in 3% and 4% with no grade 3 toxicity. Conclusions: High-risk prostate cancer patients treated with IMRT with SIB obtained favorable outcomes with few serious side effects. There were significant better results in the HR versus the VHR group, both better than the N+PSA>100 group.
5085 Poster Session (Board #197), Sat, 1:15 PM-4:15 PM
Is there a role for testosterone replacement therapy in reducing biochemical recurrence following radical prostatectomy? First Author: T Edward A, University of California, Irvine, Orange, CA
Background: Historically, the use of testosterone replacement therapy (TRT) has not been recommended in men with a history of prostate cancer (PC). However, low testosterone levels are significantly associated with metabolic complications, decreased sexual function, and (more recently) high-grade PC. In 2009, in hopes of improving sexual function outcomes in men following radical prostatectomy (RP), we began treating low-risk patients with TRT. The current study examines the impact of TRT on biochemical recurrence (BCR).
Methods: Between December 2009 and June 2018, a cohort of 850 patients underwent RP by a single surgeon. 152 (18%) men were postoperatively placed on TRT for recovery of sexual function. All data was prospectively collected and retrospectively analyzed. TRT patients were proportionally matched to 419 control patients by pathologic Gleason Grade Group (GGG) and stage. Univariate and multivariate comparisons were used to compare rates and time to BCR (two consecutive PSA ≥ 0.2 ng/dl; Cox regression modeling was used to generate a survival function at the mean of covariates.
Results: There were no statistically significant differences in preoperative PSA, age, prostate weight, pathologic GGG and stage between the control versus TRT groups. Median follow-up time was 3 years in both groups. 7/152 (4.6%) and 39/419 (9.3%) patients experienced BCR in the TRT versus control groups, respectively (unadjusted, p=0.068). In adjusted time-to-analysis, TRT was an independent predictor of recurrence-free survival, after controlling for GGG, p-stage, preoperative FT and PSA. A patient on TRT was approximately 53% less likely to experience a BCR (OR: 0.534, 95%CI: 0.288-0.993).
Conclusions: After accounting for pathologic GGG, stage, and other significant covariates, the use of TRT independently reduced recurrence post-RP. These results suggest the need for a multicenter randomized control trial.

TPS5008 Poster Session (Board #198b), Sat, 1:15 PM-4:15 PM
A phase Ib/II study of niraparib combination therapies for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Niraparib (Nirap) is a highly-selective PARP inhibitor, with potent activity against PARP-1 and PARP-2 deoxyribonucleic acid (DNA)-repair polymerases. PARP inhibition may be especially lethal in tumor cells with genetic DNA damage response deficits (DRD). Based on promising preclinical and clinical data, this study is designed as a master protocol with nirap as a backbone therapy. Combination 1 assesses the safety and efficacy of nirap plus abiraterone acetate and prednisone (AA-P). Methods: This multicenter, global, open-label study is currently open at 18 sites in 5 countries of the planned XX sites, and is enrolling patients with mCRPC who have progressed on ≥ 1 androgen-receptor targeted therapy for mCRPC. Enrollment at time of abstract submission was 25 for combination 1. When combined with AA-P, the RP2D has been determined to be nirap 200 mg. The recommended phase-2 dose (RP2D) of nirap plus JNU-283 was determined in Part 1 based on the incidence of specified adverse events and PK data to be 480 mg every 4 weeks. For Part 2 of the study, patients are assigned to receive oral niraparib plus abiraterone acetate and prednisone (AA-P).

Inclusion criteria:

- 1 or 2 prior lines of androgen-receptor targeted therapy given for mCRPC. Enrolment at time of submission was 25 for combination 1. When combined with AA-P, the RP2D has been determined to be nirap 200 mg. The recommended phase-2 dose (RP2D) of nirap plus JNU-283 was determined in Part 1 based on the incidence of specified adverse events and PK data to be 480 mg every 4 weeks. For Part 2 of the study, patients are assigned to receive oral niraparib plus abiraterone acetate and prednisone (AA-P).

Primary and point safety assessment:

- Incidence and severity of AEs

Expected enrollment:

- 150 patients in Part 1
- 150 patients in Part 2

Primary objective:

- Primary endpoint (AEs)

Secondary objectives:

- Circulating tumor cell response
- Objective response
- Circulating tumor cell response
- Incidence and severity of AEs

Clinical trial information:

NCT03431350.
TPS5089  
**Poster Session (Board #199b), Sat, 1:15 PM-4:15 PM**

An open label phase I/IIa study to evaluate the safety and efficacy of CCS1477 as monotherapy and in combination with patients with advanced solid/metastatic tumors. **First Author:** Johnathan S. De Zона, Mayo Clinic Foundation **Trust and The Institute of Cancer Research, London, United Kingdom**

**Background:** CCS1477 is a potent, selective and orally bioavailable inhibitor of the bromodomain of p300 and CBP, two homologous and critical activators of the androgen receptor (AR) and its variant forms, including mutated, amplified and spliced AR, as well as c-Myc. CCS1477 represents a new therapeutic option for prostate cancer patients who have progressed after failure of anti-androgen therapy and in combination with anti-androgens such as enzalutamide or abiraterone. **Methods:** This is a Ph IIa study to determine the maximum tolerated dose (MTD) and/or recommended Phase II dose and schedule(s) of CCS1477 and investigate clinical activity of CCS1477 monotherapy and CCS1477 in combination with abiraterone or enzalutamide in patients with metastatic castration resistant prostate cancer (mCRPC). The trial aims to enrol approximately 150 patients and is currently recruiting in the UK with plans to open additional sites in the USA (NCT03568656). Key inclusion criteria (for the mCRPC) require previous treatment with abiraterone and/or enzalutamide, taxane as well as evidence of disease progression (PCWG-3 guidelines). Single dose and steady state pharmacokinetics will be determined along with changes in plasma PSA, LDH and ALKP and in circulating tumour cell number. Anti-tumour activity will be determined by standard imaging according to PCWG-3 guidelines. Paired tumour biopsies for biomarker assessment are being collected. Cohort 1 of the monotherapy dose escalation (rolling 6 design; 3-6 patients/cohort) has completed. Enrollment to cohort 2 began in January 2019. Dose finding in combination (CCS1477 + abiraterone; CCS1477 + enzalutamide) will be open once monotherapy dose escalation completes. Following definition of a recommended phase 2 dose and schedule for monotherapy and in combination, three expansion arms in patients with mCRPC with DDR deficiency (25 patients/arm); CCS1477 monotherapy; CCS1477 + abiraterone; CCS1477 + enzalutamide. A further expansion in patients with advanced solid tumours with a mutation in p300 or CBP will also be open. **Clinical trial information:** NCT03568656.

TPS5089  
**Poster Session (Board #200a), Sat, 1:15 PM-4:15 PM**

**Nivolumab and ipilimumab treatment in prostate cancer with an immunogenic signature (NEPTUNES).** **First Author:** Ying Ning Sophia Wong, Cancer Immunology Unit, University College London Cancer Institute, London, United Kingdom

**Background:** Responses to checkpoint inhibitor (CPI) monotherapy in patients with metastatic castration resistant prostate cancer (mCRPC) have been limited. This is in part attributed to low tumour mutational burden (TMB) and low tumour infiltrating lymphocytes (TILs). Previously ~20% patients with prostate cancer have demonstrated high TILs which we hypothesize that patients with higher TMB due to mismatch repair deficiency (dMMR) or defective DNA damage response (dDDR) and patients with high TILs are more likely to respond to combination CPI with anti PD-1 and anti CTLA-4 therapy. **Methods:** NEPTUNES is a single arm phase II trial designed to assess the efficacy of nivolumab and ipilimumab in biomarker selected patients with mCRPC that have progressed following anti CTLA-4 therapy. The immunogenic signature (ImS) biomarker is defined by ≥1 of the following: 1) dMMR by immunohistochemistry (IHC); 2) dDDR detected by the UW-OncoPlex sequencing assay and; 3) high TILs on multiplexed IHC. The UW-OncoPlex assay detects mutations in ≥260 genes and provides an estimation of TMB. **Assuming an ImS+ rate of 20%, we aim to pre-screen 175 patients in order to enrol 35 patients into the main study.** The primary endpoint is composite response rate (CRR), achieved if ≥1 of the following criteria are satisfied: 1) radiological response by RECIST 1.1; 2) PSA response ≥50%; 3) conversion of circulating tumour cells (CTC) count from ≥5 cells at baseline to <5 cells at week 9. The treatment will be deemed ineffective if the CRR is <20%. Nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) is dosed every three weeks for up to 4 times, followed by a 480mg flat dose of nivolumab every 4 weeks for up to one year. Baseline biomarkers will be assessed at study onset and safety, overall survival, and radiological and PSA progression free survival. **Results:** Typical exploratory markers including TMB, mutational profiles, change in TILs and liquid biomarkers will be correlated with the primary endpoint. Since opening in February 2018, 126 patients have been pre-screened with ≥25 ImS+. To date, 9/25 ImS+ patients have been enrolled into the main study. The trial is ongoing, with patient accrual expected to complete by late 2019. References: 1 Linch, M., Goh, G., Hiley, C., Shansukhan, Y., McGahan, N., Rowan, A., Swanton, C. (2017). Immunological landscape of high-risk prostate cancer: the PROGENY study of genomic and immune parameters. Ann Oncol, 28(10), 2472-2480. doi:10.1093/annonc/mdx355. Clinical trial information: NCT03661539.

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18F-DCFPyL, impact on intended treatment plans, detection rates and PPV of clinical impact of 18F-DCFPyL PET/CT in men with suspected recurrence of prostate cancer (CONDOR). First Author: Michael J. Morris, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** Early and accurate detection of recurrent or metastatic prostate cancer remains an unmet diagnostic need for patient management. While agents for positron emission tomography (PET), such as 11C-choline and 18F-fluorocholine, have emerged as options for imaging recurrent prostate cancer, these agents are not specific for the disease. 18F-DCFPyL is a novel, low-molecular weight, PET radiopharmaceutical that binds selectively to prostate-specific membrane antigen with high affinity. In prior studies, 18F-DCFPyL PET/CT has shown reliable diagnostic performance in detecting metastatic or recurrent prostate cancer (Rowe Mol Imaging Biol 2016 18:411-119; Gorin J Urol 2018 1999:126-32). **Methods:** CONDOR is a phase 3, multicenter, open-label study designed to assess the diagnostic performance and clinical impact of 18F-DCFPyL PET/CT in men with suspected recurrent or metastatic prostate cancer. Approximately 200 patients are planned to be enrolled across 15 centers in the United States and Canada. Eligible patients ≥18 years of age must have histologically confirmed prostate adenocarcinoma, have rising PSA after definitive therapy, and negative or equivocal conventional imaging. A single 9 mCi (338 MBq) dose of 18F-DCFPyL is administered, followed by whole body PET/CT scan 1 hour later. The primary objective is to assess the correct localization rate (percentage of patients with a one-to-one correspondence between localization of at least one lesion identified on 18F-DCFPyL PET/CT and the corresponding true positive). Additional study objectives include safety, tolerability, and correct localization rate (percentage of patients with a one-to-one correspondence between localization of at least one lesion identified on 18F-DCFPyL PET/CT and the corresponding true positive). Pre-clinical data suggest that the induction of double-stranded DNA (dsDNA) breaks by BAT may be crucial to its mechanism of action. DNA repair defects, such as HRD, are particularly relevant in CRPC patients. We hypothesize that CRPC patients with DNA repair defects such as HRD, may be particularly responsive to BAT. **Methods:** The study is a phase I/II prospective single arm interventional trial (NCT03522064). Up to 50 patients will be recruited based on a Simon two-stage design with a power of 90% to detect an increase in response rate from 20% to 40%. Key inclusion criteria include i) asymptomatic or minimally symptomatic mCRPC, ii) rising PSA despite a castrate serum testosterone and iii) HRD on germline, tumor and/or circulating tumor DNA (ctDNA) analysis. Key exclusion criteria include i) ADT <1 year, ii) disease extent/sites that would cause significant risk if tumor flare occurs (e.g.: brain) and iii) significant cardiac disease. Previous PARP inhibitor therapy will be permitted in a subset. Participants will receive 1200 mg q4w in combination with ongoing LHRH antagonist/agonist or orchidectomy. The primary endpoint is PSA response rate defined as PSA reduction ≥50% from baseline. Secondary endpoints include time to PSA progression, quality of life, radiologic response, and safety and tolerability. Exploratory endpoints include changes in ctDNA and tumor DNA alterations from baseline to progression. The study is ongoing. Clinical trial information: NCT03522064.

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TPS5097  Poster Session (Board #203b), Sat, 1:15 PM-4:15 PM
A phase II Salvage Trial of AR Inhibition with ADT and Apalutamide with Radiation therapy followed by docetaxel in men with PSA recurrent prostate cancer (PC) after radical prostatectomy (STARTAR). First Author: Tian Zhang, Duke University Medical Center, Durham, NC
Background: Androgen deprivation combined with salvage external beam radiation therapy (RT) have improved survival for patients (pts) with non-metastatic hormone naive PC and PSA recurrence after radical prostatectomy (RP). Our recent STREAM trial showed addition of enzalutamide to RT and ADT had a 3-year progression free survival (PFS) of 53%. Adding effective PC treatments in this setting may further improve 3-year PFS.
Methods: STARTAR is an investigator-initiated phase II trial for salvage treatment of biochemically recurrent PC following prostatectomy. Key inclusion criteria include histologic prostate adenocarcinoma, either Gleason 7 with T3+ positive margins/1-4 positive lymph nodes or Gleason 8-10 disease, PSA relapse within 4 years of prostatectomy (minimum PSA 0.2 ng/mL to maximum PSA 4 ng/mL). Treatment involves ADT with apalutamide for 9 months, continue with with prostate bed +/- nodal RT at month 3, followed by 6 cycles of docetaxel 75mg/m2 IV every 3 weeks for 6 cycles. The primary endpoint of the study is 3-year PFS. With a one-sided alpha of 0.05 to improve 3-year PFS from 50% to 75%, we will have 92% power to show a statistically significant improvement in response.

TPS5098  Poster Session (Board #204a), Sat, 1:15 PM-4:15 PM
Cognitive effects of androgen receptor (AR) directed therapies for advanced cancer of the prostate (COGCaP). First Author: Julie Van, Vanderbilt University Medical Center, Nashville, TN
Background: Androgen deprivation therapy (ADT) is the cornerstone of treatment for prostate cancer (CaP). However, the relationship between ADT and the development of cognitive dysfunction in men with CaP is controversial. Past studies had various methodological limitations, including the inconsistency and insensitivity of measures used for cognitive testing.
Methods: COGCaP is a multi-site, prospective observational study of cognitive function and patient reported outcomes in men with CaP treated with ADT and androgen receptor (AR) directed therapies such as enzalutamide or abiraterone acetate (AA) conducted across four U.S. sites. Patients with metastatic castration-resistant or hormone sensitive CaP starting enzalutamide (N=50), or non-metastatic or metastatic castration-resistant CaP starting abiraterone (N=50) undergo cognitive and patient reported outcome assessments at baseline, 3, 6, and 12 months. The primary endpoint compares mean change in cognitive function between groups at 3 months using CANTAB, a computer-based measure of cognitive function. This design achieves a power of 80% to detect a between-group difference in cognitive function at 3 months.

TPS5099  Poster Session (Board #204b), Sat, 1:15 PM-4:15 PM
VISION: An international, prospective, open-label, multicenter, randomized phase 3 study of 177Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). First Author: A. Oliver Sartor, Tulane Medical School, New Orleans, LA
Background: The novel therapeutic drug 177Lu-PSMA-617 is a prostate specific membrane antigen (PSMA) targeting agent to deliver radionuclide therapy for the treatment of pts with metastatic castration resistant prostate cancer. Based on preclinical data that demonstrated high PSMA binding affinity & compound internalization, prolonged tumor uptake, rapid kidney clearance, & high tumor-to-background ratio, 177Lu-PSMA-617 proceeded into clinical development. Preliminary clinical evidence indicates 177Lu-PSMA-617 may demonstrate clinical benefit in pts with mCRPC in a setting where pts had no recommended standard of care. This Phase 3 study will assess the efficacy of 177Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC by measuring overall survival (OS) and radiographic progression free survival (rPFS) in a randomized, prospective, open-label trial.
Methods: The primary objective of this study is to compare the 2 alternative endpoints of rPFS & OS in pts with progressive PSMA-positive mCRPC who receive 177Lu-PSMA-617 in addition to best supportive/standard of care vs pts treated with best supportive/standard of care alone. Eligibility criteria are: PSMA expressing tumor; prior exposure to a taxane and novel androgen axis drug. Pts will be randomized in a 2:1 ratio in favor of the investigational arm at time of randomization as a standard of care. Under the alternative hypothesis, median OS on active is assumed to be 13.7 mo for a HR of 0.7306 and PFS on the active is assumed to be 6 mo for a HR of 0.67. Planned enrollment for this study is 750 patients. Enrollment began in June 2018 and continues; the IDMC last reviewed the trial for safety in January 2019 and suggested that the trial continue as planned. Clinical trial information: NCT03311555.

TPS5100  Poster Session (Board #205a), Sat, 1:15 PM-4:15 PM
PROTEUS: A randomized, double-blind, placebo (PBO)-controlled, phase 3 trial of apalutamide (APA) plus androgen deprivation therapy (ADT) versus PBO plus ADT prior to radical prostatectomy (RP) in patients with localized high-risk or locally advanced prostate cancer (PC). First Author: Mary-Ellen Taplin, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA
Background: Patients (pts) with localized high-risk PC experience disease progression rates of approximately 50% after RP (Kane et al. 2007). With the approval of next-generation androgen receptor inhibitors, neoadjuvant studies have shown that 6 months of androgen blockade may improve local disease control at the time of RP (McKay et al. Prostate Cancer Prosttic Dis. 2017; Taplin et al. JCO. 2014). The purpose of this study is to determine if treatment with APA plus ADT before and after RP in pts with localized high-risk or locally advanced PC results in an improvement in pathologic complete response (pCR) rate and metastasis-free survival (MFS) compared with PBO plus ADT.
Methods: This international multicenter trial is enrolling pts with localized high-risk or locally advanced PC who are candidates for RP. Eligibility criteria: Any Gleason score (GS) ≥ 4 + 3 with ≥ 6 positive systematic biopsies (SB); any GS ≥ 4 + 3 with ≥ 3 SB and prostate-specific antigen (PSA) ≥ 20 ng/mL; GS ≥ 9 in ≥ 1 SB or targeted biopsies (TB); or ≥ 2 SB or TB with continuous GS ≥ 8, each with ≥ 80% involvement. Stratification: GS (7 or 8), cN0 or cN1, and region (North America, Europe, or rest of world). Randomization: 1:1 to APA (240 mg) plus ADT (LHRHa) or PBO plus ADT. Pts will receive 6 treatment cycles, followed by RP, followed by an additional 6 cycles. Dual primary end points: pCR rate (to be assessed by blinded independent central pathology review) and MFS (to be assessed by blinded independent central radiology review). Secondary end points: PSA-free survival and progression-free survival. Imaging with CT or MRI and bone scan will be conducted at baseline and then every 6 months following biochemical failure until documented distant metastasis by BICR, or death. Approximately 1500 pts will be enrolled globally over 3.0 years in 240 sites in 19 countries. An independent data monitoring committee is commissioned to review trial data. Clinical trial information: NCT03767244.
Randomized prospective phase 3 trial of 68Ga-PSMA-11 PET/CT molecular imaging for prostate cancer salvage radiotherapy planning [PSMA-SRT].

First Author: Jeremie Calais, UCLA, Los Angeles, CA

Background: Salvage radiotherapy (SRT) for prostate cancer (PCa) recurrence after prostatectomy offers long-term biochemical control in about 50–60% of patients. SRT is commonly initiated in patients with serum PSA levels < 1 ng/mL, a threshold at which standard-of-care imaging is insensitive for detecting recurrence. As such, SRT target volumes are usually drawn in the absence of radiographically visible disease. 68Ga-PSMA-11 (PSMA) PET/CT molecular imaging is highly sensitive and may offer anatomic localization of PCa biochemical recurrence. However, it is unclear if incorporation of PSMA PET/CT imaging into the planning of SRT could improve its likelihood of success. The purpose of this trial is to evaluate the success rate of SRT for recurrence of PCa after prostatectomy with and without planning based on PSMA PET/CT.

Methods: We will randomize 193 patients to proceed with standard SRT (control arm 1, n = 90) or undergo a PSMA PET/CT scan (free of charge for patients) prior to SRT planning (investigational arm 2, n = 103). The primary endpoint is the success rate of SRT measured as biochemical progression-free survival (BPFS) after initiation of SRT. Biochemical progression is defined by PSA $\geq 0.2$ ng/mL and rising. The randomization ratio of 1:1.13 is based on the assumption that approximately 13% of subjects randomized to Arm 2 will not be treated with SRT because of PSMA-positive extra-pelvic metastases. These patients will not be included in the primary endpoint analysis but will still be followed. The choice of treating the prostate bed alone vs prostate bed and pelvic lymph nodes, with or without androgen deprivation therapy (ADT), is selected by the treating radiation oncologist. The radiation oncologist may change the radiation plan depending on the findings of the PSMA PET/CT scan. Any other imaging is allowed for SRT planning in both arms if done per routine care. Patients will be followed until either one of the following conditions occur: 5 years after the date of initiation of randomization, biochemical progression, diagnosis of metastatic disease, initiation of any additional salvage therapy, or death. Discussion: This is the first randomized phase 3 prospective trial designed to determine whether PSMA PET/CT molecular imaging can improve outcomes in patients with PCa early BCR following radical prostatectomy. Clinical trial information: NCT03582774.
A randomized phase 3 trial of paclitaxel (P) plus carboplatin (C) versus paclitaxel plus ifosfamide (I) in chemotherapy-naive patients with stage I-V, persistent or recurrent carcinosarcomas of the gynecologic tract: A phase 3 NRG Oncology trial.

**Background:** Carcinosarcomas of the gynecologic tract are rare cancers that are aggressive and often present at advanced stages. Published treatment regimens are limited, with no gold standard therapy identified.

**Objective:** To compare safety and efficacy of chemotherapy with paclitaxel plus carboplatin versus paclitaxel plus ifosfamide in chemotherapy-naive patients with stage I-V, persistent or recurrent carcinosarcomas of the gynecologic tract.

**Methods:** Eligibility criteria included: histologically confirmed carcinosarcoma; age ≥ 18 years; performance status 0-2; measurable disease; prior neoadjuvant chemotherapy; greater than 3 weeks since prior chemotherapy; greater than 14 days since prior radiotherapy; and written informed consent. Patients were randomized to receive either paclitaxel 175mg/m² on day 1 plus carboplatin AUC 6, or paclitaxel 175mg/m² on day 1 plus ifosfamide 1.6g/m² on days 1-3. Both chemotherapy regimens included leucovorin and dexamethasone. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), and safety. Patients were followed up for 3 years or until death or progressive disease.

**Results:** Between May 2017 and June 2018, 449 and 90 participants were enrolled in each arm. The median age was 61 years (range 31-83), and 68% of patients were postmenopausal. The Eastern Cooperative Oncology Group performance status was 0 in 52% of patients, 1 in 40%, and 2 in 18%. The median duration of follow-up was 33 months (range 3-54). The median PFS was 16 months in the paclitaxel plus carboplatin arm and 9 months in the paclitaxel plus ifosfamide arm. The 1-year PFS rate was 53% (95% CI 45-61) in the paclitaxel plus carboplatin arm and 25% (95% CI 15-35) in the paclitaxel plus ifosfamide arm. The median OS was 24 months in the paclitaxel plus carboplatin arm and 18 months in the paclitaxel plus ifosfamide arm. The 1-year OS rate was 72% (95% CI 64-79) in the paclitaxel plus carboplatin arm and 60% (95% CI 48-71) in the paclitaxel plus ifosfamide arm. The ORR was 29% (95% CI 19-40) in the paclitaxel plus carboplatin arm and 14% (95% CI 5-29) in the paclitaxel plus ifosfamide arm. The most common grade 3-4 adverse events were neutropenia and thrombocytopenia in both arms. There were no statistically significant differences in the incidence of grade 3-4 adverse events between the two arms.

**Conclusions:** Paclitaxel plus carboplatin was associated with significantly improved PFS, OS, and ORR compared to paclitaxel plus ifosfamide. The study met its primary endpoint of non-inferiority and was stopped early due to evidence of superiority. The results support the use of paclitaxel plus carboplatin as a standard treatment option for chemotherapy-naive patients with stage I-V, persistent or recurrent carcinosarcomas of the gynecologic tract.
5504
Oral Abstract Session, Mon, 1:15 PM-4:15 PM
Recurrence rates in cervical cancer patients treated with abdomino-perineal versus minimally invasive radical hysterectomy: A multi-institutional analysis of 704 cases. First Author: Shitanshu Uppal, University of Michigan, Ann Arbor, MI

Background: Compare outcomes between open and minimally invasive radical hysterectomy. Methods: Retrospective multi-institutional review of patients undergoing radical hysterectomy for stage IA1, IA2 and IB1 squamous, adenocarcinoma or adeno-squamous carcinoma between 01/01/2010 - 12/31/2017. Results: From 704 cases that met the inclusion criteria, 185 (26.3%) underwent open and 519 (73.7%) underwent minimally invasive (MIS). Women treated with open surgery were older, had larger tumors on preoperative assessment as well as on final pathology assessment, had higher proportion of patients with IB1 stage and adjuvant therapy. Patients undergoing open surgery had longer median follow-up compared to MIS (44 vs. 30.3 months, p < 0.001). The two groups were similar in regard to race distribution, body mass index, comorbidities and preoperative history. There were 13/185 (7%) recurrences and 10/185 (5.4%) deaths in the open compared to 42/519 (8.1%) recurrences and 26/519 (5%) deaths in MIS (p = n.s for both). However, on multivariate analysis, after controlling for race, comorbidities, preoperative tumor size, histology, grade and smoking status, MIS had higher odds of recurrence (OR 2.24, 95% CI 1.04 - 4.87, p = 0.04). On a second model, in addition to prior mentioned factors, we included lymphovascular space invasion, receipt of adjuvant therapy and vaginal margin status. Undergoing MIS remained associated with higher odds of recurrence (OR 2.37, 95% CI 1.11 - 5.1, p = 0.031). In sub-group analysis of cases with preoperative tumor size less than equal to 2 cm, there were 5/121 (4.1%) recurrence in open and 25/415 (6%) recurrences in MIS group (p = 0.34). Multivariate analysis did not show a higher rate of recurrence in MIS arm in this subgroup. In 26 cases of MIS where no vaginal manipulator was used, no recurrences were noted. In comparison 19/270 (7%) recurrences were noted in intra-uterine manipulator (V-care/Zumi/Rumi) and 22/210 (11%) in vaginal manipulators (EEA sizer/Colpo probes) group (p = 0.119). Conclusions: In this large retrospective analysis, patients undergoing MIS for early stage cervical cancer had higher odds of recurrence. In patients with 2 cm or less tumor on preoperative assessment, recurrence rates were similar between the two groups. Role of manipulator in increasing recurrence should be further studied in this patient population.

5506
Oral Abstract Session, Mon, 1:15 PM-4:15 PM
Olaparib monotherapy versus (vs) chemotherapy for germline BRCA-mutated (gBRCAm) platinum-sensitive relapsed ovarian cancer (PSROC) in platinum-sensitive patients (pts): Phase III SOL03 trial. First Author: Richard T. Penson, Massachusetts General Hospital, Boston, MA

Background: Data from a randomized Phase II trial (NCT00628251) of olaparib (capsules, 200 or 400 mg bid, n=32 per arm) vs pegylated liposomal doxorubicin (PLD, n=33) in gBRCAm OC pts with recurrence (capsules, 200 or 400 mg bid, n=32 per arm) vs pegylated liposomal doxorubicin. Methods: Randomized (2:1) to olaparib tablets (300 mg bid) or chemotherapy treatment of patients with measurable disease and prior lines of treatment. Results: In 129 cases with prior platinum therapy indicated efficacy for olaparib (Kaye et al. JCO [G; 1000 mg/m2 D 1 ,D 8 ,D 15 q4w ]o rP L D[ 50mg /m 2 D1 q4w]). Objective response (ORR) was 70% with olaparib vs 44% with chemotherapy. ORR with olaparib were nausea (65% vs 34% [TPC]) and anemia (50% vs 25%) and weight loss (25% vs 19%). Median 13.2 vs 8.5 months, respectively. Most common adverse events (AEs) were fatigue (75% vs 31%), nausea (65% vs 34%) and xerostomia (50% vs 25%) and by investigator assessment was 0.49 (95% CI 0.35 – 0.70; P<0.001). Most common adverse events (AEs) with olaparib were nausea (65% vs 34% [TPC] and anemia (50% vs 25%) and with TPC were palmar-plantar erythrodysesthesia (PPE, 36% vs 1% [olaparib] and nausea. Most common adverse events (AEs) in either arm were anemia (21% [olaparib] vs 0 [TPC]), PPE (0 vs 12%) and neutropenia (6% vs 11%). For olaparib vs TPC, serious AEs were reported by 24% vs 18% and AEs led to treatment discontinuation in 7% vs 20%. Conclusions: Pts with gBRCAm PSROC OC receiving olaparib monotherapy had a significant, clinically relevant improvement in ORR and PFS vs TPC, with no new safety signals. Clinical trial information: NCT02282020.

5505
Oral Abstract Session, Mon, 1:15 PM-4:15 PM
Combination of niraparib and bevacizumab versus niraparib alone as treatment of recurrent platinum-sensitive ovarian cancer: A randomized controlled Phase IIb study—NSGO/ANGIO/ENGOT-OV4. First Author: Mansoor Raza Mirza, NSGO and Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark

Background: Standard treatment of platinum-sensitive recurrent ovarian cancer (PSROC) is platinum based combination chemotherapy ± bevacizumab. However, this treatment modality is hardly curative, and is associated with significant toxicity. Both bevacizumab (BEV) and PARP inhibitors (PARPi) have demonstrated efficacy in PSROC. There is preclinical evidence of enhanced activity of the combination. This is the proof-of-concept randomized trial of PARPi-BEV combination against PARPi monotherapy as treatment in PSROC, regardless of number of previous lines of therapies. Methods: In this randomized, open-label, phase 2 study, women with measurable/evaluable, high-grade serous or endometrioid PSROC were randomized to niraparib 300mg once daily or BEV 15mg/kg IV every 3 weeks until disease progression (1:1 randomization). The primary endpoint was progression-free survival (PFS). Stratification was according to homologous recombination-deficiency [HRD] status (MyChoice HRD) and chemotherapy-free interval (CFI): 6-12 months (mo) vs. >12 mo. First-line maintenance bevacizumab was permitted. Results: Of 97 enrolled patients, 48 were randomized to niraparib monotherapy and 49 to the chemotherapy-free combination. The combined treatment significantly improved PFS compared to niraparib alone: median 11.9 vs. 5.5 mo; hazard ratio (HR) adjusted for stratification factors 0.35; 95% confidence interval (CI)[0.21 to 0.57]; P<0.001. Pre-planned exploratory subgroup analyses: patients with HRD-positive tumors (n=54) HR 0.36 (CI, 0.18-0.69); HRD-negative disease (n=43) HR, 0.47 (CI, 0.24-0.95); gBRCAmut patients (n=34) HR 0.53 (CI, 0.23-1.21); non-gBRCAmut patients (n=63) HR 0.33 (CI, 0.18-0.61); CFI of 6 to 12 mo (n=38) HR, 0.29 (CI, 0.14 to 0.56); CFI >12 mo (n=59) HR, 0.42 (CI, 0.22 to 0.80). There was no difference in treatment-emergent grade 3-4 adverse events except for the rate of hypertension (26.5% vs. 0%) and neutropenia (12.2% vs. 2.1%). Patient-reported outcomes measured using EORTC QLQ-C30 and OV28 were similar for both treatment arms. Conclusions: Both niraparib alone and the combination had meaningful activity in PSROC. Compared to niraparib alone, the chemotherapy-free regimen of niraparib and BEV significantly improved PFS in women with PSROC regardless of HRD status and duration of CFI. Clinical trial information: NCT02354131.
5508 Oral Abstract Session, Mon, 1:15 PM-4:15 PM
**EWOC-1: A randomized trial to evaluate the feasibility of three different first-line chemotherapy regimens for vulnerable elderly women with ovarian cancer (OC).**

**Methods:** A phase 2 study. First Author: Claire Falandry, GINECO-Centre Hospitalier Lyon Sud, Pierre-Benite, France

**Background:** The Geriatric Vulnerability Score (GVS) combining albumin, lymphocyte count, ADL, IADL and HADS scores has been reported (Falandry C et al Oncol 2013) to identify vulnerable elderly OC patients (pts) as those with a GVS ≥ 3. For such pts, Carboplatin (Cb) monotherapy or weekly Cb plus paclitaxel (Pa) are often proposed as an alternative to Cb-Pa given every 3 weeks. **Methods:** Pts ≥ 70 yrs with first line FIGO stage III/IV epithelial OC were screened for GVS. Those with GVS ≥ 3 were randomized to receive either arm A: Cb AUC6.5 + Pa 175mg/m², d1q3week or arm B: Cb AUC5.6 d1q3week or arm C: weekly Cb AUC2 + Pa 60mg/m² d1-d8-d15 q4week. Primary endpoint is treatment feasibility defined as the ability to complete 6 chemotherapy courses without disease progression, early treatment stopping due to unacceptable toxicity or death. Inclusion of 240 pts was planned.

**Results:** Among 444 screened pts, 120 were randomized from 12/2013 to 04/2017 (arm A = B = C = 40). Pts characteristics were well balanced between arms A-B-C respectively: median age (79-82-80 yrs), FIGO stage IV (32-37-27%), primary surgery (65-72-70%), absence of macroscopic residual (RC) (7-5-7%), ECOG = 2 (50-50-47%). Feasibility per protocol for arms A-B-C is 65%, 47% and 60% (p = 0.15). Main reasons for treatment arrest are treatment toxicity (A:20%; B:15%; C:22.5%; p = 0.771) and disease progression (A:7.5%; B:30%; C:2%; p = 0.004). Median PFS for arms A-B-C are 65%, 47% and 60% (p = 0.15). Main reasons for treatment arrest are toxicity and weekly Cb-Pa regimens, Cb single agent was reported to be less active compared to 3-weekly Cb-Pa regimens (arms A&C) was out of reach.

**Conclusion:** Compared to 3-weekly and weekly Cb-Pa regimens, Cb single agent was reported to be less active compared to 3-weekly Cb-Pa regimens (arms A&C) was out of reach. Inclusion of 240 pts was planned. **Conclusion:** Compared to 3-weekly and weekly Cb-Pa regimens, Cb single agent was reported to be less active compared to 3-weekly Cb-Pa regimens (arms A&C) was out of reach. Inclusion of 240 pts was planned.

5509 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM
**Sex hormone, insulin, and insulin-like growth factor signaling in recurrence of high stage endometrial cancer: Results from the NRG Oncology/Gynecologic Oncology Group study 210.**

**Methods:** First Author: S. Huang, Yale School of Medicine, Yale Cancer Center, New Haven, CT

**Background:** Sex hormone and insulin/IGF axis tissue and circulating biomarkers of recurrence in a prospective study of high stage endometrial cancer. Circulating insulin and estradiol, and tissue phosphorylated (activated) IGF1R/IR were independently associated with recurrence. These findings support prioritizing studies to clinical utility as prognostic biomarkers and to investigate new strategies that target these pathways for prevention and treatment of endometrial cancer.

**Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.**
Impact of adding nintedanib to neoadjuvant chemotherapy (NACT) for advanced epithelial ovarian cancer (EOC) patients: The CHIVA double-blind randomized phase II GINECO study. First Author: Gwenaël Ferron, GINECO and Institut Claudius Regaud, Toulouse, France

Background: Nintedanib, an oral inhibitor of VEGF-FGF-PDGF receptors, has been shown to prolong progression-free survival (PFS) when added to adjuvant chemotherapy after primary surgery (duBois A, Lancel Oncol 2013). CHIVA trial explored the role of nintedanib in combination with NACT. Methods: Patients (pts) with FIGO stage IIV chemotherapy-naive AEOC considered as unresectable after laparoscopic evaluation were randomized (2:1) to be treated with 3 to 4 cycles (cy) of carboplatin (AUC 5 mg/mL/min) and paclitaxel (175 mg/m²) before interval debulking surgery (IDS) followed by 2 to 3 cy of CP for a total of 6 cy, plus either 200 mg of Nin (armA) or placebo (armB) twice daily on days 2–21 q3Week at cy 1&2, 56± and maintenance therapy for up to 2 years. The primary endpoint was PFS. Results: Between Jan. 2013 and May 2015, 188 pts were included (124 arm A, 64 arm B) with a median Peritoneal Cancer Index of 22 (range 19-27). Pts characteristics were well balanced between both arms. Median PFS was 14.4 mos (95%CI 12.4-19.4) and 16.8 (13.3-21.4) in arm A and B respectively (HR=1.10, p=0.02). Median OS was 37.7 mos (29.8-41.0) and 44.1 (32.7-not reached) in arm A and B respectively (HR=1.54, p=0.053). Arm A was associated with more toxicity compared to arm B respectively (Grade 3&4 adverse events: 92 versus 71%), with increased early treatment discontinuation (9% vs 5.6%) & 2% A vs 12% B) in the protocol defined (13 mos). Pts in Arm A reported inferior RECIST ORR to pre-IDS therapy compared to Arm B (35.1 vs 55.9%). IDS was performed significantly less frequently in arm A (58.1% vs arm B 76.6%). However among pts who underwent IDS, complete cytoreduction rate (76%) and perioperative complication rate (11%) were similar in both arms. Conclusions: The addition of nintedanib to NACT increases toxicity and compromise chemotherapy efficacy leading to a reduced rate of IDS and worse PFS and OS for advanced EOC patient. Clinical trial information: NCT01062883-23.

5514 Poster Discussion Session; Displayed in Poster Session (Board #337), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Dose-dense early postoperative intraperitoneal chemotherapy in ovarian cancer: Randomized, phase II trial. First Author: Rongyu Zang, Ovarian Oncology, Shanghai Medical College, Fudan University, Shanghai, China

Methods: Eligible pts were randomized to receive either 3 cycles of chemotherapy (C) or 4 cycles of chemotherapy (G, P, PLD) in 3- (C) or 4-week (G, P, PLD) cycles (Table). Tumor responses to chemotherapy were assessed using RECIST v1.1. OS was calculated from randomization to first evidence of disease. The primary endpoint was OS. Results: Between 2009 and 2015, 218 pts were randomized, of whom 215 initiated treatment (106 to DD-EPIC and 109 to iv; for efficacy analyses). Totally, 36 pts (16% of all pts. D, day 1 ± 6, 9 mos follow-up, 122 pts died (54 in DD-EPIC and 68 in iv group). Remarkable OS benefit of DD-EPIC was recorded (67–00 vs. 18–00 mos). However, among pts who underwent IDS, complete cytoreduction rate (76%) and perioperative complication rate (11%) were similar in both arms. Conclusions: The addition of nintedanib to NACT increases toxicity and compromise chemotherapy efficacy leading to a reduced rate of IDS and worse PFS and OS for advanced EOC patient. Clinical trial information: NCT02272790.

5513 Poster Discussion Session; Displayed in Poster Session (Board #336), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Adavosertib with chemotherapy (CT) in patients (pts) with platinum-resistant ovarian cancer (PPROC): An open label, four-arm, phase II trial. First Author: Kathleen N. Moore, Stephenson Cancer Center at the University of Oklahoma HSC and Sarah Cannon Research Institute, Oklahoma City, OK

Background: Adavosertib (AZD1775; A), a highly selective WEE1 inhibitor, demonstrated activity in combination with CT in the barrier radiation effect (GINNECO) and NCT02772970 assessed the objective response rates (ORR) and safety of A in PROC. Methods: Pts with recurrent RECIST v1.1 measurable PROC received A with c, gemcitabine (G), weekly paclitaxel (P), or pegylated liposomal doxorubicin (PLD) in 3–C (4 or 5, P, PILD) cycles. Tumor assessment was performed every 2 cycles until disease progression. Primary objective: ORR, other objectives: disease control rate (DCR), progression-free survival (PFS) and safety. Results: In the 94 pts treated (median treatment duration 3 months; range 0–16 months), outcomes were greatest with A (weeks (W1–3)+ (C)) compared to arm B (W1–3) + C, with ORR (A) of 10.1% for this cohort. Most common grade ≥3 treatment-emergent adverse events (TEAEs) were A in the Table, with hematologic toxicity most notable with A (1–3 + C). TEAEs led to pts dose interruptions, reductions and discontinuations in 63%, 30% and 13% of the whole cohort, respectively. A possible positive association between CNE1 amplification and response warrants further investigation. Conclusions: A shows preliminary efficacy when combined with CT. Pts receiving A (W1–3) + C showed greatest benefit. The increased but not unexpected hematologic toxicity is a challenge and could be further studied to optimize the dose schedule and supportive medications. Clinical trial information: NCT02272790.

5512 Poster Discussion Session; Displayed in Poster Session (Board #335), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Effect of adjuvant nintedanib (Nin) on residual disease. The median progression-free survival (PFS) for Nin was 66. 95% CI 0-11 vs 46-0 mos for Nin vs Placebo (P =<0.001). Nin was associated with inferior progression curves compared to placebo (HR 0.55 (0.27-1.11) 75.2 (60.1-90.4) 52.9 (36.6-69.1)

Table: Nin vs Placebo

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Surveillance in stage I MOGCTs (malignant ovarian germ cell tumors): A MITO prospective study (multicenter Italian trials in ovarian cancer). First Author: Alice Bergamini, Università Vita-salute San Raffaele, Milan, Italy

Background: The standard of treatment of stage I MOGCTs is surgery followed by BEP (bleomycin + etoposide + cisplatin) chemotherapy, except for stage IA dysgerminoma (D) and IAG1 immature teratoma (IT). Surveillance has emerged as a possible option to avoid adjuvant chemotherapy in IB-C1 D, IA-C G2 – G3 IT, and in stage IA mixed and yolk sac tumors (YST), after prehensive surgical staging (CSS) with negative postoperative markers. The aim of this study was to analyze oncological outcome of stage I MOGCT patients included in the MITO9 study. Methods: MITO9 was a prospective observational study analyzing data collected between 2013 and 2018. 41 patients with stage I conservatively treated MOGCTs were included. Three groups were identified: group A, IA D and IAG1 IT candidate to surveillance according to guidelines; group B, stages IB-C1 D, stage IA-C G2-G3 IT, stage IA mixed and YST were consulted about the option of close surveillance vs adjuvant chemotherapy in case of CSS; group C, all other patients receiving BEP. Results: Median age was 25.6 years (range 14-40). Median follow up was 36.4 months. Group A included 12 patients, 5 IA GI IT and 7 IA D. Group B included 24 patients. Of these, 2 out of 5 patients (40%) were positive at restaging and were excluded from surveillance protocol. Seven of the 22 remaining patients (31.8%) received chemotherapy, while 15 (68.2%) were enuision of the surveillance protocol. Out of the 22, 9 (40.9%) had a stage IA D (one IC1, one IC2 and two IC3), 2 were mixed stage IA with YST tumor, 9 were G3 IT (four IA, three IC2, one IC3 and one IB). The 7 patients receiving chemotherapy were: 1 dysgerminoma IC2, 2 YST IA, 3 IT G3 (one IA and one IC2) and 1 mixed IA tumour. Group C included 5 patients, three IC YST and two mixed IC2 with YST. Survival of these patients was 100%, while disease free survival was 97.5%. Only one patient in group B, a stage IA G3 IT treated with adjuvant BEP, relapsed as mature teratoma. None of the patients in the surveillance protocol experienced relapse. Conclusions: These data suggest that close surveillance could be an alternative option to avoid adjuvant chemotherapy for stage IB-C1 D, IA-C G2-G3 IT, stage IA mixed and YST. These findings deserve further confirmation in an international collaborative operating setting.

A randomized double-blind placebo-controlled phase II trial comparing gemcitabine monotherapy to gemcitabine in combination with adozeosertib in women with recurrent, platinum resistant epithelial ovarian cancer: A trial of the Princess Margaret, California, Chicago and Mayo Phase II Consortia. First Author: Stephen Stumpf, University Health Network, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Platinum resistant ovarian cancer (OC) remains a therapeutic challenge. High grade serous OC (HGSOc) harbors TP53 mutations leading to increased dependency on S- and G2-phase checkpoints: Wee1 inhibition with Adavosertib (AZD 1773) (A) induces 25% checkpoint escape. Gemcitabine (G) is an antimetabolite that only blocks the progression of cells through the G1-S phase. We hypothesized that combining G+A would be synergistic and overcome resistance. Methods: We conducted a multicentre double-blind 2:1 randomized phase 2 trial to assess the tumor shrinkage and all clinical milestones were measured on archival tissue with Sanger sequencing, TAM-Seq and IHC. TP53 mutation will be also assessed in circulating tumor DNA (ctDNA). Whole exome and RNA sequencing were performed on paired tumor tissues. Results: 27 patients (median age 64) had received a median of 5 (range: 2-9) prior lines of systemic therapy, which included bevacizumab in 74% of patients. The most common treatment related (TR) AEs were lymphopenia (18%) and anemia (9%). The majority of TR AEs were grade 1 or 2 (93%). 6% of AEs were grade 3 with lymphopenia the most common. Two grade 4 AEs were neutropenia and lymphopenia. Of 23 patients evaluable for best objective response, 13.0% (95% CI, 2.7-33.6) had partial response (PR), 65.2% (95% CI, 42.7-83.6) had stable disease (SD), and 21.7% (95% CI, 7.4-43.7) had progression. Of the 23 evaluable patients (30.4%) had archival tumor with modified percent score 5 for PD-L1 and all achieved PR (37.2% vs 8%) or SD (47.4%, 57.2%). Overall median PFS was 4.6 months (95% CI, 2.7-6.2). Rate of PFS at 6 months was 40.4% (95% CI, 25.5-65.5). Median follow-up is 6.2 months and PFS is based on current data, but 8 patients remain on study and estimates will be updated. Conclusions: Pembrolizumab with low dose carboplatin for recurrent platinum resistant ovarian, fallopian tube, and primary peritoneal cancer-interim results. First Author: John B. Liao, University of Washington, Seattle, WA

Background: Pembrolizumab has shown activity in advanced recurrent ovarian cancer (AOC) with an 8% response rate and median progression-free survival (PFS) of 2.1 months reported in KEYNOTE-100. Because platinum chemotherapy also induce cell proliferation and enhance tumor cell recognition through PD-1/PDL-1, we assessed the safety and activity of pembrolizumab with platinum resistant AOC. Methods: Key eligibility criteria for this Phase 1/2 single arm trial were platinum resistant AOC, fallopian tube, or peritoneal cancer, progression after subsequent systemic therapy, and ECOG PS 0-1. Pembrolizumab 200mg was given on Day 1 and carboplatin AUC 2 on Day 8 and 15 of a 3 week cycle until progression, unacceptable toxicity, or consent withdrawal. Imaging was done before cycles 4 and 8, then every 3 months and unconfirmed objective response assessed by blinded independent review per RECIST 1.1. Adverse events (AEs) were reported per Common Terminology for Adverse Events v5.0. PD-L1 expression was assessed by immunohistochemistry. Results: 27 patients (median age: 64) had received a median of 5 (range: 2-9) prior lines of systemic therapy, which included bevacizumab in 74% of patients. The most common treatment related (TR) AEs were lymphopenia (18%) and anemia (9%). The majority of TR AEs were grade 1 or 2 (93%). 6% of AEs were grade 3 with lymphopenia the most common. Two grade 4 AEs were neutropenia and lymphopenia. Of 23 patients evaluable for best objective response, 13.0% (95% CI, 2.7-33.6) had partial response (PR), 65.2% (95% CI, 42.7-83.6) had stable disease (SD), and 21.7% (95% CI, 7.4-43.7) had progression. Of the 23 evaluable patients (30.4%) had archival tumor with modified percent score 5 for PD-L1 and all achieved PR (37.2% vs 8%) or SD (47.4%, 57.2%). Overall median PFS was 4.6 months (95% CI, 2.7-6.2). Rate of PFS at 6 months was 40.4% (95% CI, 25.5-65.5). Median follow-up is 6.2 months and PFS is based on current data, but 8 patients remain on study and estimates will be updated. Conclusions: Pembrolizumab with low dose carboplatin was well tolerated and showed activity in heavily pretreated platinum resistant AOC. Survival and biomarker analyses will be presented. Final clinical trial information: NCT03029598.
Minvutaxim soravansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients (pts) with platinum-resistant ovarian cancer: Final findings from the FORWARD II study. First Author: David M. O’Malley, The Ohio State University, Columbus, OH

Background: Minvutaxim soravansine is an ADC comprising a FRα-binding antibody, cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent. As part of the Phase 1b FORWARD II trial (NCT02663630), the combination of minvutaxim soravansine with bevacizumab (BEV) was evaluated in pts with FRα-positive, platinum-resistant ovarian cancer (reurrence within 6 months after last platinum). Methods: Pts received minvutaxim soravansine (6 mg/kg; adjusted ideal body weight) and BEV (15 mg/kg) on Day 1 of a 21-day cycle. Responses were assessed according to RECIST 1.1 and adverse events (AEs) were evaluated by CTCAE v4.03. Results: In total, 66 pts received combination dosing at this level: 11 during escalation and 55 in expansion. The median age was 63 years, pts received a median of 3 prior lines of systemic therapy (range 1-8), and 62% had received prior therapy with BEV. The most common AEs were diarrhea (58%), nausea (50%), and blurred vision (48%), and were primarily low grade (< grade 2). Serious AEs were largely gastrointestinal in nature, with small intestinal obstruction the most frequent individual event (4 pts, 6%). Objective responses were seen in 27 pts for a confirmed overall response rate (ORR) of 41% (95% CI, 29, 54), median progression-free survival (mPFS) interval of 7.1 months (95% CI, 4.3, 9.5), and median overall survival (mOS) interval of 20.9 months (95% CI, 4.9, 14.9). In a subset analysis of pts (n = 16) who were bevacizumab-naïve, had 1-2 prior therapies, and medium/high FRα levels (i.e., ≥50% of cells with at least moderate staining intensity) the ORR was 56% (95% CI, 30, 80), mPFS 9.9 months (95% CI, 4.1, 15.9), and mDO 12 months (95% CI, 6.0, 14.9).

Conclusions: The combination of minvutaxim soravansine with BEV exhibits favorable tolerability in pts with platinum-resistant ovarian cancer, characterized by a manageable side-effect profile. The encouraging efficacy compares favorably to reported outcomes for BEV and chemotherapy seen in similar patient populations. These data support continued exploration of the combination in ovarian cancer. Clinical trial information: NCT02663630.

Rucaparib maintenance treatment significantly improved overall survival (OS) and quality of life in patients (pts) with platinum-sensitive recurrent ovarian carcinoma (OC) and updated safety data from the phase 3 study ARIEL3. First Author: Robert L. Coleman, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: In ARIEL3, rucaparib maintenance treatment significantly improved OS and quality of life in platinum-sensitive recurrent OC pts. The updated analysis of rucaparib maintenance treatment in pts with platinum-sensitive, recurrent OC will be presented. This analysis includes pt-level information: NCT01968213.

Methods: This retrospective analysis includes pts with platinum-sensitive, recurrent OC who were bevacizumab-naïve, had 1-2 prior therapies, and medium/high FRα levels (i.e., ≥50% of cells with at least moderate staining intensity). The efficacy endpoints were time to first subsequent therapy (TFST; ITT population), time to first subsequent therapy (TSST; no crossover pts), and time to subsequent therapy (TST; pts who crossed over after progression). The primary objective was to determine objective response rate by RECIST v1.1 and progression-free survival (PFS) at 16 weeks. Secondary objectives were to evaluate safety, PFS, overall survival (OS) and mechanisms of PARPi resistance. Pts who had radiographic progression on any PARPi were eligible. Archival tumor at initial diagnosis and baseline tumor biopsy at PARPi progression were mandatory. Pts received olaparib tablets 150mg BID with cediranib 20mg QD until progression or unacceptable toxicity. CT scans were performed every 8 weeks. Whole exome and RNA sequencing were performed on paired tumors results. Results: Thirty-four pts were enrolled. BRCAl/2 mutations were found in 9/11 FS, 8/10 PR and 7/13 PE pts. By RECIST v1.1, 8 (11.8%) pts achieved partial response (PR), 6 (8.6%) achieved stable disease (SD) and 44 (61.8%) pts progressed (PD). Molecular analyses identified different mechanisms of PARPi resistance in ~77% of evaluable pts with matched pre-post PARPi progression biopsies such as reversion mutations in BRCAl/2 and other homologous repair (HR) genes; BRCAl, HR and MDR upregulation, CCNE amplification and RIG-I like receptor downregulation. Conclusions: Treatment with olaparib-ceedaraniab PARPi was feasible and met the predefined bar for efficacy in each cohort. This is the largest clinical trial prospectively evaluating PARPi failure and correlating tissue genomic mechanisms of resistance. Clinical trial information: NCT02681237.

A phase I study of veliparib incorporated into front-line platinum based chemotherapy and bevacizumab in epithelial ovarian cancer (NCT00989651): A GOG/nrg trial. First Author: Deborah Kay Armstrong, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD

Background: Veliparib, a poly-(ADP-ribose)-polymerase inhibitor, increases anti-tumor activity when combined with platinum chemotherapy and has mechanisms of anti-tumor activity different from PARPi. The objective was to determine the recommended phase II dose (RP2D) of veliparib in combination with front line treatment for epithelial ovarian cancer (EOC). Methods: Eligible patients had newly diagnosed, stage II-IV EOC. Six regimens were evaluated, 3 variations of chemo delivery with either continuous (D1-21) or intermittent (days-2-5) veliparib BID. Chemo included 1: IV q3week carboplatin (C) (AUC 6) and paclitaxel(T)(175mg/m2); 2, IV q3week C (AUC 6) and weekly T(80mg/m2, days-2-5) veliparib BID. Chemo included 1: IV q3week carboplatin (C) (AUC 6) and paclitaxel(T)(175mg/m2); 2, IV q3week C (AUC 6) and weekly T(80mg/m2, days-2-5) veliparib BID. Results: Five regimens were evaluable, Grade 3 adverse events were anemia, hypertension, diarrhea and fatigue, grade 4 events were neutropenia. Molecular analyses identified different mechanisms of PARPi resistance in ~77% of evaluable pts with matched pre-post PARPi progression biopsies such as reversion mutations in BRCAl/2 and other homologous repair (HR) genes; BRCAl, HR and MDR upregulation, CCNE amplification and RIG-I like receptor downregulation. Conclusions: Treatment with olaparib-ceedaraniab PARPi was feasible and met the predefined bar for efficacy in each cohort. This is the largest clinical trial prospectively evaluating PARPi failure and correlating tissue genomic mechanisms of resistance. Clinical trial information: NCT02681237.

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Determinations of eligibility criteria for salvage hysterectomy after definitive radiotherapy/concurrent chemoradiotherapy for residual cervical disease. First Author: Munehito Takekuma, Department of Gynecology, Shizuoka Cancer Center, Shizuoka, Japan

Background: Patients with persistent cervical cancer after definitive radiotherapy/concurrent chemoradiotherapy (RT/CCRT) have a poor prognosis. Salvage hysterectomy (HT) is potentially curative, but eligibility criteria therefor have not been determined. Methods: Part 1) Retrospective review of patients with persistent cervical cancer treated with definitive RT/CCRT at 35 institutions of the Japanese Clinical Oncology Group (JCOG) from 2005–2014. Differences between a salvage HT group and a systemic chemotherapy (CT) group after definitive RT/CCRT for residual tumor were evaluated. Clinical variables influencing a salvage HT treatment decision were evaluated using logistic regression analysis. Part 2) Questionnaire-based survey conducted by JCOG gynecologic oncologists assessing treatment choice for patients with residual cervical disease after definitive RT/CCRT. Patients with residual cervical tumor before, during and after definitive RT/CCRT were surveyed for 86 conditions and appropriate candidates for salvage HT were evaluated using heat map analysis. Results: Part 1) We identified 298 patients who underwent salvage HT or systemic CT. Median overall survival was 3.8 and 0.9 year in the HT and CT groups, respectively (HR 0.4341, 95% CI 0.336-0.559, p < 0.01). FIGO stage and lymph node metastasis at initial treatment, performance status (PS) at diagnosis of residual cervical tumor and parametrial invasion of residual cervical tumor significantly influenced salvage HT decision. Part 2) Heat map analysis showed that surveyed variables segregated into 3 groups: i) in favor of salvage HT, ii) in favor of systemic CT, and iii) either. Conditions such as FIGO stage IB1-IIA, PS of 0-1, residual tumor < 4 cm, no parametrial invasion and no residual lymph node metastasis were included in group i) in favor of salvage HT. Conclusion: Eligibility criteria could be determined based on the results of the current study, and a prospective clinical trial evaluating the survival benefit of salvage HT for residual cervical tumor after definitive RT/CCRT is being planned by JCOG.
Comparative benefit of interstitial needles in addition to intracavitary applicators in the treatment of locally advanced cervical cancer. First Author: Dorothy Chebunyanga, BC Cancer Agency/University of British Columbia, Kelowna, BC, Canada

Background: Cervical cancer is the leading cause of cancer mortality in women in Low and Middle Income Countries (LMIC). Interstitial needles (IN) have improved outcomes but the resources required in comparison to intracavitary brachytherapy (IC) alone has impeded uptake in endemic regions. We conducted a retrospective review of the utilisation of IN in the management of locally advanced cervical cancer and simulated 2D plans by loading the applicators using standard Manchester loading (ML) to explore the magnitude of benefit that interstitial needles provide. Methods: 72 brachytherapy plans of 18 patients who had undergone treatment using tandem and ring and had interstitial brachytherapy between 04/2016 and 10/2018 were reviewed. ML plans prescribed to point A were generated to represent a 2D scenario but the known HR-CTV was taken into consideration and its dosimetric outcomes were compared to those of the 3D based plans. Results: The median tumour volume was 23 cm3. IN was used in 82 % of the insertions. The median number of IN was 2 (range 0 – 6) with median percentage of IN dwell time 6.6 % (range 0.68 – 39.50), V100 was excellent 98.2%, for ML 97.3% for 3D IN and 98.7% for 3D non-IN plans. The median HRCVT D90 was 85.5 Gy/fraction (cumulative EQD2 of 101.4 Gy) for ML plans and 8.0 Gy/fraction (cumulative EQD2 of 91.4 Gy) for 3D plans. The ML plans failed to meet the OAR goals except for the rectum, which was optimized by the use of a template applicator. The optimal IN plans provided small bowel doses were 24% above the recommended constraint in the individual plans and 15% cumulative EQD2. A statistically significant relationship was found between the number of needles utilised, tumour volume (p < 0.001) and coverage (p = 0.006) but not delivered dose (p < 0.068). Conclusions: Type 2 brachytherapy can provide adequate dose coverage for many tumors but IN provide a benefit in reducing the doses to OARs in a significant number of patients. This justifies investment in resources for uptake of interstitial needles to increase access to optimal treatment of cervical cancer for women in LMIC. This research was made possible an ASCO Conquer Cancer Foundation grant.

Cervical cancer harboring a Rb1 mutation may sensitize to cisplatin via PI3K/AKT pathway by regulating tumour. First Author: Peng Lu, Zhijiang Hospital of Southern Medical University, Guangzhou, China

Background: Cervical cancer is one of the most common malignant tumors in women and major causes of cancer death in women. Although concurrent chemoradiotherapy has improved the treatment of cervical cancer, due to the heterogeneity of the tumor to chemotherapy or radiation therapy, especially the varied response to chemotherapy, the patients respond differently to the same regimen who regimen, furthermore some patients get rapid progression. Therefore, we attempted to analyze the potential relationship between genomic mutation and chemotherapy response and survival in cervical cancer patients. Methods: Clinical information and sequencing data of Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma (CESC) in Genomic Data Commons (GDC) data portal were obtained through TCGA-biolinks. Only patients with stage IB-IV CESC who received cisplatin only and were included. Cisplatin sensitivity data and sequencing data of CESC cell lines were obtained from the Genomics of Drug Sensitivity in Cancer (GDC), Cox regression analysis, Kaplan-Meier survival analysis, differential analysis of gene expression and functional enrichment were used to explore the role of different mutations in survival and cisplatin sensitivity. Results: A total of 48 patients with stage IB-IV CESC were enrolled. 77 genes with mutation frequency > 10% were included in final analysis. Multivariate analysis showed that the mutation of Rb1 was an independent predictor of overall survival (OS) (HR = 0.97, 95%CI 0.91-0.92, P = 0.026). Patients with mutant Rb1 had better overall survival (134.2 versus 86.8 months) compared with patients with wild-type Rb1. The half maximal inhibitory concentration (IC50) of the mutant Rb1 cell line to cisplatin was significantly lower than that of the wild-type cell line (3.49 versus 10.15 mM, P = 0.038), the total of 352 differently expressed genes (DEGs) were identified and the KEGG pathway enrichment analysis showed that most DEGs were enriched in the PI3K/AKT pathway (P = 0.015). Conclusions: We found that Rb1 mutation was an independent survival predictor in stage IB-IV CESC, and CESC patients with Rb1 mutation may be more sensitive to cisplatin.

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Background: To evaluate the safety and efficacy of nimotuzumab plus concurrent intensity-modulated radiation therapy (IMRT) and chemotherapy for the treatment of locally advanced cervical squamous cell cancer (LACSCC).  
Methods: From December 2013 to March 2017, 31 patients with stage (FIGO 2009) IB2-IVA cervical squamous cell cancer were enrolled in this single-arm clinical trial at an academic medical center and received concurrent chemoradiotherapy plus nimotuzumab. All patients underwent at least 1 year of follow-up. The prescription radiation dose was 50.4 Gy/28 F on the pelvic field with or without extended-field radiation. An additional 30-36 Gy to Point A was delivered with high-dose-rate techniques. Cisplatin 40 mg/m² and nimotuzumab 200 mg were infused intravenously once weekly during radiotherapy. The main and secondary outcome measures were toxicity evaluated using CTCAE 4.0, and the short-term outcome evaluated by RECIST 1.1. Results: The median follow-up duration was 29.7 months (13.3-61.2 months). All patients received external beam radiotherapy, brachytherapy, and nimotuzumab six times. Twenty-seven patients received six cycles of chemotherapy while four received only 4-5 cycles. There was no life-threatening toxicity. The incidence of acute grade 3 or 4 bowel or bladder toxicity was 51.6% (16/31) and grade 3 gastrointestinal tract reaction was 9.7% (3/31). The incidence of late toxicities was 22.6% (7/31), and these included vaginal-rectal fistula, intestinal obstruction, rectal hemorrhage, hematuria, and vaginal stenosis. Complete response was achieved in 30 cases (96.8%). The 1-year disease-free survival (DFS), local progression-free survival (LPFS), and overall survival (OS) rates were 87.1%, 90.3%, and 100%, respectively. The corresponding 3-year values were 74.8%, 90.3%, and 86.7%. Conclusions: Nimotuzumab plus concurrent IMRT and chemotherapy may represent a well-tolerated and effective treatment regimen in patients with LACSCC.

Background: Cervical cancer remains a global health challenge particularly in low to middle income countries with under-resourced healthcare systems. We present the experiences of two centers practicing in variable resource environments to determine predictors of improved radiochemotherapy outcomes.  
Methods: This retrospective review describes baseline demographic and clinicopathologic characteristics of cervical cancer patients treated with concurrent chemoradiation and chemotherapy during 2014 and 2017 at the National Radiotherapy Oncology and Nuclear Medicine Center (NRONMC) in Korle Bu Teaching Hospital, Accra, Ghana and Moffitt Cancer Center, Tampa, Florida, USA.  
Results: Ghanaian patients presented at an older median age (56 vs. 49 years, p < 0.001), with predominantly stage IB2 disease (43% vs. 16%, p < 0.001) and squamous cell histology (89% vs. 79%, p < 0.001). Median treatment duration was longer for Ghanaian patients (58 vs. 52 days, p < 0.001). Ghanaian patients were less likely to receive concurrent chemotherapy (68% vs. 100%, p < 0.001) and interstitial brachytherapy implants (0% vs 19%, p < 0.001). No Ghanaian patients received a radiation boost to pelvic or paraortic lymph nodes (p = 0.001). Ghanaian patients had lower cervical control (64% vs. 93%, p < 0.001) and overall survival (82% vs. 95%, p = 0.02) at 24 months, respectively. For stage IB1, IA2, IIB, IIB, 24 month local control rates for NRONMC vs. Moffitt patients were (60% vs. 93%; p = 0.05), (89% vs. 100%; p = 0.35), (91% vs. 91%; p = 0.89), (53% vs. 91%; p = 0.02) and 24 month OS rates were (85% vs. 100%; p = 0.06), (100% vs. 100%; p = 0.48), (85% vs. 96%; p = 0.2), (73% vs. 91% vs. 0.24), respectively. Treatment duration > 56 days predicted poorer overall survival on multivariable analysis (MVA). Stage ≥III disease predicted poorer local control on MVA.  
Conclusions: Significant differences were noted in treatment and disease characteristics between the two centers. Feasible improvements for patients treated at NRONMC include removing financial barriers to chemoradiotherapy access, improving radiotherapy delivery capacity to reduce treatment delays, and simplifying protocols to reduce advanced disease. Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
5536 Poster Session (Board #359), Sat, 1:15 PM-4:15 PM

Omission of adjuvant therapy in stage I clear cell ovarian cancer: Review of the British Columbia (BC) cancer experience. **First Author:** Shiri Lucy Liu, BC Cancer, Vancouver, BC, Canada. **Background:** Standard guidelines recommend adjuvant chemotherapy for stage I clear cell ovarian cancer (CCOC), despite data demonstrating excellent outcomes. Since 2012, the BC Cancer provincial treatment guidelines for surgically staged stage I A/B and IC1 (defined by intraoperative rupture only) CCOC has been to offer observation only. We reviewed the clinical outcomes of stage I CCOC patients since policy implementation. **Methods:** A retrospective, population-based cohort study of all stage I OC patients operated on between April 2012 and December 2017 was conducted. Patient, tumor, surgical and clinical outcome data were collected. Survival analysis was conducted using Kaplan-Meier methods. **Results:** 78 patients with stage I disease were identified (see Table). Among stage IC1 patients, 9 received adjuvant therapy despite provincial policy, 6 of which were due to sharp dissection. 40 patients with stages IA/B and IC1, who underwent post-operative observation, were included in the analysis. Median duration of follow-up was 36 months. Median age at diagnosis was 55 years and >50% patients had a Charlson Comorbidity Index of 0 (N = 26) and an Eastern Cooperative Oncology Group performance status of 0 (N = 15) prior to diagnosis. Lymph node dissection was not performed in 20 patients. All 16 cases tested immunohistochemically for mismatch repair were intact, and 2 of 6 cases with tumour genomic sequencing had an AURKA aberration. There were 4 recurrences (10%), 3 of which were metastatic. 5-year overall survival for stage IC1 (p = 0.645). In comparison, 5-year overall survival for stage IC1 was 90% for stage IC1 (p = 0.90). **Conclusions:** The BC Cancer provincial treatment guidelines for surgically staged stage I CCOC has been to offer observation only. We reviewed the clinical outcomes of stage I CCOC patients since policy implementation.

5538 Poster Session (Board #361), Sat, 1:15 PM-4:15 PM

Efficacy and safety of tivozanib in recurrent, platinum-resistant ovarian, fallopian tube or primary peritoneal cancer. **First Author:** Wendy M Szwig, Northwestern University Feinberg School of Medicine, Chicago, IL. **Background:** Tivozanib is a potent, selective pan-vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor with a long half-life. This study assessed its activity in patients with recurrent, platinum-resistant ovarian cancer (OC), fallopian tube cancer (FTC) or primary peritoneal cancer (PPC). **Methods:** This open-label phase II study used a Simon’s two-stage design. Eligible patients had recurrent, platinum-resistant OC, FTC or PPC. ECOG PS of 0-1; normal organ function; and measurable or detectable disease. There was no limit on the number of prior regimens. Treatment consisted of tivozanib 1.5 mg orally once daily (3 weeks on/1 week off). The primary endpoint was response rate. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity assessment. If 1 partial response (PR) was observed in stage I (n = 12), enrollment proceeded to stage II. The null hypothesis was rejected for ≥ 4 responses in 30 patients. **Results:** Thirty-one patients were enrolled, and 30 were treated. Twenty-three had OC (76.7%), 5 FTC (16.7%) and 2 PPC (6.7%). Twenty-six had measurable (86.7%) and 4 detectable disease (13.3%). The median age was 60, and median number of prior regimens was 4 (range 1-9). Four PRs [13.33%] were recorded. Twelve patients had stable disease (SD) (40%). The clinical benefit rate (PR + SD) was 53%. Seven patients (23.33%) survived progression-free for > 6 mos. One patient continued treatment for > 2 yrs. The median PFS was 4 mos [range 1-25] and median OS was 8 mos [range 1-39]. There were no treatment-related deaths. Grade 3-4 related toxicities were hypertension [8], fatigue [3], fistula [2], hypotension [2], intestinal perforation, obstruction, stroke, proteinuria, hypomagnesemia, hypoalbuminemia, portal hypertension, nausea and anemia [1 each]. Frequent grade 1-2 related toxicities included fatigue [19], hypertension [13], anorexia [12], arthralgia [11], diarrhea [11], weight loss [10], hoarseness [8], headache [8] and nausea [7]. Exploratory analyses in tumor samples are ongoing. **Conclusions:** Tivozanib is active in patients with recurrent OC, FTC or PPC, without substantial toxicity, supporting its further development. Clinical trial information: NCT01853644.

5537 Poster Session (Board #360), Sat, 1:15 PM-4:15 PM

A randomized, double-blind, placebo-controlled phase Ib/II study of ralimetinib, a p38 MAPK inhibitor, plus gemcitabine (G) and carboplatin (O) versus GC for women with recurrent platinum-sensitive ovarian cancer. **First Author:** Ignace Vergote, BGOG and University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium. **Background:** p38 mitogen-activated protein kinase (MAPK) regulates cytokine production in the tumor microenvironment and enables therapeutic resistance of cancer cells. Ralimetinib (R) is a selective small-molecule inhibitor of p38α and p38β MAPKs. **Methods:** Main inclusion criteria: ≥18 y; recurrent platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer after first-line treatment. Phase (Ph) Ib was to determine the recommended Ph2 dose (RP2D) of R administered 12-hourly (Q12H) on Days 1-10 (21-day cycle [Q21D]) in combination with gemcitabine (G: 1000 mg/m2 on Days 3 and 10) and carboplatin (C: AUC 4 on Day 3) for 6 cycles. In Ph2, patients (pts) were randomized double-blind, 1:1 to RP2D R+GC or placebo (P+GC), for 6 cycles, followed by R 300 mg Q12H or P on Days 1-14, Q28D until disease progression. The stratified log-rank test compared progression-free survival (PFS; primary endpoint) between treatment groups in Ph2, at a 1-sided α level of 0.2. **ClinicalTrials.gov:** NCT01663857.

Study assessed its activity in patients with recurrent, platinum-resistant ovarian, fallopian tube or primary peritoneal cancer. **First Author:** Wendy M Szwig, Northwestern University Feinberg School of Medicine, Chicago, IL. **Background:** Tivozanib is a potent, selective pan-vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor with a long half-life. This study assessed its activity in patients with recurrent, platinum-resistant ovarian cancer (OC), fallopian tube cancer (FTC) or primary peritoneal cancer (PPC). **Methods:** This open-label phase II study used a Simon’s two-stage design. Eligible patients had recurrent, platinum-resistant OC, FTC or PPC. ECOG PS of 0-1; normal organ function; and measurable or detectable disease. There was no limit on the number of prior regimens. Treatment consisted of tivozanib 1.5 mg orally once daily (3 weeks on/1 week off). The primary endpoint was response rate. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity assessment. If 1 partial response (PR) was observed in stage I (n = 12), enrollment proceeded to stage II. The null hypothesis was rejected for ≥ 4 responses in 30 patients. **Results:** Thirty-one patients were enrolled, and 30 were treated. Twenty-three had OC (76.7%), 5 FTC (16.7%) and 2 PPC (6.7%). Twenty-six had measurable (86.7%) and 4 detectable disease (13.3%). The median age was 60, and median number of prior regimens was 4 (range 1-9). Four PRs [13.33%] were recorded. Twelve patients had stable disease (SD) (40%). The clinical benefit rate (PR + SD) was 53%. Seven patients (23.33%) survived progression-free for > 6 mos. One patient continued treatment for > 2 yrs. The median PFS was 4 mos [range 1-25] and median OS was 8 mos [range 1-39]. There were no treatment-related deaths. Grade 3-4 related toxicities were hypertension [8], fatigue [3], fistula [2], hypotension [2], intestinal perforation, obstruction, stroke, proteinuria, hypomagnesemia, hypoalbuminemia, portal hypertension, nausea and anemia [1 each]. Frequent grade 1-2 related toxicities included fatigue [19], hypertension [13], anorexia [12], arthralgia [11], diarrhea [11], weight loss [10], hoarseness [8], headache [8] and nausea [7]. Exploratory analyses in tumor samples are ongoing. **Conclusions:** Tivozanib is active in patients with recurrent OC, FTC or PPC, without substantial toxicity, supporting its further development. Clinical trial information: NCT01853644.
Results of the VENUS study: Bevacizumab efficacy and safety in platinum-sensitive recurrent ovarian cancer (OC)—A real-life ambispective study.

First Author: Isabelle Laure Pauvert-Rolland, Centre Léon-Bérard, Lyon, France

**Background:** The VENUS study reports on the efficacy/safety of bevacizumab (Bev) in patients (pts) treated in the real-life setting. **Methods:** In this multicentric ambispective VENUS study, all pts were naive of any anti-VEGF and received Bev +/- chemotherapy. Pts were followed until progression or death, for a maximum of 3 years since Bev initiation. De novo side effects were defined as symptoms for which patients were naive at baseline. **Results:** 149 pts were included (27 centres), 10 excluded and 8 were lost of follow-up. 52 were retrospectively median age 64 years (55-70), 84.1% were advanced. Median duration Bev was 8.6 months, min 1 max 36 months. Initial Bev dose was 15 mg/kg Q4W for 65.3%, 10.0 for 22.5%, 7.5 for 10.2 and 5.0 for 2%. 2 pts presented with thrombotic micro-angiopathy (1.4%). Before Bev, hypertension (HTN) was present in 28.9%, proteinuria in 11.3%. Incidence of de novo HTN was 25%, 43 pts (31.2%) experienced de novo Grade 1-2 Pu, for a total of 56 events, no grade 3-4 was observed. A total of 12 Grade 4 events occurred: 9 neutropenia and 3 thrombopenia. Mean overall survival (OS) and progression free survival (PFS) were 30.0 and 13.3 months, respectively. **Conclusions:** 1) 1/3 of pts were treated at low doses in this real-life study; 2) safety of Bev in real-life was manageable and as expected. 3) OS and PFS were consistent with those reported in the OCEANS study: Median OS and PFS were 26.0 and 12.5 months, respectively.

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5542 Poster Session (Paper #365), Sat, 1:15 PM-4:15 PM

Ofranergene obadenovec (VB-111) in platinum resistant ovarian cancer: with an immune-therapeutic effect.

**First Author:** Yael Chava Cohen, Tel Aviv Sourasky Medical Center and Sakler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

**Background:** VB-111 is a targeted anti-cancer gene therapy with a dual mechanism: anti angiogenic/vascular disruption and induction of an anti-tumor directed immune response. We report final results of a phase I/II study of VB-111 in combination with paclitaxel in patients with platinum-resistant ovarian cancer. **Methods:** Study NCT01844986 was a prospective open label, dose escalating study assessing combination treatment of VB-111 Q8W and weekly Paclitaxel. In the phase I part of the study patients were treated with escalating doses of intravenous VB-111 and Paclitaxel. In phase 2 patients were treated with therapeutic doses of 1x1013 Viral Particles and paclitaxel 80mg/m2.

**Results:** Assessments included safety, overall survival (OS), PFS, tumor response (CA125 and RECIST) and histopathology. **Results:** 21 patients with recurrent platinum-resistant ovarian cancer were enrolled and treated in 2 US sites. Patients received a mean of 2.3 ± 1.8 repeat doses of VB-111. 17/21 received the therapeutic dose. Median age was 65 (41-79) with a median of 3 (1-4) prior lines of therapy. Half of the subjects were Platinum refractory, and half were Pre-treated with antiangiogenics. No DLTs were observed. VB-111 was well tolerated and was associated with generally mild flu-like symptoms. In the therapeutic dose cohort, a 50% CA125 GCG response rate was seen in evaluable patients including durable responses, and responses in patients with platinum refractory disease and post anti-angiogenic failure. The median OS was 498 days in patients treated with Therapeutic Dose compared to 173 days in Sub-therapeutic dose (p = 0.028). Tumor Specimens taken after treatment demonstrated tumor infiltrated with cytotoxic CD8 T-cells and regions of apoptotic cancer cells. **Conclusions:** Treatment with VB-111 in combination with weekly Paclitaxel was safe and well tolerated. Favorable tumor responses and overall survival outcomes were associated with induction of an immunotherapeutic effect manifested as tumor infiltration with CD-8 T-cells. Encouraging results are the basis for further exploration in the ongoing, placebo controlled, pivotal OVAL study. Clinical trial information: NCT017191970.
Background: MORAb-202 is an antibody drug conjugate consisting of fasting letuzumab (a humanized monoclonal antibody that binds to FRA) paired with a cathepsin B-cleavable linker to eribulin mesylate (a multitubule dynamics inhibitor). We report preliminary results from a FIH Ph1 study of MORAb-202 in pts with FRA-positive solid tumors. Methods: MORAb-202 was administered by intravenous injection once every 3 weeks during neo-adj chemotherapy, were modeled in 133 patients (out of 15 pts had FRA-positive solid tumors). The longitudinal kinetics of 529 CA125 values, assessed every 3 weeks during neo-adj chemotherapy, were modeled in 133 patients (out of 15 pts had FRA-positive solid tumors). Clinical trial information: NCT03389642.

Conclusions: MORAb-202 escalation to 0.9mg/kg was manageable with encouraging initial antitumor activity in pts with FRA-positive solid tumors. Clinical trial information: NCT03389642.

Methods: The data of the CHIVA randomized phase II trial, comparing carboplatin-paclitaxel +/- nintedanib before IDS (NCT01583322), were used. A semi-mechanistic model was built to describe CA125 longitudinal kinetics during the first 100 treatment days. The relationships between KELIM and IDS CC scores, PFS & OS, were assessed with other major prognostic factors (grade, histology, gCGC CA125 response, FIGO stage, and arm) using multivariate logistic regression (logit), C-index & survival tests. Results: The longitudinal kinetics of 529 CA125 values, assessed every 3 weeks during neo-adjuvant chemotherapy, were modeled in 133 patients (out of 188). KELIM (as a continuous covariate) was the only significant predictive factor of CC0 IDS likelihood using multivariate analyses (OR = 12.37, 95% CI [4.32-39.67]). CC0 IDS probability can be estimated with patient KE- LIM and IDS CC scores, PFS & OS, were assessed with other major prognostic factors (grade, histology, gCGC CA125 response, FIGO stage, and arm) using multivariate logistic regression (logit), C-index & survival tests. Results: The longitudinal kinetics of 529 CA125 values, assessed every 3 weeks during neo-adjuvant chemotherapy, were modeled in 133 patients (out of 188). KELIM (as a continuous covariate) was the only significant predictive factor of CC0 IDS likelihood using multivariate analyses (OR = 12.37, 95% CI [4.32-39.67]). CC0 IDS probability can be estimated with patient KELIM:  0.12. Non-parametric survival models confirmed the independent predictive values of KELIM categorized by terciles regarding PFS & OS (Table). The parametric model linking KELIM (as a continuous covariate) with OS allows to predict the patient survivals (months) based on their estimated KELIM (HR = 0.20, [0.10-0.39]). Conclusions: The prognostic & predictive values of the modeled CA125 kinetics during neoadjuvant chemotherapy for predicting the likelihood of optimal interval debulking surgery in ovarian cancer patients: Data from CHIVA trial (a GINECO study). First Author: Patrick Robelin, Hospices Civils de Lyon, Pierre-Bénite, France. 4.1% decrease in the slope of the com- pare the probability of pts initiating next treatment or death, whichever occurred first, within 6 months. Results: 0.5,535 pts diagnosed with OC, 147 BCAw pts received 3 cycles of platinum-based chemotherapy. Although the higher cost associated with olaparib in SOLO1 was found to be more cost-effective in the 1st-line setting, with an ICER of $12,149 per month of life gained when compared directly to SOLO2. Conclusions: Although the higher cost associated with olaparib in SOLO1 reflects the longer time patients stay on drug due to extended PFS, the ICER supports early use in the disease course as first-line maintenance therapy among women with gBRCAmut advanced ovarian carcinoma.

Modelled CA-125 kinetics during neoadjuvant chemotherapy for predicting the likelihood of optimal interval debulking surgery (IDS) in ovarian cancer patients: Data from CHIVA trial (a GINECO study). First Author: Patrick Robelin, Hospices Civils de Lyon, Pierre-Bénite, France. Background: A pre-operative predictive biomarker of CC0 interval debulking patients: Data from CHIVA trial (a GINECO study). Modeled CA-125 kinetics during neoadjuvant chemotherapy for predicting the disease control rate was 75% (12/16 pts). Exposure to MORAb-202 was obtained from SOLO1, the phase 3 placebo-controlled randomized upfront maintenance study among gBRCAmut patients (median PFS greater than 49.8 vs 13.6m: HR 0.30; 95% CI, 0.23-0.41; p < 0.001, NCT01844986) and SOLO2, the phase 3 placebo-controlled randomized maintenance study among gBRCAmut patients with platinum-sensitive recurrence and at least two prior lines of therapy (median PFS 19.1 vs 5.5m: HR 0.30; 95% CI, 0.22-0.41; p < 0.0001, NCT01874353). Investigator-assessed median PFS and toxicity data from the trials were incorporated in a Markov model with disease progression and death. Using TreeAge Pro 2015, the costs of pre-treatment testing (eg. gBRCAmut), medications, and management of adverse effects were analyzed. Incremental cost-effectiveness ratios (ICERs) per month of life gained and individual PFS-life years (PFLYs) were calculated and compared. Results: As of Nov 16, 2018, 16 pts with confirmed FRA-positive solid tumors were enrolled and treated with MORAb-202 across 4 dose levels in Part 1 (0.3mg/kg: n = 3 [2 endometrial and 1 ovarian], 0.45mg/kg: n = 3 [3 ovarian], 0.68mg/kg: n = 3 [1 NSCLC, 1 ovarian, and 1 TNBC], 0.9mg/kg: n = 7 [4 ovarian, 1 endometrial, 1 NSCLC, and 1 TNBC]); all completed > 1 cycle. One pt in the 0.9mg/kg experienced DLTs of alanine aminotransferase increased (grade 3) and gamma-glutamyl transferase increased (grade 4). Treatment-emergent adverse events (TEAEs) were assessed in 19 pts (93.8%). The most common TEAEs were leukopenia and neutropenia (50% each). The objective response rate based on RECIST v1.1 was 37.5% (6/16 pts) in Part 1 with 1 complete response (ovarian) at 0.9mg/kg and 5 partial responses including 2 pts (both ovarian) at 0.9mg/kg, 1 pt (endometrial) at 0.3mg/kg, and 2 pts (1 NSCLC and 1 TNBC) at 0.68mg/kg. The disease control rate was 75% (12/16 pts). Exposure to MORAb-202 was dose proportional across the dose range investigated. Conclusions: MORAb-202 escalation to 0.9mg/kg was manageable with encouraging initial antitumor activity in pts with FRA-positive solid tumors. Clinical trial information: NCT03389642.

Background: Development of platinum resistance is a major clinical challenge in ovarian cancer (OC) treatment. In the phase 3 ENGOT-OV16/NOVA trial of the poly(ADP-ribose) polymerase inhibitor (PARPi) niraparib, 55% of BRCA4 wild-type (BCAw) patients (pts) receiving placebo developed platinum resistance after their last platinum-based therapy (ie, progressive disease) within 6 months of their last chemotherapy cycle. Niraparib, a PARPi approved for the maintenance treatment of adult pts with recurrent OC following platinum-based CT, significantly prolongs progression-free survival (PFS). This real-world data analysis investigated the risk of platinum eligibility loss for BCAw pts who did not receive maintenance therapy after platinum treatment. Methods: This retrospective study (identified 5,535 pts with OC from January 2011–October 2018 using data from Flatiron, a longitudinal, demographically and geographically diverse database derived from records of > 265 cancer clinics and > 2 million US cancer pts. BCAw pts who had received ≥2 lines of platinum-based CT, had disease progression ≥6 months after their previous line of therapy, and had no maintenance therapy (PARPi, bevacizumab, or CT agents) after their current treatment were included. Kaplan-Meier analysis was used to estimate the probability of pts initiating next treatment or death, whichever occurred first, within 6 months. Results: 0.5,535 pts diagnosed with OC, 147 BCAw pts received inclusion/exclusion criteria of this analysis (similar to ENGOT-OV16/NOVA placebo arm). An estimated 56% of pts received the next treatment or died within 6 months after their last platinum-based therapy. Median time to next therapy or death was 5.1 months (95% confidence interval, 3.1–7.2). Conclusions: Our real-world data analysis shows that 56% of BCAw pts who received platinum-based treatment without maintenance therapy had recurrent OC within 6 months, classifying them as platinum resistant. Use of maintenance treatment options, such as niraparib, has been shown to significantly prolong PFS after platinum-based CT and may be beneficial in extending the platinum-free interval, enabling pts to remain eligible for further platinum therapy.
5548 Poster Session (Board #371), Sat, 1:15 PM-4:15 PM
Risk factors for progression or death in ovarian cancer patients who completed first-line platinum treatment. First Author: Shannon Neville Westin, The University of Texas MD Anderson Cancer Center, Houston, TX
Background: Limited real-world information is available in ovarian cancer (OC) regarding prognostic factors for disease progression or death after initial treatment. Here, we assessed potential prognostic risk factors in OC patients (pts) who completed first-line (1L) platinum-based chemotherapy (CT) using real-world data. Methods: This retrospective study identified 5535 pts diagnosed with OC from January 2011–October 2018 from the Flaton database, a longitudinal, demographically and geographically diverse database derived from health records from >265 cancer clinics and >2 million US cancer pts. Stage III/IV/OC pts who completed 1L platinum-based CT after primary debulking or interval debulking surgery were included. Pts who received a poly(ADP-ribose) polymerase inhibitor (PARPi) in 1L treatment or as maintenance therapy after 1L treatment were excluded. Cox proportional hazards model was used to assess the association between baseline factors (neoadjuvant CT, disease stage, residual disease, BRCA status, ECOG, age, platelet count, hemoglobin, and neutrophil count) and time to next treatment (TTNT; a proxy for progression-free survival) or overall survival (OS) in these pts. Results: 1068 of 5535 pts were eligible for inclusion/exclusion criteria. Neoadjuvant treatment, stage of disease, residual disease after surgery, and BRCA mutation (BRCAmut) status were significant prognostic factors for either TTNT or OS. Neoadjuvant chemotherapy pts had a shorter TTNT (hazard ratio (HR) = 1.37; 95% CI: 1.01–1.88) and OS (HR = 1.64; 95% CI: 1.00–2.72) vs BRCAmut pts who were unmutated or were adjusting for other covariates. Stage IV pts had a shorter TTNT (HR = 1.26; 95% CI: 1.01–1.58) and OS (HR = 1.24; 95% CI: 0.9- 1.09) than stage III pts. OS was also worse in pts with vs without residual disease (HR = 1.27; 95% CI: 0.94–1.72) and worse in BRCAwt than BRCAmut pts (HR = 1.37; 95% CI: 1.0-1.82). Conclusions: In this retrospective analysis of a large real-world database, BRCA mutation was associated with higher risk of death. Receipt of neoadjuvant CT, higher stage of disease at diagnosis, or presence of residual disease after surgery were also associated with a shorter TTNT or higher risk of death. These real-world data confirm previously identified prognostic factors.

5550 Poster Session (Board #373), Sat, 1:15 PM-4:15 PM
Randomized phase III trial comparing pegylated liposomal doxorubicin (PLD) 40 mg/m 2 and 40 mg/m 2 in patients with platinum-resistant Mullerian carcinoma (JGOG3018). First Author: Akira Yabuno, Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Hidaka, Japan
Background: The standard dose of single-agent pegylated liposomal doxorubicin (PLD) 50 mg/m 2 every 4 weeks, but 40 mg/m 2 has recently been used in clinical practice, though there is no evidence available to support its use. Methods: A Phase III, randomized, multicenter, non-inferiority study comparing progression-free survival (PFS) of patients with platinum-resistant Mullerian carcinoma (epithelial ovarian, fallopian tube, or primary peritoneal carcinoma) treated with an experimental arm (40 mg/m 2 PLD) versus a standard arm (50 mg/m 2 PLD) until 10 courses, disease progression, or unacceptable toxicity was conducted. Eligible patients had ≤ 2 prior lines of treatment was by performance status (PS) and PFS of prior chemotherapy (<3 months versus ≥3 months). The primary endpoint was PFS, and secondary endpoints were overall survival (OS), toxicity profile, clinical response, and tolerability. The target total number of patients was 412. Results: The trial was closed due to accrual futility as patient recruitment was slow, with 272 patients randomized to the experimental arm (n=137) and the standard arm (n=135). The final analysis was performed with 234 deaths and 269 events for PFS. Median patient age was 62 years; 58% of patients had a treatment-free interval less than 3 months, and 81% of patients had PS 0. In the experimental versus standard arm, median PFS was 4.0 months versus 4.0 months (HR 1.065, 95% CI: 0.830-1.366), and median OS was 14.0 months versus 14.0 months (HR 1.078, 95% CI: 0.831-1.397). Adverse events ≥Grade 2 included oral cavity mucositis more frequent in the standard arm than in the experimental arm (26.7 vs 13.5%, respectively; p<0.0089), but there was no difference in ≥Grade 2 hand-foot-skin reactions (19.8% vs. 15.0%, respectively; p=0.333).
Conclusions: The non-inferiority of PFS with the reduced dosing schedule was not confirmed because the trial was closed prematurely, but PFS and OS were similar. These results suggest a reduction of the standard dose of PLD beneﬁted pts by reducing the low-rate of oral cavity mucositis, particularly among patients with platinum-resistant Mullerian carcinoma treated with the lower dose regimen. Clinical trial information: UMIN0000031300.

5551 Poster Session (Board #374), Sat, 1:15 PM-4:15 PM
Efficacy of maintenance olaparib for newly diagnosed, advanced ovarian cancer patients: a phase II SOLO1 trial. First Author: Michael Friedlander, Prince of Wales Clinical School, University of New South Wales, and Royal Hospital for Women, Sydney, Australia
Background: In SOLO1 (NCT01844986), maintenance olaparib resulted in a significant improvement in progression-free survival (PFS) for newly diagnosed, BRCA1- and/or BRCA2-mutated, advanced ovarian cancer pts compared with placebo (HR 0.30, 95% CI 0.23–0.37; median not reached vs 13.8 months; Moore et al. N Engl J Med 2015). We updated PFS in SOLO1 for the subgroups of pts with BRCA1 mutations (BRCA1m) or BRCA2 mutations (BRCA2m). Methods: All pts were in clinical complete or partial response to platinum-based chemotherapy and were randomized to maintenance olaparib (300 mg twice daily; tablets) or placebo (p=0.0001) for 2 years. Pts were followed for disease status and development of adverse events. Results: Median follow-up of PFS was 41 months in the olaparib and placebo arms. Of 391 randomized pts, 282 had BRCA1m (72%), 106 had BRCA2m (27%) and three (1%) had both (Table). Two pts in the olaparib arm had somatic BRCA1m (one BRCA1m, one BRCA2m); all others had germline BRCA1m. At the primary data cut-off, 155 pts in the BRCA1-mutated group (95%), 43 in the BRCA2-mutated group (72%) were confirmed in the BRCA1m or BRCA2m group. The percentage of BRCA1-mutated pts who received olaparib and were progression-free at 1, 2 and 3 years was 66%, 69% and 53% (vs 52%, 36% and 26% receiving placebo) and for BRCA2-mutated pts was 92%, 85% and 80% (vs 55%, 32% and 29%, respectively). Conclusions: Significant PFS benefit with olaparib versus placebo was demonstrated for all pts, regardless of whether they had BRCA1m or BRCA2m. Statistical tests were not used to compare BRCA1- and BRCA2-mutated pts, but those with BRCA2m appeared to receive greater benefit from maintenance olaparib than those with BRCA1m. Clinical trial information: NCT01844986.

PFS by BRCA1m and/or BRCA2m.

BRCA1m
BRCA2m
BRCA1m
BRCA2m
Placebo
Placebo
Placebo
Placebo
Olaparib
Olaparib
Olaparib
Olaparib
n=191
n=91
n=40
n=66
n=191
n=40
n=191
n=66
Median PFS, months
3.8
4.0
0.38 (0.30–0.56)
0.20 (0.10–0.37)
NC
NC
HR (95% CI)
0.41
0.41 (0.30–0.56)
0.20 (0.10–0.37)
NR
NR

NC, not calculable; NR, not reached.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Prolonged time from primary surgery to chemotherapy is associated with worse survival in ovarian cancer (OC); however, the impact of prolonged time from neoadjuvant chemotherapy (NACT) to interval debulking surgery (IDS) is unknown. Given increasing utilization of NACT, we seek to evaluate the role of delays from NACT to IDS (TIDS) on survival. Methods: At a single center, we prospectively identified 224 women with newly diagnosed stage III/IV OC given NACT from 7/1/15 to 12/1/17. Clinical characteristics were abstracted by two independent reviewers. Delays in TIDS were defined as time from last preoperative carboplatin to IDS > 6 weeks. Fisher’s exact/Wilcoxon rank sum tests were used to compare clinical characteristics by delay in TIDS. Kaplan Meier method was used to estimate progression-free (PFS) and overall survival (OS) from date of IDS. Log-rank test/multivariate CoxPH models were used to examine differences by delay groups, adjusting for covariates. Results: Of the 224 women, 159 underwent IDS, and 34 (21%) experienced TIDS delays. These women were older (median 68 vs. 65 years, p = 0.05) and had more preoperative NACT cycles (median 6 vs. 4, p = 0.003). Patients with delays in TIDS also had a longer interval from pathological diagnosis to start of NACT (TNACT), median 22 vs. 17 days, p = 0.01, and interval from IDS to postoperative chemotherapy (TPOC), median 37 vs. 30 days, p = 0.01; however, neither TNACT nor TPOC predicted survival, p > 0.05. On univariate analysis, delays in TIDS were significantly associated with worse OS (HR 2.9 95% CI 1.2-6.8, p = 0.009); however, this was attenuated in multivariate models (HR 1.66 95% CI 0.8-3.4, p = 0.17), adjusting for age, and complete gross resection (CGR). On univariate analysis, delays in TIDS were not associated with PFS (HR 1.55 95% CI 0.97-2.5, p = 0.062), and in multivariate models, increase in number of preoperative NACT cycles (p = 0.005) and absence of CGR (p < 0.001) were the only variables predictive of worse PFS. Conclusions: Delays in TIDS are associated with OS, but not after adjustment for age, stage and CGR, suggesting a need to maximize cytoreduction regardless of delays in NACT. The role of preoperative NACT cycles on survival should be further studied.

Olaparib maintenance therapy in patients (pts) with a BRCA1 and/or BRCA2 mutation (BRCAm) and newly diagnosed advanced ovarian cancer (OC): SOLO1 China cohort. First Author: Lingying Wu, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

Background: SOLO1 (NCT01844986) is a randomized, double-blind, Phase III trial evaluating the efficacy and safety of the PARP inhibitor, olaparib, as maintenance monotherapy in newly diagnosed advanced OC pts with a BRCAm. A separate pt cohort evaluated the efficacy and safety of olaparib in Chinese pts in this setting. Methods: The China cohort of SOLO1 planned to enroll ~53 newly diagnosed OC pts who had completed first-line platinum-based chemotherapy and were in clinical complete or partial response. This sample size provided around a 90% chance to observe an HR of 0.62. Pts were randomized 2:1 to olaparib (300 mg bid; tablet) vs placebo. The primary endpoint was investigator-assessed progression-free survival (PFS; modified RECIST v1.1). Sensitivity analysis of PFS was performed by blinded independent central review (BICR). Results: All 64 randomized pts received study treatment (olaparib, n = 44; placebo n = 20). Median follow-up was 30 months in both arms. Median PFS was not reached in the olaparib arm and was 9.3 months in the placebo arm (Table). The most common AEs in the olaparib group were nausea (n = 28, 63.6%), anemia (n = 25, 56.8%) and vomiting (n = 18, 40.9%). Grade ≥3 AEs occurred in 58.6% of olaparib vs 30.0% of placebo pts; the most common grade ≥3 AE was anemia (n = 16, 36.4%). Grade ≥3 adverse events (AE), reductions (62%) or discontinuations (58%, 27.3% and 6.8% of pts, respectively (n = 30.0%, 10% and 0% of pts in the placebo arm). Conclusions: In the China cohort of SOLO1, a clinically relevant improvement in investigator-assessed PFS was observed in newly diagnosed OC pts receiving olaparib maintenance therapy. Olaparib treatment led to a 54% reduction in risk of progression or death vs placebo. The safety results were consistent with the known profile of olaparib in Chinese pts. Clinical trial information: NCT01844986.

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<th>Group</th>
<th>5 year DSS</th>
<th>Statistics</th>
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<tr>
<td>ECadm-ARID1A&lt;sup&gt;wt&lt;/sup&gt;</td>
<td>100%</td>
<td>HR&lt;sub&gt;0.14(0.02-1.11)&lt;/sub&gt;, p&lt;sub&gt;0.0623&lt;/sub&gt;</td>
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<tr>
<td>ECadm-ARID1A&lt;sup&gt;mut&lt;/sup&gt;</td>
<td>77%</td>
<td>HR&lt;sub&gt;0.24(0.08-0.67)&lt;/sub&gt;, p&lt;sub&gt;0.0063&lt;/sub&gt;</td>
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<tr>
<td>EC&lt;sup&gt;mut&lt;/sup&gt;</td>
<td>60%</td>
<td>HR&lt;sub&gt;0.48(0.14-1.69)&lt;/sub&gt;, p&lt;sub&gt;0.2551&lt;/sub&gt;</td>
</tr>
<tr>
<td>ECadm&lt;sup&gt;mut&lt;/sup&gt;</td>
<td>80%</td>
<td>HR&lt;sub&gt;0.38(0.09-1.66)&lt;/sub&gt;, p&lt;sub&gt;0.1977&lt;/sub&gt;</td>
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<tr>
<td>EC&lt;sup&gt;mut&lt;/sup&gt;</td>
<td>30%</td>
<td>Reference</td>
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PFS, investigator-assessed (48.4% maturity) 18 13 NR 0.46 (0.23, 0.67; 0.0320) PFS, BICR (39.1% maturity) 13 12 NR 0.39 (0.17, 0.67; 0.0168) CI, confidence interval; HR, hazard ratio; NR, not reached.
Cost-effectiveness analysis of laparoscopic disease assessment in ovarian cancer.

**Methods:** We performed a cost-effectiveness analysis from a payer's perspective to compare (1) a conventional strategy, where standard new patient evaluation was used to assign pts to either primary cytoreduction (PCS) or neoadjuvant chemotherapy with interval cytoreduction (NACT), and (2) an alternative approach, where pts considered candidates for PCS would undergo laparoscopy to evaluate disease resectability using a validated scoring system, which were then triaged to either PCS or NACT based on this evaluation. Diagnostic work-up, surgical and adjuvant treatment, perioperative complications, and progression-free survival (PFS) were included in the model. The derived model parameters from the literature and our institution's experience with laparoscopic triage. Utility estimates for health states related to primary treatment were assessed prospectively and taken from the literature. Costs were estimated using Medicare reimbursement. Effectiveness was defined in quality-adjusted progression-free years (QALYs). We performed multiple sensitivity analyses.

**Results:** Under baseline model parameters, the expected cost of treating one pt under the conventional and alternative strategies was $26,539 and $26,653, respectively. The expected quality-adjusted progression-free survival for pts in the conventional and alternative strategies was 0.70 and 0.94 QALYs, respectively. The incremental cost-effectiveness ratio was $473.97 per QPFLY saved. The alternative strategy became cost-saving if pts found to have resectable disease by laparoscopy underwent cytoreduction during the same procedure. The conventional strategy may be preferred if PCS increased PFS over NACT by ≥5 months. **Conclusions:** For newly diagnosed advanced stage OC pts, laparoscopic assessment of disease resectability prior to PCS was a cost-effective strategy. A conventional strategy may be preferred if PCS produced substantially longer PFS. Sensitivity analysis suggests the benefit of utilizing laparoscopic triage is influenced by mitigation of serious perioperative morbidity and associated costs.

**Patient preferences for maintenance PARP therapy in ovarian cancer treatment.

**Methods:** We conducted a survey study of patients with recurrent, previously treated ovarian cancer who enrolled in Phase I clinical trials with a median of 1 (range 0-5) prior Phase 1 clinical trial enrollments. 53/132 (40%) of patients were treated on multiple Phase I trials with a median of 5 (range 2-10) prior Phase 1 clinical trial enrollments. Patient characteristics, diagnosis. Historically, clinical benefit of Phase I trials in this patient population has been uncertain. We assessed prognostic factors and survival in women with recurrent, previously treated ovarian cancer who enrolled in Phase I clinical trials.

**Results:** Our study shows OC patients treated with bevacizumab-containing regimens sequentially at the time of progression have significantly prolonged survival outcomes compared to those patients who received no re-treatment with bevacizumab.

**Survival and clinical outcomes of ovarian cancer patients enrolled in phase I clinical trials.

**Methods:** We performed a retrospective analysis of all ovarian cancer patients who enrolled in Phase I clinical trials at the University of Colorado Cancer Center. Patient characteristics, treatment-related toxicities, and survival data were assessed. Descriptive statistics and Cox proportional hazards models were utilized to identify risk factors associated with survival time. **Results:** A total of 132 individual patients were treated on Phase I clinical trials. Patients had a median age of 59 years (range 33-88) with a median of 5.5 (range 1-13) previous chemotherapy lines. 53/132 (40%) of patients were treated on multiple Phase I trials with a median of 1 (range 0-5) prior Phase I clinical trial enrollments. All patients had an ECOG performance status of 0 or 1. Overall response rate (defined as complete or partial response) was 9% and disease control rate (defined as complete or partial response or stable disease as best response) was 33%. Median overall survival (OS) was 11.5 months (95% CI: 9.3-13.7). Two patients died on trial due to progression of disease while no patients died due to treatment-related toxicity. In multivariate analysis, independent risk factors predicting shorter survival were elevated CA-125 (HR 2.8; 95% CI: 1.6-5.2) and albumin < 3.5 g/dL (HR 2.5; 95% CI: 1.65-3.79). BMI > 25 predicted longer survival (HR 0.65; 95% CI: 0.44-0.96). **Conclusions:** Phase I clinical trials for heavily pretreated ovarian cancer patients are safe by a standard of no patients experiencing toxicity-related deaths in our study. They are clinically efficacious with patients experiencing OSes of 11.5 months, which is comparable to existing approved therapies. Elevated CA-125 and low albumin levels predict shorter survival, while BMI > 25 predicts longer survival. Phase I clinical trial options should be considered for all heavily pretreated ovarian cancer patients if available to them.
Effect of estrogen and progesterone receptor expression on progression-free and overall survival outcomes in low-grade serous ovarian cancer. First Author: Marta Llaurado Fernandez, University of British Columbia, Vancouver, BC, Canada

Background: Research on ER/PR receptor function in low-grade serous ovarian cancer (LGSC) and the determinants of response to treatment are lacking. A recent study (Seohouri et al., 2018) described ER/PR immunohistochemistry (IHC) cut-points that distinguished PFS. Thus, we report on a group of patients with ER/PR expression by IHC in tumor samples of patients with LGSC and used this information to evaluate survival outcomes. Methods: Clinical information and FFPE sections were obtained from the Canadian Ovarian Experimental Unified Resource (COEUR). Tissue microarray (TMA) sections were stained for ER/PR using standard IHC techniques (MK). 50 stage 3 and 5 stage 4 patients were analyzed. ER/PR expression was scored using a simple scoring system (0-1% cells staining, 1-50%, and > 50%) and Allred scoring. We compared Kaplan-Meier (KM) survival (PFS and OS) curves using Log rank testing and Cox regression was used to model predictive/prognostic factors. A p-value of 0.05 was considered significant. Results: The mean age of the population was 59.5 years (SD: 13.7). Ninety percent of patients were treated by surgery followed by platinum-based chemotherapy (PBC). Simple scoring did not discriminate outcomes as well for ER levels. PR Allred score (< 2, vs 2-< 6 vs > 6) clearly discriminated KM curves for PFS (p = 0.036) and OS (p = 0.01). For Allred ER score (< 7 vs >7-< 8 vs > 8) did not distinguish PFS (p = 0.4) but notably most patients received PBC after surgery. ER Allred score significantly distinguished OS (p = 0.008). Significant factors on Cox regression for PFS were residuum (p = 0.008, 95%CI:1-2.3-1.1) and PR (p = 0.05, 95%CI:0.39-0.99), whereas for OS ER (p = 0.01, 95%CI:0.2-0.8) and reidium (p = 0.04, 95%CI:1-2.8). Conclusions: ER/PR expression by Allred scoring was associated with PFS and OS. Patients will benefit from much needed research on ER/PR prediction/prognosis in LGSC. This work can inform clinical trials selection/statification and patient selection for endocrine treatment.

Real life efficacy and safety data of bevacizumab-based front line treatment in advance or metastatic ovarian cancer patients: Focus on patients with malignant ascites—A phase IV study. First Author: Michail Nikolau, Hellenic Oncology Research Group (HORG), Athens, Greece

Background: The standard of care for Epithelial Ovarian cancer (EOC) is the combination of a taxane plus a platinum compound (TC) whereas the addition of bevacizumab (bev) to this regimen (TC-bev) has been shown to improve the PFS. Patients (pts) with ascites have more aggressive disease and less overall survival. The aim of the study was to evaluate the safety of the TC-bev regimen in the real life clinical practice. Methods: A multi-center observational study, approved by the ethics committees of the participating centers, including 314 pts with stage III/IV EOC, was conducted (11.2011-06.2014) in Greece. Two independent cohorts, with similar clinico-pathologic characteristics, were treated with front-line TC (n = 109) or TC-bev (n = 205) according to the physician’s choice. B3 (40.5%) and 40 (36.7%) in the TC-bev and TC groups presented with ascites. Results: Disease control was achieved in 90.7% and in 78.9% of patients treated with TC-bev and TC, respectively (p = 0.003). Pts with ascites treated with TC-bev experienced a better overall response rate (ORR) (68.7% VS 55%) and less progression disease (PD) compared to patients receiving TC (13.2% Vs 30.8%). The median PFS in all pts was 21.5mo and 12.4mo (p < 0.001) and median PFS in ascites pts was 18.1mo and 10.3mo in the TC-bev and TC cohort, respectively (p = 0.001). The median OS was not reached in the TC-bev group and it was 36.9mo in the TC group, (p = 0.059) while in the ascites pts also has not reached and it is 22.5m, respectively (p = 0.023). The 3 year survival rate in all pts was 59.4% and 50.4% and in ascites pts was 55.3% and 30% in the TC-bev and TC respectively. Neutropenia was the most common grade 3/4 adverse event in 16.6% and 9.1% in TC-bev- and TC- treated patients (p = 0.072) with no other adverse event ≥ 5%. Conclusions: These real life data demonstrate that the combination of TC-bev represents an active and well tolerated regimen offering survival benefit in patients with stage III/IV EOC and especially in patients with ascites. Additional larger prospective studies are required to confirm these observations. Clinical trial information: NCT01982500.

Impact of BRCA mutation status and time to platinum resistance on patients with advanced ovarian cancer. First Author: Alexandra Tyulyandina, Federal State Budgetary Institution «N.N. Blokhin National Medical Research Center of Oncology» of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russian Federation

Background: The influence of germline BRCA1/2 mutations (gBRCAmt) on ovarian cancer patients (pts) long-term survival remains controversial. Methods: 228 pts with serous and endometrial ovarian cancer stage Ic-IV were enrolled in the retrospective study. Next-generation sequencing testing of BRCA1/2 in blood was employed. Progression-free survival (PFS), overall survival (OS) and time to platinum resistance (TPR) were analyzed. TPR was defined as time from first line chemotherapy to registration of platinum resistance relapse. Results: The rate of pathogenic gBRCAmt was defined in 29.4% (67/228) pts. There was no any significant difference between BRCA1/2 mutation carriers and non-carries in both PFS (18.3 and 16.7 months, p = 0.27, HR 0.79, 95%CI 0.52-1.20) and OS (71.9 and 79.1 months, p = 0.69, HR 0.88, 95%CI 0.46-1.68). However, TPR was significantly longer in pts with gBRCAmt than in germline BRCA wild type (gBRCAwt) pts (51.4 and 34.4 months, p = 0.05, HR 0.60, 95% CI 0.36-0.98). Pts with gBRCAmt had poor prognosis after registration of platinum resistance. gBRCAwt pts had longer survival than gBRCAmt after platinum-resistance relapse: 33.7 and 16.9 months respectively (p = 0.05; HR 1.85, 95%CI 1.02-4.08). Conclusions: Our finding provided possible explanation of equal survival of pts with or without BRCA1/2 mutations. Long-term sensitivity to platinum-based chemotherapy allowed pts with gBRCA1/2mt to control the disease for a long period of time. However the non-platinum regimens had less efficacy in pts with gBRCAmt than gBRCAwt after platinum resistance.

Impact of the Affordable Care Act on early-stage diagnosis and treatment for women with ovarian cancer. First Author: Anna Jo Smith, Johns Hopkins Department of Gynecology and Obstetrics, Baltimore, MD

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Saturday, June 1. Onsite at the Meeting, this abstract will be printed in the Saturday edition of ASCO Daily News.
PARPi in pts with PS rOC, according to BRCA status. In the absence of direct comparison in randomized trials (RCTs), we have performed a NMA to evaluate differences in terms of efficacy between BEV and PARPi vs CT in the three cohorts are reported in the table. 

**Conclusions:** According to indirect comparisons, PARPi performed the best for the treatment of PS-rOC, especially in BRCAm pts who had not previously received PARPi. BEV could be still an option in BRCAwt pts.

### Treatments

<table>
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<tr>
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<th>AC</th>
<th>BRCAm</th>
<th>BRCAwt</th>
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<tbody>
<tr>
<td>PARPi vs BEV</td>
<td>0.70 (0.54-0.91)</td>
<td>0.46 (0.36-0.59)</td>
<td>0.87 (0.63-1.20)</td>
</tr>
<tr>
<td>PARPi vs CT</td>
<td>0.38 (0.31-0.47)</td>
<td>0.25 (0.21-0.31)</td>
<td>0.48 (0.36-0.63)</td>
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<tr>
<td>BEV vs CT</td>
<td>0.55 (0.31-0.47)</td>
<td>0.55 (0.48-0.63)</td>
<td>0.55 (0.47-0.64)</td>
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**Incidence of Breast Cancer**

<table>
<thead>
<tr>
<th>Time since EOC Diagnosis</th>
<th>Prior SOLO-1</th>
<th>Predicted POST SOLO-1</th>
</tr>
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<tbody>
<tr>
<td>2-year</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>5-year</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>10-year</td>
<td>11%</td>
<td>17%</td>
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### Methods

**An IRB-approved, multi-institutional study retrospective chart review was performed.**

**Background:** Patients with BRCA mutations are at increased risk of developing both breast (BC) and epithelial ovarian cancer (EOC). Optimal breast cancer surveillance guidelines for BRCA mutation carriers following EOC has not been defined due to high risk of EOC recurrence. The recent SOLO-1 trial demonstrated a survival benefit of olaparib maintenance therapy for newly diagnosed women with advanced stage EOC. Olaparib reduced the risk of disease-progression or death by 70% compared to placebo with a median progression-free survival (PFS) of 36 months.

**Methods:** An IRB-approved, multi-institutional study retrospective chart review was performed. Patients had BRCA-associated EOC diagnosed between 1990-2015 without a history of prior BC or mastectomy. All women received combination chemotherapy for EOC. The observed breast cancer free survival was adjusted to reflect the enhanced 3-year PFS observed in olaparib-treated women from the SOLO-1 trial. Kaplan-Meier survival curves were performed. **Results:** 191 patients with BRCA-associated EOC were included (135 BRCA1, 55 BRCA2, 1 BRCA1 and BRCA2). Median age was 53 years. Most women had advanced stage, high-grade EOC (75%). The median overall survival was 7.7 years for BRCA 1, and 9.7 years for BRCA2 mutation carriers. Annual mammography and MRI were performed in 43% and 34% of women, respectively, with a median of 4 mammograms and 3 MRI per patient. 15 women (8.3%) were diagnosed with BC over a median follow up of 80 months: 7 (44%) DCIS and 9 (56%) invasive ductal carcinoma. 14 (88%) women had early stage (0-2) BC. 28 (15%) of women had risk-reducing mastectomy performed an average of 2.1 years following their EOC diagnosis. The incidence of BC increased from 5.6% to 11% at 5- and 10-years post EOC, and in the predicted model with olaparib, from 10% to 17% at 5- and 10-years, assuming olaparib does not impact breast cancer incidence.

**Conclusions:** The risk of metastatous BC following BRCA-associated EOC increases over time. In the post SOLO trial era, BC surveillance strategies in women with EOC should be optimized to reflect improved outcome.
5568 Poster Session (Board #391), Sat, 1:15 PM-4:15 PM
Elucidation of PARP inhibitor activity in BRCAwt recurrent ovarian cancer by hr mutational gene profile analysis. First Author: Mansoor Raza Mirza, Nordic Society of Obstetrics and Gynecology, University Hospital Copenhagen, Denmark

Background: Niraparib is an oral, selective poly(ADP-ribose) polymerase inhibitor (PARPi) approved for maintenance treatment of BRCA mutated (BRCAmut) and BRCA wild-type (BRCAwt) recurrent ovarian cancer patients (pts) who are in response to platinum-based chemotherapy. In the non-germline BRCA mutated (non-gBRCAmut) cohort of the ENGOT-OV16/NOVA trial, clinical benefit with niraparib vs placebo was seen in pts regardless of their Myriad myChoice HRD test status (BRCAwt and homologous recombination deficiency [HRD] score), with a hazard ratio (HR) of 0.38 in HRD-positive (HRDpos) and 0.58 in HRD-negative (HRDneg) pts. To determine if treatment benefit in HRDneg pts may result from mutations in other homologous recombination repair (HRR) genes, we examined the relationship between progression-free survival and other HRR gene mutations in the NOVA non-gBRCAmut cohort. Methods: A retrospective, exploratory biomarker analysis was conducted using all available tumor samples from 331 pts enrolled in the NOVA non-gBRCAmut cohort. Mutation status of HRR genes was evaluated using a 43-gene NGS assay (Myriad Genetics), including BRCA1, BRCA2, and 16 additional HRR genes. Results: In this exploratory analysis of the NOVA non-gBRCAmut cohort, niraparib demonstrated clinical benefit in pts with somatic BRCA mutation (HR, 0.27) and in BRCAwt pts (HR, 0.47). In addition, BRCAwt pts with other HRR gene mutations also derived benefit from niraparib (HR, 0.31). As did BRCAwt/HRDpos pts (HR, 0.49). When BRCAwt and BRCAwt/HRDpos pts were categorized by HRD score, clinical benefit was also observed in both HRDpos and HRDneg pts, with HRs of 0.33 and 0.60, respectively. These results suggest that, although these biomarkers have good positive predictive value, they are not good negative predictors for niraparib benefit in this indication. Conclusions: This retrospective, exploratory analysis of the ENGOT-OV16/NOVA non-gBRCAmut cohort suggests that although pts with somatic BRCA mutation and other HRR mutations benefit from niraparib treatment, clinical benefit is also seen in HRDneg pts without HRR mutations, perhaps related to other genomic, epigenetic, or functional alterations within ovarian tumors yet to be defined.

5569 Poster Session (Board #392), Sat, 1:15 PM-4:15 PM
Multi-parametric FDG PET/MI as an early predictor of response to neoadjuvant chemotherapy in patients with epithelial ovarian cancer. First Author: Melissa Kristen Frey, Weill Cornell Medical College, New York, NY

Background: For patients with ovarian cancer undergoing neoadjuvant chemotherapy, the effectiveness of treatment is not evaluable by conventional methods until all or much of the treatment has been given. The purpose of this study is to investigate the performance of FDG PET, dynamic contrast-enhanced (DCE) and intra-voxel incoherent motion (IVIM) MR as early predictors of treatment response. Methods: Subjects with a new diagnosis of epithelial ovarian cancer underwent 3 cycles of standardized chemotherapy followed by cytokeduction. FDG PET/MR including DCE and IVIM was performed at baseline (T0), after cycle 1 (T1) and after cycle 3 (T2) of chemotherapy. Final responses were categorized at T2 by RECIST 1.1. Image volumes at T1 were analyzed as predictors of final response. Parametric images of molecular diffusion restriction (D), tissue perfusion (D*), vascular volume fraction (F), blood- > interstitium constant of transfer (Ktrans), interstitium- > plasma constant of transfer (Kep), extravascular/extracellular volume % (Ve) and plasma volume % (Vv) were investigated along with routine measures of SUV and ADC. Results: Nine subjects were enrolled, 8 were responders by RECIST at T2 and one had stable disease. At T0 the mean, min, and max SUVmax of dominant tumor deposits was 11.5, 6.3, 19.0, respectively. Mean, min, and max values were 1.0, 0.75 and 1.63 for ADCmean and 0.62, 0.30, 0.96 for ADCmin. At T1, ADCmean increased in 8 subjects by +0.22% (s.d. +/- 13%) and decreased by -3% in one subject. ADCmin increased in 8 subjects by +21% (s.d. +/-11%) and decreases by -23% in one subject. D0 increased for 8 subjects (average +29% s.d. +/- 13%) and decreased by -10% in one. D*, F, Kep, Ktrans, Ve and Vp had no recognizable pattern. At T2, SUVmax, SUVmin, and ADCmean maintained their change direction across all subjects with measurable lesions. The only subject with a complete response at T2 had the highest ADCmin and a change at +44% from baseline. Conclusions: Combined multi-parametric FDG PET/MI (T1). The subject with stable disease at T2 had no significant difference in changes amongst all metrics. Conclusions: FDG PET/MI/SUVmax and ADCmean values obtained after one cycle of neoadjuvant chemotherapy were consistently associated with partial anatomical treatment responses after three cycles. Molecular findings in patients with advanced stage ovarian cancer may allow for early discontinuation of ineffective and toxic treatment.

5570 Poster Session (Board #393), Sat, 1:15 PM-4:15 PM
Correlation of surgeon radiology assessment with laparoscopic scoring in patients with advanced-stage ovarian cancer. First Author: Network: Fleming, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: To determine the correlation between surgeon radiology assessment and laparoscopic scoring in patients with newly diagnosed advanced stage ovarian cancer. Methods: Following IRB approval, 14 gynecologic oncologists from a single institution participated in a blinded review of radiology imaging from 20 patients with advanced stage ovarian cancer. All patients previously underwent laparoscopic debulking surgery (TRS) using a validated scoring method from April 2013 to December 2017. The patients with predictive index value (PIV) scores < 8 were offered primary surgery and those with a score ≥ 8 received neoadjuvant chemotherapy (NACT). Surgeons viewed contrasted CT imaging reports and images from all patients in a blinded fashion and recorded PIV scores using the same validated scoring method. Linear mixed models were conducted to calculate the correlation between radiology and laparoscopic score for each surgeon and as a group. Once the model was fit, the inter-class correlation (ICC) and 95% confidence interval was calculated. Results: Radiology review was performed on 20 patients with advanced stage ovarian cancer who underwent laparoscopic scoring assessment. Most patients had stage IIIC disease (85%) and median laparoscopic score was 9 (range 0-14). Surgeon faculty rank included Assistant Professor (n = 5), Associate Professor (n = 4), and Professor (n = 1). Median experience during the study period with laparoscopic assessment was 13 cases (range 1-28) and TRS was 22.5 cases (range 2-48). The kappa inter-rater agreement was -0.017 (95% CI 0.023 to 0.005) indicating low inter-rater agreement between radiology review and actual laparoscopic score. The ICC in this model was 0.06 (0.02-0.21) indicating that surgeons do not score the same across all the images. When using a clinical cutoff of PIV of 8, the probability of agreement between radiology and actual laparoscopic score was 0.56 (95% CI: 0.49-0.73). Number of laparoscopic cases, TRS cases, or faculty rank was not significantly associated with agreement. Conclusions: Surgeon radiology review did not correlate highly with actual laparoscopic scoring assessment findings in patients with advanced stage ovarian cancer. 44% of patients in our study may have been inadequately triaged by radiology review alone, which may have led to suboptimal TRS. Our study highlights the utility of laparoscopic scoring assessment to determine resectability over radiology assessment alone in ovarian cancer.

5571 Poster Session (Board #394), Sat, 1:15 PM-4:15 PM
Comprehensive genomic analysis of mucinous ovarian cancer reveals unique therapeutic vulnerabilities. First Author: Dane Anthony Cheasley, Peter MacCallum Cancer Centre, North Melbourne, Australia

Background: Mucinous ovarian carcinoma (MOC) is a rare subtype of epithelial ovarian cancer that responds poorly to ovarian chemotherapies and has an unknown etiology. It is diagnostically challenging and can be confused with metastases from gastro-intestinal tract primaries. The GAMuT study is a multi-national effort to understand molecular drivers and cell of origin of this rare tumor and to elucidating identifying targets for a genetic approach to MOC and potential novel therapeutic options. Methods: We performed RNAseq (n = 67), exome sequencing (n = 61), SNP arrays (n = 67) and whole genome sequencing (n = 5) on MOC and precursor lesions. A subset of ~500 genes was further evaluated by targeted sequencing, including 129 MOC, 23 borderline mucinous tumours (non-invasive) and 23 extra-ovarian mucinous metastases. Immunohistochemistry and mycology data was collected for CK7, CK20, ER, PAX8, p53 and HER2 (n = 162-256). Extensive pathology review was performed and associated clinical data obtained. Results: Comparison with TCGA and other data sets showed that MOC are distinct from mucinous tumours from other organs, including colorectal, appendiceal and gastric cancers. Our data supports a clear genetic progression model from benign and borderline precursors to both low- and high-grade MOC. TP53 mutation, ERBB2 amplification and increasing copy number changes were key events associated with progression to invasive disease, including a novel amplication on 5p13. Copy number aberration burden was significantly associated with poor survival. We identified several recurrent mutational events suggesting utility of an existing targeted therapy, including ERBB2 amplification (26%), ERBB3 mutation (4%) and BRAF mutation (9%). MOC could be included in clinical trials for novel agents targeting TP53 missense mutation (46%), RNF43 mutation (12%), PIK3CA mutation (8%) and KRAS/HRAS mutations (60%). Other frequent events included CDKN2A inactivation (57%), ARID1A mutation (9%) and TP53 inactivating mutations (15%). Conclusions: MOC of any grade can derive from a primary ovarian tumour precursor, and is distinct from extra-ovarian metastases. MOC is genetically diverse and advanced disease should be assessed for targetable mutations which may provide novel therapeutic options.
Background: The PARR Olaparib has been approved in maintenance setting for undiagnosed cancers in study design and analysis. Together, this cfDNA-based assay detected a cancer-like signal that was seen between ascites cytological samples and matched tumors. 9 VUS occurred in BRCA2 variant and a concurrent uncertain significance (VUS) in 25 (11.3%) cases, including 3 cases with a BRCA1 P variant and a concurrent BRCA2 VUS. In detail, 47 P variants and 16 VUS were identified in BRCA2 whereas 15 P/LP mutations and 9 VUS occurred in BRCA1. Complete concordance in tumor BRCA test results were seen between ascites cytological samples and matched tumors.

Conclusions: The tumor BRCA test could be implemented in routine diagnostic setting for the diagnosis of non-mucinous and non-borderline OC patients. The test could be performed on FFPE specimens, had a high successful rate and a TAT setting, at diagnosis of non-mucinous and non-borderline OC. The test could be performed on 5 archetypal cytological samples from ascites. Results: All the cases were considered adequate for the NGS analysis according to the tumor cell content (more than 10%) and the DNA yield extracted (more than 10 ng). The tumor BRCA test had a successful rate of 99.1%. The median Turn-Around Time (TAT) was 17 calendar days, from 33 days of the first trimester to 14 days of the last trimester of this analysis. Overall BRCA1 or BRCA2 pathogenic (P)/likely pathogenic (LP) mutations were found in 62 (28.1%) cases and variants of uncertain significance (VUS) in 25 (11.3%) cases, including 3 cases with a BRCA1 P variant and a concurrent BRCA2 VUS. In detail, 47 P variants and 16 VUS were identified in BRCA2 whereas 15 P/LP mutations and 9 VUS occurred in BRCA1.

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Conclusions: The tumor BRCA test could be implemented in routine diagnostic setting for the diagnosis of non-mucinous and non-borderline OC patients. The test could be performed on FFPE specimens, had a high successful rate and a TAT setting, at diagnosis of non-mucinous and non-borderline OC. The test could be performed on 5 archetypal cytological samples from ascites. Results: All the cases were considered adequate for the NGS analysis according to the tumor cell content (more than 10%) and the DNA yield extracted (more than 10 ng). The tumor BRCA test had a successful rate of 99.1%. The median Turn-Around Time (TAT) was 17 calendar days, from 33 days of the first trimester to 14 days of the last trimester of this analysis. Overall BRCA1 or BRCA2 pathogenic (P)/likely pathogenic (LP) mutations were found in 62 (28.1%) cases and variants of uncertain significance (VUS) in 25 (11.3%) cases, including 3 cases with a BRCA1 P variant and a concurrent BRCA2 VUS. In detail, 47 P variants and 16 VUS were identified in BRCA2 whereas 15 P/LP mutations and 9 VUS occurred in BRCA1.
Association of Ki67 expression levels and therapy outcome in low-grade serous ovarian cancer. First Author: J.P. Grabowski, Chanté Campus Virchow-Klinikum, Berlin, Germany.

**Background:** Low-grade serous ovarian cancers (LGSOC) characterize different clinical pattern and lower chemotherapy responsiveness. The expression level of Ki67 is associated with prognosis differences in this patient group. However, Ki67 has not been evaluated as prognostic marker and a predictor of therapy outcome until now. **Methods:** Patients with LGSOC and Ki67 expression results were identified in institutional database. Receiver-operator characteristics (ROC) curve analysis was performed to find cut off values of Ki67 to discriminate patients with residual tumor mass after surgery from maximal debulked patients, and platinum sensitive patients from platinum resistant patients. Odd ratios (OR) and 95% confidence intervals (95% CI) were calculated using univariate and multivariate logistic regression analysis. Two-sided tests p < 0.05 and are considered statistically significant at a 95% confidence interval. The statistical analysis was performed with the IBM SPSS Statistics 25.0. **Results:** A total of 68 patients with LGSOC were included. All patients underwent surgery and 15 (22.1%) patients had residual mass (> 0 mm) after cytoreduction. Sixty-one (89.7%) patients received platinum based first-line chemotherapy. Forty-three patients revealed a recurrence ≥6 months and eleven < 6 months. Patients with Ki67 < 3.6% had significantly higher therapy-free interval (TFI≥6 months), (OR = 13.9, 95%CI 1.62-118.40, p = 0.016). In the multivariate analysis of TFI over 6 months including CA 125, age at diagnosis, peritoneal carcinomatosis and ascites (> 500ml) Ki67 < 3.6% remained significantly (OR = 17.6, 95%CI 1.56-197.52, p = 0.020). Moreover, Ki67 = 3.6% were associated with higher risk of residual mass after surgery (OR = 6.75, 95%CI 1.39-32.87, p = 0.018). **Conclusions:** It is the first study showing association between Ki67% expression and duration of TFI to platinum-based chemotherapy as well as outcome of the surgery in LGSOC. Further prospective trials should be planned to develop predictive models in this patient.

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**Poster Session (Board #400), Sat, 1:15 PM-4:15 PM**

**5577**

**Real-world data analysis of ovarian cancer (OC) maintenance utilization among maintenance eligible patients.** First Author: David Garofalo, Integra Connect, West Palm Beach, FL

**Background:** Approximately 1% of US women will be diagnosed with epithelial OC during their lifetime. OC patients who achieve a response to platinum-based chemotherapy may benefit from maintenance therapy, with the goal of inducing a lasting remission or extending the time interval before progression without any deleterious impact on quality of life. This analysis, based on real world data sourced from US community oncology practices, was designed to assess the current utilization of maintenance therapy among maintenance eligible patients. **Methods:** This analysis utilized the Integra Data Exchange (DTX) database, a deidentified data source from community oncology practice systems (EMR, practice management, paid claims). This retrospective study included 3,629 OC patients with at least two visits between 7/16/16 and 4/16/18. 398 patients who completed 2nd line or later platinum-based chemotherapy for 4-9 cycles and/or had a complete/partial response between 1/1/17 and 7/31/18 were included. Potential maintenance therapy options were monotherapy of PARP inhibitors, bevacizumab, and non-platinum-chemotherapy agents. Rate of maintenance therapy after platinum-based treatment was assessed. **Results:** Our real-world analysis found that 49% of 398 maintenance eligible patients received maintenance therapy at least once following response to 2nd line or later platinum chemotherapy. Among those that received maintenance, 46% received PARPi, 28% bevacizumab, and 26% non-platinum chemotherapy. Further, 56% of women with BRCA mutations received maintenance treatment, compared with 49% of women without BRCA mutations. **Conclusions:** Though there are several options available, 51% of OC women studied who could potentially benefit from maintenance treatment did not receive maintenance. Only 56% of BRCA mutation carriers were targeted for maintenance therapy in the real world. Among patients that receive maintenance therapy following 2nd line or later platinum chemotherapy 46% received a PARPi based regimen. 1) Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA); results from a double-blind, phase 3, randomized controlled trial. Lancet Oncol. 2018 Aug;19(8).

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**Poster Session (Board #401), Sat, 1:15 PM-4:15 PM**

**5578**

**Real-world bevacizumab utilization and outcomes in first-line ovarian cancer.** First Author: Matthew J. Monberg, Merck & Co., Inc., Kenilworth, NJ

**Background:** Bevacizumab (B) is approved in combination with carboplatin and paclitaxel, followed by B monotherapy, for the treatment of advanced ovarian cancer (OC) following surgery. We sought to describe B utilization and outcomes of B in first-line (1L) OC within the US and EU. **Methods:** This cross-sectional study included patients who were actively receiving treatment for OC. Data were collected at a single time point from 2496 patient forms between December 2017 and March 2018 from 343 participating oncologists across the US, France, Italy, Germany, and the UK. Patients were platinum sensitive if progression was noted > 6 months after front line platinum therapy and resistant if the interval was 0-6 months. This analysis included all patients who received chemotherapy with no maintenance or 1L chemo with bevacizumab maintenance. **Results:** B was used in combination with chemo at 1L and as 1L maintenance monotherapy in 11% total study patients. Those receiving 1L + B were more likely to have Stage IV disease, have good performance status (PS) at diagnosis, and receive BRCA testing than patients receiving chemo only. Treatment response, platinum sensitivity, and activities of daily living are shown in the Table. Results did not vary by BRCA status. **Conclusions:** This study highlights differences in patient characteristics and outcomes between patients receiving who received 1L chemo only and those receiving who received B, however, this study was not designed to formally compare 1L treatment options.

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**Poster Session (Board #402), Sat, 1:15 PM-4:15 PM**

**5579**

**Real-world data analysis of ovarian cancer (OC) maintenance utilization among maintenance eligible patients.** First Author: David Garofalo, Integra Connect, West Palm Beach, FL

**Background:** Approximately 1% of US women will be diagnosed with epithelial OC during their lifetime. OC patients who achieve a response to platinum-based chemotherapy may benefit from maintenance therapy, with the goal of inducing a lasting remission or extending the time interval before progression without any deleterious impact on quality of life. This analysis, based on real world data sourced from US community oncology practices, was designed to assess the current utilization of maintenance therapy among maintenance eligible patients. **Methods:** This analysis utilized the Integra Data Exchange (DTX) database, a deidentified data source from community oncology practice systems (EMR, practice management, paid claims). This retrospective study included 3,629 OC patients with at least two visits between 7/16/16 and 4/16/18. 398 patients who completed 2nd line or later platinum-based chemotherapy for 4-9 cycles and/or had a complete/partial response between 1/1/17 and 7/31/18 were included. Potential maintenance therapy options were monotherapy of PARP inhibitors, bevacizumab, and non-platinum-chemotherapy agents. Rate of maintenance therapy after platinum-based treatment was assessed. **Results:** Our real-world analysis found that 49% of 398 maintenance eligible patients received maintenance therapy at least once following response to 2nd line or later platinum chemotherapy. Among those that received maintenance, 46% received PARPi, 28% bevacizumab, and 26% non-platinum chemotherapy. Further, 56% of women with BRCA mutations received maintenance treatment, compared with 49% of women without BRCA mutations. **Conclusions:** Though there are several options available, 51% of OC women studied who could potentially benefit from maintenance treatment did not receive maintenance. Only 56% of BRCA mutation carriers were targeted for maintenance therapy in the real world. Among patients that receive maintenance therapy following 2nd line or later platinum chemotherapy 46% received a PARPi based regimen. 1) Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA); results from a double-blind, phase 3, randomized controlled trial. Lancet Oncol. 2018 Aug;19(8).

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**Poster Session (Board #403), Sat, 1:15 PM-4:15 PM**

**Clinical outcome of sequential chemotherapy after immune checkpoint inhibitors in advanced ovarian cancer.** First Author: Luisa Bonilla, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

**Background:** Immunomodulation through check point inhibition is an important treatment strategy in many cancers. In ovarian cancer (OC) response rates with immune checkpoint inhibitors (ICI) alone are around 10%. Chemotherapy antitumoural effect is driven by cytotoxicity and immunomodulatory effect. ICI treatment reduces tumour induced immune-tolerance improving immune competence. Clinical trial for chemotherapy effect. We choose to investigate clinical outcomes of chemotherapy post ICI in women with OC. **Methods:** The Tumor Immunotherapy Program (TIP) database at the Princess Margaret Cancer Centre identified patients with OC treated with chemotherapy after ICI from 2011 to 2018. Evaluation of clinical outcomes including response rate (RR), progression free survival (PFS) and overall survival (OS) was assessed for pre ICI, ICI and post ICI. **Results:** 40 women with OC were treated with chemotherapy after ICI. 90% had high grade serous histology, 7.5% carcinosarcoma and 2.5% low grade serous. Median number of pre ICI treatment lines was 3 (1-8) and 2 (1-6) in the post ICI setting. Median time of pre ICI treatment was 6.5m and 5m in the first post ICI treatment. Median time of pre ICI RR was 35%. First treatment in post ICI RR was 35%. RR for each treatment used in post ICI was 9% for liposomal doxorubicin, 25% for single agent platinum, 29% for weekly paclitaxel and 57% for chemotherapy with bevacizumab. Median PFS in the pre ICI treatment was 6.5m and 5m in the first post ICI treatment. Median PFS and OS for all the population was 53m and 54m respectively. **Conclusions:** ICI are associated with modest activity in OC, planned clinical trials exploring systematic sequential therapy integrating ICI, targeted agents and chemotherapy are needed.
5581  Poster Session (Board #404), Sat, 1:15 PM-4:15 PM
Tumor stroma proportion to predict platinum chemotherapy resistance in primary ovarian carcinomas: A prospective study. First Author: Emil Lou, University of Kentucky, Hopkins, KY.

Background: Platinum chemotherapy resistance occurs in approximately 25% of patients with ovarian carcinoma and represents a major barrier to effective care of this patient population. To date there are no effective nor validate predictive biomarkers of chemoresistance of ovarian carcinomas. We performed a prospective trial designed to enroll patients with ovarian masses suspicious for ovarian cancer, with the goal of identifying tumor-based predictive biomarkers of platinum resistance. Methods: 60 women were enrolled on the study. Tumor specimens were collected from 49 of these women with newly diagnosed pelvic masses, of which 29 were found to have histopathologically proven primary ovarian carcinoma. Of these primary malignant cases, 24 had specimens accessible for assessment of tumor-stroma proportion and data available regarding chemosensitive vs chemoresistant status. The medical record was used to assess tumor stroma proportion and tumor stroma proportion scored as high proportion. Patients with chemoresistance had tumor stroma proportions >50%; 73.7% of cancer patients with chemoresistant tumors had proportions >50% (p-value 0.047). Expression of miR29b or 199a did not significantly correlate with chemoresistance status. Conclusion: Tumor stroma proportion is a useful predictive biomarker of platinum chemoresistance. If validated in larger datasets, it would be a relatively inexpensive and helpful tool for tailoring treatment strategies and clinical decision-making in women with ovarian cancer.

5582 Poster Session (Board #405), Sat, 1:15 PM-4:15 PM
A phase II trial of durvalumab with or without tremelimumab in patients with persistent or recurrent endometrial carcinoma and endometrial carcinosarcoma. First Author: Maria M Rubinstein, Memorial Sloan Kettering Cancer Center, New York, NY.

Background: Monoclonal antibodies Durvalumab (D) and Tremelimumab (T) inhibit binding of programmed cell death ligand 1 (PDL1) to PD1 and inhibit activation of cytotoxic T-lymphocyte-associated protein 4 (CTLA4), respectively, in improving immunosurveillance. There is rationale to study D and T based on recent genomic and tumor microenvironment evaluation of endometrial cancer (EC). Methods: Eligible patients (pts) were randomized to D or T. Pts received D 1500 mg intravenously (IV) every 4 weeks (wks), DT therapy pts received D 1500 mg IV every 4 wks and T 75 mg IV every 4 wks for 4 cycles, followed by D 1500 mg IV every 4 wks until progression or unacceptable toxicities. Pts were stratified by histology with 10 carcinosarcoma or MSI-H EC pts per arm. Efficacy assessments were every 8 wks and treatment related adverse events (TRAEs) were assessed per CTCAE v.4.03. The primary endpoint was overall response rate (ORR) by RECIST v1.1. Descriptive statistics and 90% one sided CI are reported. Progression free survival (PFS) rate at 24 wks (PFS24m) was estimated by Kaplan Meier method. OS was analyzed using the Kaplan-Meier method, log-rank test, Cox proportional hazards models, and propensity score-matched analyses. In order to control the selection biases, we performed Landmark analysis, and survival analysis by the sequence of chemotherapy and TAH. Separate survival analysis was performed for patients who received chemotherapy plus definitive pelvic radiotherapy (RT) or chemotherapy plus TAH and definitive pelvic RT. Results: From 2010 to 2014, 1,809 uterine cancer patients with distant organ metastasis were enrolled at participating centers. The RR of 13 cases; 0.001). Separate survival analyses showed chemotherapy plus definitive pelvic RT or chemotherapy plus TAH and RT were both superior to chemotherapy alone. Conclusions: In this large contemporary analysis, uterine cancer patients with distant organ metastasis receiving TAH and chemotherapy had substantial longer survival than patients treated with chemotherapy alone. Prospective trials evaluating TAH for metastatic uterine cancer are warranted.

5583 Poster Session (Board #406), Sat, 1:15 PM-4:15 PM
Association of total hysterectomy with survival among newly diagnosed uterine cancer patients with distant organ metastasis. First Author: Yue-feng Wang, University of Tennessee Health Sciences Center, Memphis, TN.

Background: There is growing evidence that definitive local therapies (surgery or radiotherapy) may increase patient’s survival for some types of metastatic cancers. However, the role of total abdominal hysterectomy (TAH) for newly diagnosed uterine cancer with distant organ metastasis has not been established. The objective of this study is to determine the potential overall survival (OS) benefit associated with TAH for distant metastatic uterine cancer. Methods: The National Cancer Database was analyzed to evaluate OS for newly diagnosed uterine cancer patients with metastasis to brain, lung, liver, bone or distant lymph node, treated with chemotherapy with or without TAH. Those without treatment, treated with definitive pelvic radiotherapy, or without baseline variables were excluded. OS was analyzed using the Kaplan-Meier method, log-rank test, Cox proportional hazards models, and propensity score-matched analyses. In order to control the selection biases, we performed Landmark analysis, and survival analysis by the sequence of chemotherapy and TAH. Separate survival analysis was performed for patients who received chemotherapy plus definitive pelvic radiotherapy (RT) or chemotherapy plus TAH and definitive pelvic RT. Results: From 2010 to 2014, 1,809 uterine cancer patients with distant organ metastasis received chemotherapy alone and 1,388 patients received chemotherapy plus TAH. At a median follow-up of 13.4 months, addition of TAH to chemotherapy was associated with improved survival on univariate (HR 0.57; P < 0.001) and multivariate analysis (HR 0.59; P < 0.001) compared to chemotherapy alone. Propensity score-matched analysis demonstrated superior median survival (19.8 vs 11.0 months) and 2-year OS (44% vs 28%) with TAH (multivariate HR 0.59; P < 0.001). Landmark analyses limited to long-term survivors of ≥0.5, ≥1, and ≥10 years showed improved OS with TAH in all subgroups (all P < 0.05). The benefit of TAH was present among not only those involving one metastatic site (HR 0.59; P < 0.001), but also those involving multiple metastatic sites (HR 0.60; P < 0.001). Separate survival analyses showed chemotherapy plus definitive pelvic RT or chemotherapy plus TAH and RT were both superior to chemotherapy alone. Conclusions: In this large contemporary analysis, uterine cancer patients with distant organ metastasis receiving TAH and chemotherapy had substantial longer survival than patients treated with chemotherapy alone. Prospective trials evaluating TAH for metastatic uterine cancer are warranted.

5584 Poster Session (Board #407), Sat, 1:15 PM-4:15 PM
A phase II, open labeled, single-arm study of dose-dense paclitaxel plus carboplatin in advanced or recurrent uterine corpus cancer. First Author: Kensuke Hori, Department of Obstetrics and Gynecology, Kansai Rosai Hospital, Amagasaki, Japan.

Background: We studied the effectiveness and safety of dose-dense paclitaxel plus carboplatin in advanced or recurrent uterine corpus cancer. Methods: The patient eligibility criteria were women aged 20–75 years with histologically confirmed uterine corpus cancer, FIGO stage III who had residual tumors, FIGO stage IV, and recurrence after first-line radical treatment, or second-line chemotherapy or radiotherapy. They received paclitaxel (80 mg/m², days 1, 8, 15) + carboplatin (area under the curve 5, day 1 every 3 weeks). The primary endpoint was the response rate (RR). The secondary endpoints were feasibility, progression-free survival, overall survival, and adverse effects. The threshold RR was set to 40%. The number of necessary cases calculated with a type I error of 5% and power of 80% was 44. Considering the existence of dropped cases, we set the target number of cases in this study to 48. Results: Forty-eight patients were registered, and 45 were eligible to receive the treatment. The median age of the patients was 61 years (43–76). Twenty-two patients had recurrence; the others had primary advanced corpus cancer. On histology, there were 10 cases of serous carcinoma, 3 cases of endometrioid carcinoma G3, 2 cases of carcinosarcoma, and 2 cases of clear cell carcinoma. Twenty-eight patients (62%) could receive 6 or more cycles of chemotherapy. The RR (complete, 13 cases; partial, 20 cases) was 73.3% (60.7–86.0% 95% confidence interval). Conclusions: Dose-dense paclitaxel plus carboplatin was safe and effective for advanced or recurrent uterine corpus cancer. Clinical trial information: R00019874 UMIN000017138.

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Lynch-like syndrome in endometrial cancer: Features of a growing population.

First Author: Sushmita Gordhandas, NewYork-Presbyterian/Weill Cornell Medical Center, New York, NY

Background: Current guidelines recommend screening all endometrial cancers (EC) and colorectal cancers (CRC) for defects in DNA mismatch repair (MMR). Tumor screening combined with germline genetic testing can categorize patients into three groups: intact-MMR, Lynch syndrome (LS), and Lynch-like syndrome (LLS). Our objective was to describe features of this growing population of patients with EC in Germany and compare to existing CRC literature.

Methods: A systematic search of databases between 1990-2018 identified studies of EC patients with tumor testing (MMR immunohistochemistry or microsatellite instability) and germline assessment for LS. Data on clinicopathological features and outcomes were abstracted when available. Associations between LS, LLS, and intact-MMR were analyzed using descriptive statistics.

Results: The comprehensive search produced 3,427 publications; 29 met inclusion criteria. Abstracted data and features of each group are presented in the table. Conclusions: In EC, LLS closely resembles LS with younger age at diagnosis, more advanced stage and higher grade as compared to patients with intact-MMR. LLS in EC is similar to intact-MMR in regard to histology, and family history of LS-associated cancer. The CRC literature is limited, but reports LS and LLS have similar stage, grade and histology. In CRC, LS and LLS are diagnosed at a younger age, and are more likely to have family history of LS-associated cancers compared to intact-MMR. Features of EC with intact-MMR, LLS, and LS.

Impact of non-compliance with guidelines in early type 1 endometrial cancers management, study from FRANCOYIN group. First Author: Hélène Costaz, Centre GF Leclerc, Dijon, France

Background: To standardize surgical practices, ESMO-ESGO-ESTRO consensus conference published in 2016 new guidelines on the management of endometrial cancer. The main objective of this study was to evaluate the impact of non-compliance with current surgical guidelines on disease-free survival and overall survival.

Methods: 852 patients with presurgical stage I and II type 1 endometrial cancer were included in a multicenter retrospective study, conducted between January 2000 and November 2015. The main objective of this study was to evaluate the impact of non-compliance with current surgical recommendations on overall survival and disease-free survival.

Results: Our study shows that 34.3% of patients (n = 292) did not benefit from optimal surgical treatment. These patients did not have a lob-maortic lymphadenectomy (LAL) and were at high risk of recurrence.

There is a significant difference in disease-free survival in favor of patients undergoing surgery according to the recommendations, (Hazard Ratio (HR): 0.37 (Confidence interval (95% CI): 0.26-0.54), p < 0.001). In multivariate analysis, optimal surgical procedure performance is an independent factor for disease-free survival with HR at 2.04 (95% CI: 1.14-3.68), p = 0.01. There is a significant difference in overall survival in favor of patients undergoing surgery according to the recommendations, (HR: 0.31 (95% CI: 0.19-0.49), p < 0.001). In multivariate analysis, there is a trend toward significance with HR: 2.24 (95% CI: 1.5-05), p = 0.05. Older patients, patients with a larger BMI, patients with no indication of LALT at the preoperative ESMO classification, and no node involvement in are factors contributing to the decision of not to perform LALT: p < 0.001, p = 0.03, p < 0.001 and p < 0.001 respectively. Conclusions: This study shows that patients with early type 1 endometrial cancer have improved recurrence-free survival and a statistical trend for an increased overall survival when recommended surgery is performed. Despite the current context of therapeutic de-escalation, we must strive to achieve the recommended optimal surgery, even if it requires secondary surgical revision, to avoid underestimation of patients with early stage of disease. To improve endometrial cancer prognosis, amelioration of the preoperative assessment by increasing the sensitivity of emboli detection should be considered.

Mismatch repair deficiency as a predictor of adjuvant radiotherapy response in endometrial endometrial carcinoma. First Author: Stefan Kromoss, Department of Women’s Health, Tuebingen University Hospital, Tuebingen, Germany

Background: Adjuvant radiotherapy improves progression-free survival in intermediate and high-risk endometrial cancer. However, so far there is no evidence of improved overall or disease-specific survival after adjuvant radiotherapy. There is accumulating evidence that MMR proteins are involved in DNA repair following radiotherapy. We investigated the predictive value of MMR status in terms of survival benefit after adjuvant radiotherapy in patients with stage IB/II, grade 3 endometrial endometrial carcinoma (EEC).

Methods: A retrospective multicenter cohort study was performed to compare patients with histopathologically confirmed stage IB/II grade 3 EEC with and without adjuvant radiotherapy. Patients were classified according to the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMiSe) identifying ECGs as either MMR-deficient, POLE, p53abn or p53wt. Multi-variable Cox regression analysis explored associations between patient characteristics, adjuvant treatment and outcome.

Results: A total of 128 patients were analyzed, including 57 patients (43.0%) with MMR-deficient EECs. Baseline characteristics were comparable, except a higher proportion of MMR-deficient EECs were stage II (36.8% vs. 15.5%, p = 0.066). Eighty-two patients (64.1%) received adjuvant radiotherapy (external beam (n = 55), vaginal brachytherapy (n = 27)). In multivariate analysis, adjuvant radiotherapy was independently associated with improved disease-specific survival in patients with MMR-deficient EECs (hazard ratio 0.19 (95% CI: 0.05 - 0.77), but not in patients with MMR-proficient EECs (hazard ratio 0.92, 95%-CI 0.37 - 2.31). Conclusions: Adjuvant radiotherapy improved disease-specific survival in patients with MMR-deficient EECs, but not in those with MMR-proficient EECs. This study demonstrates the predictive ability of MMR IHC to identify women who likely have increased benefit from radiotherapy.

Genomic biomarkers of recurrence in low-grade, early-stage endometrial adenocarcinoma. First Author: Katie Lee Hawang, Harvard Radiation Oncology Program, Boston, MA

Background: Endometrial cancer is the most common gynecologic malignancy in developed countries with over 60,000 new cases diagnosed in the United States each year. Adjuvant therapy is often omitted for low-risk, early-stage disease (FIGO stage IA, grade 1) but 1 in 20 women suffer recurrence after surgery alone. Hence, there is an important need for biomarkers of recurrence in this population to guide therapeutic management. Methods: We retrospectively analyzed 74 patients with FIGO stage 1A, 1 grade 1 endometrioid endometrioid adenocarcinoma treated at our institution with hysterectomy alone between 2009-2016. All patients had targeted genomic assessment of their tumors (OncoPanel; somatic mutations, copy number variations and structural variants across 300 cancer genes). The primary outcome of interest was freedom from recurrence (FFR). Outcomes were compared by the logrank test and survival estimates calculated by Kaplan-Meier method. Results: We identified 14 patients who recurred at a median time of 23.6 months after surgery and 60 patients without recurrence at a median follow-up of 38.9 months. Age (median 57 years; log-rank p = 0.91) and BMI (median 31 kg/m2; log-rank p = 0.21) were not associated with risk of recurrence. The median somatic mutation count in the cohort was 8. Patients with more than 8 somatic mutations had a significantly higher risk of recurrence (3-year FFR: 74% vs 90%; log-rank p = 0.004). At the level of individual genes, there were four genes that were significantly associated with recurrence: CTNMB1, RHPN2, SF2, SQSTM1) as determined by a validated 300-gene panel used in routine clinical practice as prognostic biomarkers for patients with low-risk, early-stage endometrial endometrioid adenocarcinoma. These patients may benefit from the addition of adjuvant therapy. Validation with larger cohorts and prospective studies is warranted.

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5589 Poster Session (Board #412), Sat, 1:15 PM-4:15 PM
The prognostic significance of white adipose tissue inflammation in advanced-stage, high-grade, and serous endometrial cancers. First Author: Vance Brown, Memorial Sloan Kettering Cancer Center, New York, NY
Background: Obesity is associated with worse outcomes in endometrial cancer, but the underlying mechanisms are poorly understood. In other obesity-related cancers, white adipose tissue inflammation (WATi) is an independent predictor of shortened cancer-specific survival. We hypothesized that WATi occurs in patients with endometrial cancers and is a prognostic marker of shortened survival. Methods: We conducted a retrospective cohort study in which patients with stage III or IV grade 3 endometrioid (G3) or any endometrial cancer were included. Eligible subjects had archived omental and/or perinodal adipose tissue available, WATi was detected by the presence of dead/dying adipocytes surrounded by CD68+ macrophages forming a crown-like structure (CLS). Clinicopathologic data were abstracted from medical records. For association with WATi, Wilcoxon rank sum test was used for continuous variables, Fisher’s exact test for categorical variables. Log rank test was used to assess the association of WATi and survival. Results: A total of 95 patients who underwent debulking surgery from 2001–2017 were included (median age, 67 years; range, 33-86 years). Of these, 51 (54%) had WATi. The prevalence of WATi was unaffected by race, tumor histology or stage. Patients with WATi had a higher median body mass index (BMI) than those without WATi (32.17 and 27.33 kg/m², respectively; \( P = 0.001 \)) and were more likely to be obese (P = 0.01). Patients with the most severe WATi \(( n = 20)\) had shorter progression-free survival (PFS) and a trend suggesting shorter overall survival (OS) than those with less severe or no WATi \(( n = 75)\) (median PFS 15.8 vs 59.2 months, respectively, \( P = 0.001 \)); median OS 33.9 vs 59.4 months, respectively, \( P = 0.059 \)). Conclusions: Visceral adipose inflammation is prevalent in obese patients with advanced endometrial cancer and severe endometrioid G3. Severe inflammation was associated with significantly worse PFS.

5590 Poster Session (Board #413), Sat, 1:15 PM-4:15 PM
Identifying a potential biomarker for anti-PD-1 immunotherapy in patients with advanced stage, surgically-resectable endometrial cancer. First Author: Katherine Cynthia Fuh, Washington University, St. Louis, MO
Background: The FDA approval of pembrolizumab for patients with MSI-H or dMMR tumors has led to the treatment of a select cohort of endometrial cancer (EC) patients. We sought to ascertain tumor immune modulatory effects in the front-line setting for advanced stage III/IV EC patients regardless of MSI-H or dMMR. The primary objective was to determine the safety of preoperative and maintenance pembrolizumab. The secondary objective was to examine pembrolizumab-induced changes in peripheral immune effector phenotype in order to identify potential biomarkers of clinical response. Methods: In an open label, single-arm Phase I trial, 8 EC patients were treated with 2 doses of preoperative pembrolizumab IV prior to surgery followed by chemotherapy and 4 doses of pembrolizumab IV. As an initial study, pre- and post-treatment (on the day of surgery) peripheral blood was collected from 3 patients as well as a healthy control and processed for high-dimensional single-cell mass cytometry (CyTOF) using an optimized antibody panel. Results: Six of 8 patients completed the treatment. One patient had rapid cancer progression and another had an exacerbation of comorbidities. Peripheral blood from 3 patients with pathologic response were then immunoprofiled using CyTOF. Data analysis revealed that the frequencies of CD8+ T cells, B cells and CD56+CD16+ NK cells were lower, whereas the frequency of CD14+CD16+HLADR+ classical monocytes was higher in the cancer patients compared to controls. Conclusions: This is the first trial to evaluate the use of neoadjuvant pembrolizumab in advanced stage EC patients. Here, we present peripheral immune correlate data and show an increase in markers of activation in patients with pathologic responses to pembrolizumab. Additional data from this ongoing study will help us to identify candidate predictive biomarkers. Clinical trial information: NCT02630823.

5591 Poster Session (Board #414), Sat, 1:15 PM-4:15 PM
Trends of endometrial cancer incidence from 2000 to 2015 in the United States. First Author: V V Pavan Krase, Mukhtinathalapati, John Striper Hospital of Cook County, Chicago, IL
Background: Recent studies have shown that obesity related cancers are increasing in incidence in the US as the rates of obesity rise and some cancers, like colorectal cancer, are occurring in younger age groups. We studied trends in incidence of endometrial cancer (EC), one of the obesity related cancers, in a population wide analysis. Methods: We analyzed data from all cases of EC between 2000 and 2015 from 18 US cancer registries using the National Cancer Institute’s Surveillance, Epidemiology and End Results Program. SEER*Stat was used to query the database for annual percent changes (APC), incidence rates and percent change in incidence across different age groups, years of diagnosis, histologic subtypes, grade and race. We also studied the reported rates and trends of obesity in the US. Results: APC of adjusted EC incidence between 2000 and 2015 was +0.9% (95% confidence interval (CI) 1.1-0.6, p-value <0.05). Incidence of EC rose from 17.8 per 100,000 to 19.7 per 100,000 during the same duration. APC for EC incidence for age groups 20-39 and >40 were +3.2% (p-value <0.05) and +8.6% (p value <0.05), respectively. For the age group 20-39, endometrioid EC was the only histologic subtype that rose in incidence, with an APC of +5.5% and absolute percentage change of 156%. The APC of EC in 20-39 age group was more for whites (3.5%, p-value <0.05) and Asians (2.2%, p-value<0.05) than blacks (1.8, p-value <0.05). CDC reported an increase in obesity rates in adults from 30.5% in 2000 to 37.7% in 2014. Table shows trends of EC incidence in age groups 20-39 and >40 years across various histologic subtypes. (Abbreviations: S significant, NS not significant, NC not counted, NC not counted). Conclusions: Endometrial cancer, especially of endometrioid histology, is increasing in incidence and is occurring more often in the younger population. The concomitant rise in obesity rates during the same period point towards a possible causality of the increased in incidence of EC. Population based strategies needed to decrease the trends in obesity so as to decrease the risk of endometrial cancer in younger women.

5592 Poster Session (Board #415), Sat, 1:15 PM-4:15 PM
p53 and p16 expression profiles reveal three prognostically relevant subgroups in vulvar squamous cell carcinoma (VSCC). A TMA based study by the AGO-CaRE-translational study group. First Author: Linn Lena Woelber, AGO & Department of Gynecology and Gynecologic Oncology, University Medical Center Hamburg-Eppendorf, Germany, Hamburg, Germany
Background: Currently, there are two major pathways for tumorigenesis of vulvar squamous cell carcinoma (VSCC) – an HPV-dependent with p16 overexpression as a surrogate for HPV-associated transformation and an HPV-independent route linked to lichen sclerosus, characterized by p53 mutation. A possible correlation of HPV dependency with a favourable prognosis has been proposed. Methods: The AGO CaRE-1 study is a retrospective survey of pts with primary VSCC FIGO stage ≥IB (UICC-TNM version 6) treated at 29 gynecologic cancer centers in Germany 1998-2008 (n = 1,618). For this CaRE-translational sub-study available FFPE tissue was collected centrally (n = 648). A tissue micro array (TMA) was constructed; p16 and p53 expression was determined by immunohistochemistry (IHC). HPV status and subtype were analyzed by PCR. Results: p16 IHC was interpretable in 550 TMA spots and considered positive in 166/550 (30.2%). HPV DNA was detected in 78.4% of the p16+ tumors, with HPV 16 being the most common subtype (88.3%). Pts with p16+ tumors were younger at diagnosis (63 vs. 70 yrs for p16−; p = 0.001); showed lower rates of lymph-node involvement (29.0% vs. 39.7%; p = 0.021). p53 IHC was interpretable in 597 spots, 187/597 (31.3%) were considered positive. Pts with p53+ tumors were older at first diagnosis (71 vs. 66 yrs; p = 0.001) and showed lymph-node involvement more often (43.3% vs. 31.1%; p = 0.007). There were no relevant number of tumors with neither p16 nor p53 overexpression (221/550); while co-expression of p53 and p16 was rare (12/535). For survival analyses, three groups were defined: p53+(n = 163), p16+p53+(n = 151) and p16-p53-(n = 221). 2-y disease-free (DFS) and overall survival (OS) rates were significantly different between the groups: DFS: p53+ 47.0%; p16−/p53− 53% and p16+p53+ 65.5% (p < 0.001); OS: 70.4%, 72.6% and 82.7% (p = 0.003), respectively. Adjustment for age and nodal status showed consistent p16 and p53 effects regarding DFS. Conclusions: p16 overexpression is associated with an improved prognosis in VSCC p53 positive patients, indicating that VSCC patients with neither p16 nor p53 overexpression are an adverse outcome. Our data provide evidence of a clinically relevant third subgroup of VSCC with a p53−/p16− phenotype showing an intermediate prognosis that needs to be further characterized.
TPS5594
Poster Session (Board #417a), Sat, 1:15 PM-4:15 PM

BEATcc (ENGOT-Cx10/GECICO 68-G/GOG3030/JGOG1084): A randomized, open-label, phase III study of cisplatin and paclitaxel chemotherapy with pembrolizumab (CTx plus B) versus without atezolizumab (Atz) as first-line treatment for metastatic, persistent, or recurrent (m/r) carcinoma of the cervix (CCx). First Author: Ana Odkin, Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: The combination of CTx plus B is first-line treatment for most patients (pts) with m/r CCx not amenable for local therapy based on GOG240 results. GOG240 regimen showed an improvement in overall survival (OS) compared to CTx alone: 16.8 vs. 13.3 months (HR 0.77, 95% CI 0.62-0.95, p = 0.007). However, further improvement in first-line treatment outcomes is an unmet need. Immune-checkpoint inhibitors are breakthrough therapies in several tumor types, and their development in CCx is supported by a strong scientific rationale. Human papillomavirus infection (HPV) causes more than 90% of CCx cases, PD-L1 is a HPV biomarker and is found frequently upregulated in CCx. Nivolumab and pembrolizumab (Pb) (anti-PD-1 antibodies) have shown response rates of 26.3% and 14.3%, respectively, in pretreated m/r CCx. This has led to the recent FDA approval of Pb in pretreated PD-L1+ m/r CCx. The BEATcc trial (NCT03556839) evaluates the addition of the anti-PD-L1 Atez to GOG240 regimen as first line treatment for m/r CCx, following the synergistic rationale between anti-VEGF agents and PD-L1/PD-1 blockade.

Methods: Eligible pts: m/r CC with adequate organ function. Pts will be randomized 1:1 to either Arm A (control): C 50 mg/m² + Tx 175mg/m² + B 15 mg/kg (CTx plus B) i.v. D1 Q3W or Arm B (experimental): CTx plus B + Atz 1200 mg i.v. D1 Q3W. Stratification factors: prior chemo-radiation, histology and Chemotherapy backbone (CTx vs carboplatin-Tx). Treatment is planned until disease progression, unacceptable toxicity or withdrawal of consent. Pts with a complete response after ≥6 cycles or those with unacceptable CTx toxicity may be allowed to continue only on biologics therapy. An Independent Data Monitoring Committee will analyze the safety of the first 12 pts in the experimental arm completing 2 treatment cycles. The primary endpoint is OS. The study started enrolling in October 2018 and will enroll approximately 404 pts across Europe, Japan, and the US. Clinical trial information: NCT03556839.

TP5595
Poster Session (Board #411b), Sat, 1:15 PM-4:15 PM

KEYNOTE-826: A phase 3, randomized, double-blind, placebo-controlled study of pembrolizumab plus chemotherapy for first-line treatment of persistent, recurrent, or metastatic cervical cancer. First Author: Ronnie Shapira-Frommer, Sheba Medical Center, Ramat-Gan, Israel

Background: Cervical cancer arises in the setting of persistent infection with high-risk human papillomavirus subtypes. Many patients with early-stage and locally advanced carcinoma can be salvaged with radical surgery and chemoradiation, respectively. However, women with recurrent/metastatic disease represent a poor prognostic group with high unmet clinical needs. In 2014, because viral tumor antigen-specific T cells reside predominantly in programmed cell death 1–expressing T-cell compartments, checkpoint inhibition may unleash a diverse antitumor T-cell response. Based on the synergistic rationale between anti-VEGF agents and PD-1/PD-L1 blockade. The strongest for short course, hypofractionated radiation regimens. We hypothesize treatment with atezolizumab with hypofractionated radiation therapy will improve objective response rate (ORR) compared with atezolizumab alone in patients with recurrent, persistent, or metastatic cervical cancer. Methods: The study is designed as a prospective, single arm, nonrandomized, open-label, phase II trial of stereotactic body radiation therapy (SBRT) with 24 Gy in 3 fractions to patients with ≥2 metastatic sites followed 1 week later by atezolizumab (1200 mg IV every 3 weeks) for patients with recurrent, persistent, or metastatic cervical cancer. Dose reductions will not be allowed. The primary objective of the study is to evaluate the ORR by Immune-Modified Response Evaluation Criteria in Solid Tumors (irRECIST) criteria following SBRT and atezolizumab. Secondary endpoints include progression-free survival, overall survival, local control, and adverse events. Correlative aims include assessing blood and tissue biomarkers (i.e., PD-L1, mutation burden, TCR repertoire etc.) for association with clinical benefit. A total of 26 patients will be enrolled. An interim analysis will be performed to assess efficacy after 13 patients become evaluable. This study is open with 2 patients enrolled at the time of submission. Clinical trial information: NCT03614949.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: CCRT with PD-1/PD-L1 pathway blockade may promote a more immunogenic treatment combinations involving standard-of-care platinum-based chemotherapy (chemo), VEGF inhibitor bev, anti-PD-L1 antibody durva and PARP inhibitor olap, in women with newly diagnosed advanced OC. Methods: Eligible pts for this double-blind, randomized, Phase III study must have newly diagnosed, advanced, high-grade epithelial OC and either completed primary surgery or plan to have interval debulking surgery. Depending on their tumor BRCA mutation (tBRCAm) status (determined by central test), pts will join one of two independent cohorts. Pts in the non-tBRCAm cohort (n=906) will be randomized (1:1:1) before cycle 2 to: a) chemo + bev + placebo (for 6 cycles); b) chemo + bev + durva (5 cycles); c) chemo + bev + durva (6 cycles) followed by bev + durva (1120 mg q3w [total 15 months]) + placebo (tablets) maintenance treatment; or c) chemo + bev + durva (6 cycles) followed by bev + durva + olap (300 mg bd tablets [24 months]) maintenance treatment. Pts in the open-label tBRCAm cohort (n=166) will receive: a) chemo + bev + durva (6 cycles) followed by bev + durva + olap maintenance therapy, with optional use of bev. The primary endpoint of progression-free survival will be assessed by modified RECIST 1.1. Key secondary endpoints include overall survival, overall response rate and duration of response. Enrollment began in January 2019. Clinical trial information: NCT03737643.

Methods: ANITA (NCT03598270) is a phase III, randomized (1:1), double-blind, multi-center study to assess the efficacy of the addition of Atz to platinum-based doublet CT followed by maintenance niraparib in combination with placebo or Atz, according to randomization, if experiencing response or stable disease by RECIST after CT. Stratification factors: 1) Platinum-based regimen (paclitaxel-carboplatin vs gemcitabine-carboplatin vs PLD-carboplatin); 2) Platinum-free interval (6-12 vs 13-24 months); and 3) BRCA status (mutated vs non-mutated). Dose of Atz is 1200 mg q3w or 840 mg q2w depending on the platinum-based regimen selected. Niraparib initial dose (300 vs 200 mg) is decided based on body weight and platelet counts after CT according to RADAR analysis. Primary endpoint is PFS based on investigator assessment by RECIST v1.1. Clinical trial information: NCT03598270.

Initial Randomization Scheme

<table>
<thead>
<tr>
<th>Treatment period</th>
<th>Arm 1*</th>
<th>Arm 2</th>
<th>Arm 3</th>
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<tbody>
<tr>
<td>Chemotherapy</td>
<td>SOC + IV placebo</td>
<td>SOC + IV placebo</td>
<td>SOC + durvalimab + olap (if progression in arm 1, or 2 of pts based on their biomarker status). Clinical trial information: NCT03602859.</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Oral bev + durva</td>
<td>Orally administered durvalimab + bev (for 2 years)</td>
<td>Orally administered durvalimab + placebo (for 2 years)</td>
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*No BRCAm pts will be randomized to arm 1 following SOLO1 results.
**TPS5601**  
Poster Session (Board #420b), Sat, 1:15 PM-4:15 PM  
AGO-OVAR 2.29 (ENGOT-ov34): Atezolizumab in combination with bevacizumab and chemotherapy versus bevacizumab and chemotherapy in recurrent ovarian cancer (ROC). First Author: Frederik Maene, AGO & National Center for Tumor Disease/Department of Gynecology, University of Heidelberg, Heidelberg, Germany  

**Background:** A standard non-platinum based treatment option in patients with relapsed ovarian cancer is bevacizumab in combination with paclitaxel or pegylated liposomal doxorubicin, but responses are still short-lived. Checkpoint-inhibitors as single agent have limited activity in ovarian cancer. However, the role of the checkpoint-inhibitor like atezolizumab, in addition to chemotherapy and bevacizumab in ovarian cancer is so far undefined. **Methods:** AGO-OVAR 2.29 is a randomized (1:1), double blinded, phase III trial evaluating the efficacy and safety of atezolizumab plus bevacizumab and chemotherapy (weekly paclitaxel or pegylated liposomal doxorubicin) compared with placebo plus bevacizumab and chemotherapy in patients with recurrent ovarian-, fallopian tube, or primary peritoneal cancer with 1st or 2nd relapse within 6 months after platinum-based chemotherapy or 3rd relapse. A tumor biopsy available at study entry for PD-L1 testing is mandatory. Patients are treated with chemotherapy plus bevacizumab +/- atezolizumab/placebo until progression or prohibitive toxicity. Co-primary endpoints are overall survival and progression-free survival. It is planned to randomize 664 patients. A safety interim analysis will be done when 24 patients have been randomized and completed at least cycle 1. As of 1st February 2019, 24 patients have been randomized. Clinical trial information: NCT03353831.

**TPS5602**  
Poster Session (Board #421a), Sat, 1:15 PM-4:15 PM  
ENGOT-OV43/KEYLYNK-001: A phase III, randomized, double-blind, active-controlled study of pembrolizumab plus chemotherapy with olaparib maintenance for first-line treatment of BRCA-nonmutated advanced epithelial ovarian cancer. First Author: Ignace Vergote, BGOG and University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium  

**Background:** There is a significant unmet need to develop new regimens for BRCA1/2-nonmutated advanced ovarian cancer (OC). The PARP inhibitor olaparib is approved for women with platinum-sensitive, recurrent OC regardless of BRCA1/2 status and, more recently, for newly diagnosed women with BRCA-mutated OC. In the TOPACIO/KEYNOTE-162 study, the combination of the PD-1-blocking antibody pembrolizumab (pembro) and niraparib demonstrated efficacy in platinum-resistant relapsed OC irrespective of BRCA1/2 status. ENGOT-OV43/KEYLYNK-001 (ClinicalTrials.gov, NCT03740165) is a phase 3, randomized, double-blind, active- and placebo-controlled study of pembro plus paclitaxel-carboplatin chemotherapy (CT) followed by olaparib maintenance for first-line treatment of patients with BRCA1/2-nonmutated advanced epithelial OC (EOC). **Methods:** Patients with stage III or IV BRCA-nonmutated EOC, primary peritoneal cancer, or fallopian tube cancer will be stratified by surgery status (no residual tumor after primary debulking surgery [PDS], residual tumor after PDS, or planned interval debulking), bevacizumab use, and PD-L1 status (combined positive score < 10 or ≥10). After one lead-in cycle of CT, patients will be randomized 1:1:1 to receive: CT + pembro followed by olaparib maintenance; CT + pembro followed by placebo; or CT + placebo followed by placebo. The CT regimen will be administered for 5 cycles, and pembro 200 mg Q3W will be administered for 35 infusions. Olaparib 300 mg BID maintenance therapy will start after the end of CT as concomitant treatment with pembro until discontinuation or for 2 years if the patient has a complete response. Bevacizumab use is permitted at investigator’s discretion and determined pre-randomization. Primary endpoints are investigator-assessed progression-free survival (PFS) per RECIST 1.1 criteria and overall survival. Key secondary endpoints are PFS per RECIST 1.1 assessed by blinded independent central review, PFS after next-line treatment, and safety. Enrollment is currently ongoing. Clinical trial information: NCT03740165.

**TPS5603**  
Poster Session (Board #421b), Sat, 1:15 PM-4:15 PM  
Pembrolizumab (MEDI4736) with focal sensitizing radiotherapy in platinum-resistant ovarian, primary peritoneal or fallopian tube epithelial cancer. First Author: Frederik Marme, AGO & National Center for Tumor Disease/Department of Gynecology, University of Heidelberg, Heidelberg, Germany  

**Background:** Ovarian cancer (OC) is the most lethal gynecologic cancer, accounting for ~185,000 deaths worldwide in 2018. Most patients (pts) initially respond to platinum-based chemotherapy (chemo), but more than 50% of pts recur. Pts who recur in ≤6 months have platinum-resistant OC (PROC), which is associated with poor prognosis. Standard therapy for PROC includes chemo ± bevacizumab (bev). However, many pts receive single-agent chemo, which demonstrates limited response and survival (~12% ORR, 3-4 mo PFS, ~12 mo OS). Therefore, there is an urgent need for novel therapeutic strategies. Tissue factor (TF) is a novel oncogenic target expressed in OC. Tisotumab vedotin (TV) is a first-in-class antibody drug conjugate conjugating a TF-targeted fully human monoclonal antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E. TV has shown encouraging antitumor activity and a manageable safety profile in PROC in the multicohort phase 1/2 innovaTV 201 study. innovaTV 208 is a multicenter, open-label, phase 2 trial with a safety run-in phase for a dose-dense regimen (DDR) evaluating the efficacy and safety of TV in pts with PROC. Methods: innovaTV 208 will enroll ~142 adult pts with platinum-refractory epithelial ovarian, primary peritoneal, or fallopian tube cancer; measurable disease by RECIST v1.1, and ECOG score 0-1. Eligible pts must have received bev-containing treatment for OC. Pts with platinum-refractory disease, increased risk of bleeding, active ocular surface disease, or grade >1 peripheral neuropathy will be excluded. A safety run-in phase for the DDR will be performed in up to 12 pts who received ≤512 mg IV bev-containing regimens for PROC. In the DDR, TV will be given at previously decided lower doses IV 3Q4W for the same dose intensity as the standard 1Q3W dose; the primary endpoint is incidence of DLTs. In phase 2, pts who received ≤1 prior cytotoxic chemo regimen for PROC will be randomized to receive TV administered as IV Q3W or as IV Q4W, if shown to be tolerable. The primary endpoint for phase 2 is confirmed ORR by RECIST v1.1. Secondary endpoints include DOR, time to response, DCR, CA-125 response rate by GCIG criteria, DFS, OS, pharmacokinetics, and safety. Clinical trial information: NCT03657043.

**TPS5604**  
Poster Session (Board #422a), Sat, 1:15 PM-4:15 PM  
Phase I (safety assessment) of durvalumab (MEDI4736) with focal sensitizing radiotherapy in platinum-resistant ovarian, primary peritoneal or fallopian tube epithelial carcinoma. First Author: Anna Tinker, British Columbia Cancer Agency, Vancouver, BC, Canada  

**Background:** Radiation (RT) of malignant neoplasms can induce immunogenic tumor cell death, alter the tumor micro-environment and enhance recruitment of anti-tumor T cells. Co-administration of focal RT and an immune checkpoint-inhibiting agent may overcome tumor suppressive mutants and potentiate systemic responses. A phase I study is underway to assess the safety of RT combined with PD-L1 inhibition in patients with recurrent epithelial ovarian/fallopian tube/ peritoneal carcinomas (OV). **Methods:** Women with platinum resistant epithelial OV, EOC, or primary peritoneal cancer and in ≤2 lines of treatment are eligible. 1 lesion evaluable by RECIST criteria (v1.1) and 2 additional lesions suitable for RT (minimal treatment volume 4cc) are required. Pre- and on-treatment biopsies for correlative studies are mandatory. The primary objectives are to assess the safety and tolerability of the focal RT combined with the immune checkpoint inhibitor, durvalumab (D), as defined by dose-limiting toxicities (DLTs), and to define the maximum tolerated RT dose and treatment schedule. The secondary objectives are to evaluate the clinical activity of focal RT and D (RECIST v1.1, GCIG CA-125, and immune-related response criteria), progression free survival and overall survival. D 1500 mg delivered intravenously every 28 days = one cycle. RT to the 2 selected target lesions is delivered 24-36 hours prior to the infusion of D. The RT starting dose-level is 240 Gy (4 fractions) per lesion (given Days -1, 1 and 28 of Cycle 1 and Days 1 and 2 of Cycle 2). A 3+3 design will permit more extensive exploration of toxicity if DLTs are observed (Table). Investigator assessed DLTs are defined by CTCAE v4.03 and include the following: any grade ≥3 adverse event suspected to be related to D or RT (necrosis or recall reactions at previously irradiated sites, RT induced bowel perforation, any unexpected grade 3 or greater toxicity at the site of RT), any grade ≥2 allergic or autoimmune event that involves vital organ function, and any other grade ≥3 allergic or autoimmune events that do not resolve to grade 1 before the next scheduled dose of D. Treatment may continue up to 12 months. Enrollment began August 2018. To date, no DLTs have been observed at dose level 1 (n=3) and enrollment is ongoing. Clinical trial information: NCT03255943.
A phase 3 trial evaluating efficacy and safety of lenvatinib in combination with pembrolizumab in patients with advanced endometrial cancer. First Author: Vicky Makker, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Lenvatinib (LEN) is a multikinase inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT. Pembrolizumab (PEMBRO) is a monoclonal antibody targeting programmed cell death receptor 1 (PD-1). Preliminary analyses of a phase 1/2 study of LEN + PEMBRO showed promising antitumor activity and a manageable safety profile in advanced endometrial cancer (EC). Methods: A multicenter, randomized, open-label, phase 3 study (KEYNOTE-775/E7080-G000-309; clinicaltrials.gov NCT03517449) will evaluate efficacy and safety of LEN + PEMBRO vs treatment of physician's choice (TTP) in patients with advanced EC. Patients must be aged ≥ 18 years, have advanced EC that progressed after 1 prior platinum-based therapy, have measurable disease per RECIST v1.1, and an Eastern Cooperative Oncology Group performance status ≤ 1. Patients must have mismatch repair (MMR) status confirmed by central laboratory via immunohistochemistry on archived or fresh tumor biopsy. – 780 patients (~120 MMR-deficient; ~660 MMR-proficient) will be randomized to receive LEN 20 mg orally once daily and PEMBRO 200 mg intravenously (IV) every 3 weeks (Q3W) or TTP. Patients will be randomized first according to MMR status; MMR-proficient patients will be further stratified by ECOG PS, geographic region, and prior history of pelvic radiation. TTP is either doxorubicin 60 mg/m² by IV Q3W or paclitaxel 80 mg/m² by 1-hour IV infusion weekly (3 weeks on/1 week off). The dual primary endpoints are progression-free survival (PFS; per RECIST v1.1 by blinded independent central review) and overall survival (OS). The PFS analysis will occur at the planned interim analysis (~363 OS events in MMR-proficient patients; ~524 FFS events), and the study will have 99% power to detect a hazard ratio (HR) of 0.55 with a 1-sided 0.0005 significance level. A final OS analysis will occur at 518 OS events, when the study will have 90% power to detect a HR of 0.75 with a 1-sided 0.0245 significance level. Secondary endpoints include objective response rate, health-related quality of life, safety and tolerability, and pharmacokinetics. Clinical trial information: NCT03517449.

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NRG GY012: A randomized phase II study comparing single-agent olaparib, single agent cediranib, and the combination of cediranib/olaparib in women with recurrent, persistent or metastatic endometrial cancer. First Author: Helen Mackay, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: The Cancer Genome Atlas and others identified genomic events suggesting that endometrial cancer (EC) should be susceptible to DNA repair inhibition. Mutations in classical homologous recombination genes occur in 22% of EC, ARID1A 41% and PTEN loss occurs in 55% of EC. Data from preclinical models suggest poly ADP-ribose polymerase (PARP) inhibitors alone or in combination may be an effective therapeutic strategy in EC (Hansen 2016). Combinations of angiogenic inhibitors and PARP inhibitors have demonstrated synergistic effects and have been well tolerated in other tumor types. This study has been designed to compare 2 experimental arms exploring DNA repair inhibition versus cediranib alone which has previously shown promising activity in GOG 229J (Bender 2015).

Methods: This is a multicenter randomized three arm study for patients with recurrent, metastatic or persistent EC. Patients are randomized 1:1:1 to cediranib PO 30 mg OD; olaparib 300 mg PO BID or the combination of cediranib 20 mg PO OD with olaparib 300 mg PO BID. All treatment cycles are 28 days. Primary endpoint is progression free survival (PFS). The study is powered to detect an increase in median PFS from 3.6 (based on cediranib alone) to 7.2 months with 90% power, using a one-sided test with \( \alpha = 0.05 \) per comparison. Forty patients will be enrolled per arm, with an interim futility analysis planned. Eligibility includes endometroid, serous, and mixed histology EC; at least 1 prior line of chemotherapy (no more than 2 lines for metastatic disease), prior endocrine or immunotherapy is allowed; ECOG PS \leq 2; adequate hepatic, bone marrow, coagulation and renal function. Archival tumor tissue and blood samples are being collected for translational studies. The study is open across the NRG network; 24 patients are enrolled to date. Amendments are planned to include additional arms investigating combination strategies targeting DNA repair and angiogenesis. Clinical trial information: 03660826.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Ado-trastuzumab emtansine in patients with HER2 amplified salivary gland cancers (SGCs): Results from a phase II basket trial. First Author: Bob T. Li, Memorial Sloan Kettering Cancer Center, New York, NY

Background: SGCs are rare tumors with no approved therapy for metastatic disease. HER2 amplification occurs in 8% among all SGC histologies, and 25-33% of the aggressive salivary duct carcinoma (SDC) histologic subtype. We hypothesized that ado-trastuzumab emtansine, a HER2 targeted antibody drug conjugate, may be clinically active in these patients. Methods: A cohort of patients with HER2 amplified SGCs were enrolled into a multi-histology basket trial with ado-trastuzumab emtansine, treated at 3.6mg/kg iv every 3 weeks. The primary endpoint was overall response rate (ORR) by RECIST v1.1 or PERCIST. A Simon two-stage optimal design was applied with type I error rate under 2.7%, power of 90%, 95% CI 56-100% including 5 complete responses after prior trastuzumab, pertuzumab and anti-androgen therapies. After a median follow up period of 12.7 months, median DOR (range 2-19+ months) and median PFS (95% CI 4-22+ months) were not reached. Toxicities included grade 1 or 2 infusion reaction, thrombocytopenia and transaminists; there were no treatment related deaths. HER2 amplification by NGS (fold change ≥2.8 & ≥22.8) correlated with HER2/CEP17 ≥2 by FISH (B/8 tested) or IHC3+ (10/10 tested). FLIM-FRET tested positive in 3/3. Conclusions: Ado-trastuzumab emtansine is highly efficacious in patients with HER2 amplified SGCs as identified by NGS. This study has met its primary endpoint, and cohort expansion is warranted to confirm these results. Clinical trial information: NCT02675829.

Gemcitabine and cisplatin (GP) induction chemotherapy (IC) plus concurrent chemoradiation (ICCRT) versus ICRT alone in locoregionally advanced nasopharyngeal carcinoma (NPC): A phase 3, multicenter, randomized controlled trial. First Author: Jun Ma, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: GP regimen has been established as the standard first-line treatment option for patients with recurrent/metastatic NPC. However, its efficacy in locoregionally advanced disease remains unclear. Methods: Patients with locally advanced, untreated NPC were randomized to GP regimen (cisplatin 75mg/m²–cetux 250mg/m² with mandatory G-CSF support followed by every 2W cetux 500mg/m² maintenance) or CCRT (cisplatin–cetuximab (cetux) followed by weekly cetux maintenance) was cisplatin 100 mg/m², q3w for 3 cycles, concurrently with intensity-modulated radiotherapy or CRT alone. The primary endpoint was failure-free survival (FFS). The calculated sample size was 238 per group, with an 80% power (two-sided α 0.05) to detect a treatment failure hazard ratio (HR) of 0.52. Results: From Dec 2013 to Sep 2016, 480 patients from 12 centers were randomly assigned to IC+CCRT (n = 242) or CCRT alone (n = 238) group. Baseline characteristics were well balanced. After a median follow-up of 39 months, 3-year FFS was 85.8% in the IC+CCRT group and 77.2% in the CCRT alone group (intent-to-treat population; HR 0.53, 95% confidence interval 0.34–0.81; P = 0.003). In GP+CCRT group, 239 patients started GP IC and 231 (96.7%) completed all three cycles. The most common grade 3 adverse events (AE) in IC+CCRT and CCRT group were mucositis (28.9% vs. 32.1%), neutropenia (28.0% vs. 10.5%), and leukopenia (26.4% vs. 20.3%). Conclusions: Adding GP IC to CCRT significantly improved FFS in locoregionally advanced NPC and is well tolerated with favorable toxicity profile. Clinical trial information: NCT01872962.
6004 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: Long-term results of a phase 3 multicenter randomised controlled trial. First Author: Ming-Yu Chen, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Initial 3-year results from our clinical trial in locoregionally advanced nasopharyngeal carcinoma (NPC) patients showed that induction chemotherapy (IC) with cisplatin and fluorouracil (PF) resulted in improved disease-free survival (DFS) with a marginally significant effect on distant metastasis-free survival (DMFS), but the effect of IC on locoregional relapse-free survival (LRDFS) and overall survival (OS) did not differ significantly. Here, we present 5-year follow-up results.

Methods: Our trial was a randomized, open-label phase 3 trial comparing IC followed by concurrent chemoradiotherapy (CCRT) versus CCRT alone in patients with stage III-IVB (except T3N0-1) NPC. The IC followed by CCRT group received cisplatin (90 mg/m² d1) and fluorouracil (800 mg/m² d1-5) every three weeks for two cycles before CCRT. Both groups were treated with 80 mg/m² cisplatin every three weeks concurrently with radiotherapy. The primary endpoints were DFS and DMFS. We did efficacy analyses in the 476 randomized patients (intention-to-treat population).

Results: After a median follow-up of 82.6 months, the 5-year IC followed by CCRT group survival rate was 73.4% (95% confidence interval (CI) 67.7-79.1) in the IC followed by CCRT group and 63.1% (95% CI 56.8-69.4) in the CCRT alone group (P = 0.005). The 5-year DMFS rate was also significantly higher in the IC followed by CCRT group (82.8%, 95% CI 77.9-87.7) than in the CCRT alone group (73.1%, 95% CI 67.2-79.0; P = 0.013). Our updated overall survival benefit of IC: the 5-year OS rate was 80.8% in the IC followed by CCRT group versus 76.8% in the CCRT alone group (P = 0.045). There were no significant differences in the rate of grade 3–4 late adverse events during follow-up between the two groups. Conclusions: IC followed by CCRT provides long-term DFS, DMFS, and OS benefits compared with CCRT alone in locoregionally advanced NPC and, therefore, can be recommended for these patients.

Clinical trial information: NCT00705627.

6007 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Neck dissections based on sentinel lymph node navigation versus elective neck dissections in early oral cancers: A randomized, multicenter, non-inferiority trial. First Author: Yasuhisa Hasegawa, Asahi University Hospital, Gifu, Japan

Background: The objective of the study is to evaluate the non-Inferiority of survival, the superiority of postoperative disability, and the complication of the neck in neck dissections based on sentinel lymph node navigation in early oral cancer patients, compared with standard elective neck dissections.

Methods: This study was a randomized, multicenter, non-inferiority trial at 16 institutions in Japan. Eligibility criteria included histologically confirmed squamous cell carcinoma in the oral cavity; clinical categories T1 and T2, N0M0 by UICC TNM classification 7th edition, clinical depth of invasion (DOI) of T1 was over 4mm (defined as late T1), previously untreated; age at least 18 years; and written informed consent. We randomly assigned patients (1:1) to receive either sentinel lymph node biopsy (SNB) or standard elective neck dissections (ND) with stratification of T category (late T1 vs T2) and sub type (tongue vs others). The primary endpoint was 3-year overall survival with a non-inferiority margin of 12%. Sentinel nodes (SNs) were detected using radioisotope method and examined with multislice frozen section analysis intraoperatively, following HE and cytokeratin stain for a PD-L1 and CTLA-4, which in combination may be synergistic.

Results: Between November 2011 and January 2016, 271 patients were enrolled and randomized to SNB group (134 patients) and ND group (137 patients) with a median follow-up of 37 months (IQR 36-39). Pathological positive nodal status was 34% (46/132) in SNB group and 26% (34/133) in ND group (Chi-square P = 0.10). 3-year overall survival in SNB group was 89% (95% CI 82-93%), which was non-inferior to that in ND group (86%, 95% CI 79-91%). 3-year relapse-free survival was 80% (95% CI 72-86%) in SNB group and 81% (95% CI 73-87%) in ND group. Arm abduction of postoperative 1 and 3 months in ND group was disturbed significantly compared with SNB group. Conclusions: SNB navigated ND could replace elective ND without survival disadvantage and reduce postoperative disability of the neck in patients with early oral cancer. Clinical trial information: 00006510.

6008 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

A phase II randomized trial for early-stage squamous cell carcinoma of the oropharynx: Radiotherapy versus trans-oral robotic surgery (ORATOR). First Author: Anthony Chuang-Hui Nicholas, Western University and London Health Sciences Centre, London, ON, Canada

Background: The incidence of OPSCC has risen rapidly, due to an epidemic of human papillomavirus (HPV) infection. Radiation therapy (RT) has historically been the standard treatment, but transoral robotic surgery (TORS) has surpassed RT in the US as the most common approach, based on assumptions of reduced toxicity or improved quality of life (QOL). No randomized trials have previously compared these treatments. The ORATOR trial (NCT01590355) enrolled patients with T1-T2 NO-2 (≤4 cm) OPSCC amenable to TORS. We randomly assigned patients, stratified by p16 status, to RT (70 Gy/35 fractions, with chemotherapy if N1-2) vs. TORS (≥ advent (chemo)[RT based on pathology]. The primary endpoint was a definitive comparison of swallowing QOL at 1 year using the MD Anderson Dysphagia Inventory (MDADI), powered to detect a 10-point improvement (a clinically meaningful change (CMC)) in the TORS arm. Secondary endpoints included adverse events (AEs), other QOL outcomes (including EORTC scales, the Voice Handicap Index-10, Neck Dissection Impairment Index, and Patient Neuro-toxicity Questionnaire), overall- and progression-free survival (OS, PFS). All analyses were pre-specified and intention-to-treat.

Results: Between 2012 and 2017, 68 patients were randomized (n = 34 in each arm), in Canada and Australia. Median age was 59 years; 87% were male. Primary tumor sites were palatine tonsil (74%) or base of tongue (25%). Arms were well-balanced for baseline factors, including p16 status (88% in each arm). Median follow-up was 27 months. MDADI scores at 1-year were statistically superior in the RT arm (mean ± SD: 86.9 ± 11.4 vs. 80.1 ± 13.0 in the TORS arm; p = 0.042), but not meeting the definition of a CMC. For the other QOL metrics, outcomes were similar at 1-year. Feeding tube rates at 1-year were 3% (n = 1) vs. 0% respectively. Rates of treatment-related grade ≥3 AEs were similar (88% in each arm). Median follow-up was 27 months. MDADI scores at 1-year were statistically superior in the RT arm (mean ± SD: 86.9 ± 11.4 vs. 80.1 ± 13.0 in the TORS arm; p = 0.042), but not meeting the definition of a CMC. For the other QOL metrics, outcomes were similar at 1-year. Feeding tube rates at 1-year were 3% (n = 1) vs. 0% respectively. Rates of treatment-related grade ≥3 AEs were similar (88% in each arm). Median follow-up was 27 months. MDADI scores at 1-year were statistically superior in the RT arm (mean ± SD: 86.9 ± 11.4 vs. 80.1 ± 13.0 in the TORS arm; p = 0.042), but not meeting the definition of a CMC. For the other QOL metrics, outcomes were similar at 1-year. Feeding tube rates at 1-year were 3% (n = 1) vs. 0% respectively. Rates of treatment-related grade ≥3 AEs were similar (88% in each arm). Median follow-up was 27 months. MDADI scores at 1-year were statistically superior in the RT arm (mean ± SD: 86.9 ± 11.4 vs. 80.1 ± 13.0 in the TORS arm; p = 0.042), but not meeting the definition of a CMC.
Background: The molecular landscape of OPCs and its association with neoplastic progression is largely unknown. We report the results of high throughput DNA/RNA profiling of OPCs from pts in the Erlotinib Prevention of Oral Cancer trial (EPOC), with long-term prospective follow-up. The top mutated genes in OPCs were TP53 (29%), CDKN2A (15%), NOTCH1 (11%) and PIK3CA (7%), which were also frequently mutated (albeit at higher rates) in CEs from EPOC or TCGA. There was a progressive increase of tumor mutation burden (TMB, P < 0.05) and frequency of high-risk TP53 mutations (P = 0.02) from hyperplasia, to dysplasia, to invasive Oc's (P < 0.05). Median TMB was higher in OPCs from pts who developed OC (2.45 mut/Mb) vs those who did not (1.22 mut/Mb) (P < 0.01). Pts with TP53 mutated OPCs had shorter OS-free survival compared to TP53 wild-type (HR 1.81, 95% CI 1.32-2.90, P = 0.01). A prognostic score was derived from a Cox regression model which identified 1.2-mRNA transcript profile and a 12-gene RNA expression signature score in OPCs, and OC risk. This study may provide a framework for future studies of OPCs.

Methods: Eighty-seven patients with OPC progressed following platinum-based therapy (NCT02369874). Methods: Pts were randomized 1:1:1 to D+T vs SOC (HR: 0.88; 95% CI: 0.72-1.08; P = 0.20) or D+T vs SOC (HR: 1.04; 95% CI: 0.85-1.26; P = 0.76). Efficacy data are provided in the table. Treatment-related AEs and ORR were similar to previous studies of SOC in pts with R/M HNSCC. The primary endpoint was overall survival (OS) with dual primary objectives of D+T vs SOC and D vs SOC. Additional endpoints included objective response rate (ORR), duration of response (DoR), and adverse events (AEs). Results: 240 pts were randomized to D, 247 to D+T and 249 to SOC. An imbalance for Eastern Cooperative Oncology Group performance status (ECOG PS) was seen in favor of the SOC arm (D, PS 0 = 26%, PS 1 = 74%; D+T, PS 0 = 26%, PS 1 = 74%; SOC, PS 0 = 32%, PS 1 = 68%). The risk of death was not statistically significantly different for D compared with SOC (HR: 0.88; 95% CI: 0.72-1.08; P = 0.20) or D+T vs SOC (HR: 1.04; 95% CI: 0.85-1.26; P = 0.76). Efficacy data are provided in the table. Treatment-related AEs Grade ≥3 were reported in 10.1% of pts (regardless of causality Grade ≥3 AEs were 41.4%) in the D arm, 16.3% (51.2%) for D+T, and 24.2% (44.2%) for SOC. Following treatment, 2% of pts in D, 5% in D+T and 15% in SOC received immunotherapy. Conclusions: D and D+T did not demonstrate a statistically significant improvement in OS compared to standard chemotherapy in pts with R/M HNSCC. Median OS and ORR of D arm were similar to other studies with checkpoint inhibitors. The SOC arm outperformed what has been seen for SOC arms in previous studies; subsequent immunotherapy may have confounded the OS analyses. The safety profile for D and D+T in R/M HNSCC is consistent with previous trials. Clinical trial information: NCT02369874.

EAGLE: Phase 3, randomized, open-label study of durvalumab (D) with or without tremelimumab (T) in patients (pts) with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC).

First Author: Lisa F. Licitra, Head and Neck Cancer Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy

Background: EAGLE is a phase 3 study evaluating efficacy of D (anti-PD-L1 mAb) monotherapy and D+T (anti-CTLA-4 mAb) vs standard of care (SOC) in pts with R/M HNSCC who progressed following platinum-based therapy (NCT02369874). Methods: Pts were randomized 1:1:1 to D vs SOC (HR: 0.88; 95% CI: 0.72-1.08; P = 0.20) or D+T vs SOC (HR: 1.04; 95% CI: 0.85-1.26; P = 0.76). Efficacy data are provided in the table. Treatment-related AEs Grade ≥3 were reported in 10.1% of pts (regardless of causality Grade ≥3 AEs were 41.4%) in the D arm, 16.3% (51.2%) for D+T, and 24.2% (44.2%) for SOC. Following treatment, 2% of pts in D, 5% in D+T and 15% in SOC received immunotherapy. Conclusions: D and D+T did not demonstrate a statistically significant improvement in OS compared to standard chemotherapy in pts with R/M HNSCC. Median OS and ORR of D arm were similar to other studies with checkpoint inhibitors. The SOC arm outperformed what has been seen for SOC arms in previous studies; subsequent immunotherapy may have confounded the OS analyses. The safety profile for D and D+T in R/M HNSCC is consistent with previous trials. Clinical trial information: NCT02369874.
Background: Cetuximab monotherapy results in a median overall survival (OS) of approximately 6 months (mo) in platinum-resistant recurrent/metastatic head and neck squamous cell carcinoma (HNSCC). HNSCC unselected to human papillomavirus (HPV) is driven by hyperactivation of the CDK4/6 and cyclin D1 (CD1) regulatory complex, resulting in cell cycle progression and tumor growth, suggesting that CDK4/6 inhibition can be a rational therapeutic strategy in this setting. Palbociclib (PAL) is a selective CDK4/6 inhibitor that may reverse cetuximab resistance by countering the actions of deregulated CD1. PAL plus an epidermal growth factor receptor inhibitor synergistically reduced cell viability of HPV-unrelated HNSCC cell lines. In a single-arm, multicenter trial of platinum-resistant, cetuximab-naive, HPV-unrelated HNSCC, PAL in combination with cetuximab resulted in a median OS of 9.5 mo. Methods: In a double-blind randomized phase II trial, patients (pts) with platinum-resistant, cetuximab-naive, HPV-unrelated HNSCC were treated with cetuximab plus either PAL (arm A) or placebo (arm B). Pts were stratified by performance status (PS) and prior immunotherapy (IT). 120 pts were required for 1:1 randomization to have ≥80% power to detect a hazard ratio (HR) of 0.6 (corresponding to a median OS of 10 mo) vs 6 mo in arm B (stratified by PS: HR=0.82 [95% CI, 0.54–1.25], P=0.18). Median PFS was 3.9 mo in arm A and 4.6 mo in arm B (stratified by PS: HR=1.00 [0.7–1.5], P=0.5). Hematologic AEs were more common in arm A. Only 11 pts (9%) received IT after being treated on the trial. Conclusions: Among pts with platinum-resistant, HPV-unrelated HNSCC, PAL plus cetuximab resulted in a trend of prolongation of median OS compared with cetuximab. Clinical trial information: NCT02499120.

Results: of a phase 2a, multicenter, open-label, study of RM-1929 PIT in patients with locoregional, rHNSCC who could not be satisfactorily treated with surgery, radiation, or platinum chemotherapy was conducted to evaluate the safety and efficacy of the drug, RM-1929. For each treatment, nonthermal red light (690 nm) was applied to the tumors 24 hours post IV infusion of the drug. Surface illumination was administered for superficial tumors and interstitial illumination via intratumoral placement of fiber optic diffusers for deep tumors. Therapeutic response was assessed using CT RECIST 1.1 by an independent blinded radiologist. Results: Thirty HNSCC patients were enrolled. There were no dose-limiting toxicities and one Grade 1 photosensitivity reaction. Most reported AEs were mild to moderate in severity with 96.7% in Grade 1 and 3.3% in Grade 2, respectively. There were 13 (43.3%) patients who had at least one SAE. 86% (19/22) of SAEs were deemed unlikely related to treatment, including all 3 fatal SAEs. Three SAEs were reported of possibly/probably related to treatment (site/oral pain, tumor hemorrhage, and airway obstruction). ORR was 52% (9/17) in Grade 1 and 86% (17/20) in Grade 2 respectively. Discordant treatment response in primary tumors and lymph node metastases occurred in 10.3% of pts. One pt died due to an unknown cause that was assessed as treatment-related.

Conclusions: The observed substantial antitumor activity, durable responses, and acceptable safety profile of RM-1929 PIT treatment was generally well tolerated with majority of AEs as mild to moderate in severity. Preliminary data showed favorable response rates in a heavily treated population. A global phase 3 clinical trial is currently underway. Clinical trial information: NCT02429279.

Discordant treatment response in primary tumors and lymph node metastases after four weeks of preoperative PD-1 blockade in head and neck squamous cell carcinoma (HNSCC). First Author: Adam Luginbuhl, Thomas Jefferson University Hospital, Department of Otolaryngology, Philadelphia, PA

Background: Discordant radiographic responses are described in other tumor types in response to immunotherapy with response at some anatomic sites and progression in others. Here we determined the frequency of discordant treatment effects (TE) in HNSCC patients treated with immunotherapy in the context of a neoadjuvant trial. Methods: 23 Patients with resectable primary HNSCC were 1:1 randomized to receive nivolumab (240 mg IV Q 2 weeks x 2) or nivolumab and tadalafil 10 mg daily. Surgery was performed 4 weeks after the first nivolumab infusion. Resection specimens were graded histopathologically by two pathologists. Areas exhibiting TE (defined by fibrosis with chronic inflammation, foamy macrophage reaction and multinucleated giant cells) were expressed relative to the total tumor area. This was assessed in the primary tumor and all lymph nodes (LN). Each primary lesion and individual LN was defined as a) no response 0%TE, b) minimal response 1-19%TE, c) response 20-99% or d) complete response 100%. Concordance was defined if primary lesion and LNs were in the same ordinal data set. Results: 11/23 (48%) of subjects experienced discordant TE in the primary tumor and LNs. Within this cohort, 3 patients had a complete pathologic response both at the primary site and LNs. In contrast, 12/23 patients (52%) revealed discordant TE between the primary tumor sites (average of 17% TE) and involved LNs (average of 62% TE), (p= 0.018; signed rank test). Interestingly, in the discordant group, TE effects in LNs were invariably greater than in primary lesions. In 5 of 11 patients with multiple involved LNs, the TE varied between nodes. This included patients with advanced LNs demonstrating 0% and 100% TE in the same level. Systemic and local immune parameters as they relate to concordant and discordant TE in individual patients will be presented including a type 1 immune bias. Conclusions: Early histologic evaluation of TE in patients with HNSCC receiving immunotherapy demonstrate a wide variety of discordant TE between the primary lesion and LNs. These findings will lend insight into complex interactions of cancer cells with the microenvironment. Clinical trial information: NCT03238365.
6017 Poster Discussion Session: Displayed in Poster Session (Board #6), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Recombinant humanized anti-PD-1 monoclonal antibody (JS001) in patients with refractory/metastatic nasopharyngeal carcinoma: Interim results of an open-label phase II clinical study. First Author: Fenghua Wang, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Metastatic nasopharyngeal cancer (NPC) patients progressed after standard therapy have limited treatment options. Toripalimab, also known as JS001, a humanized IgG4 antibody specific for human PD-1, has been approved for 2nd line treatment of metastatic melanoma in China. We report the results from a phase listudy in metastatic NPC patients treated with toripalimab.(Clinical trial ID: NCT02915432). Methods: This multi-center, open-label, phase II registration study is designed to evaluate the safety and efficacy of toripalimab in metastatic NPC patients who have failed systemic treatment. Toripalimab is given at 3 mg/kg IV Q2W until disease progression or intolerable toxicity. Tumor PD-L1 expression, plasma EBV DNA level and other biomarkers will be correlated with clinical response. Results: Enrollment of 190chemo-refractory metastatic NPC patients was completed by Feb 2019 from 17 participating centers. The median age was 46 years, with 89.5% patients receiving at least 2 lines of prior systemic therapies. Treatment-related adverse events (TRAEs) occurred in 92% patients, which were mostly grade 1 or 2. Common TRAEs includedinclusion, hypothyroidism, AST increased, proteinuria, pyrexia, cough, constipation, ALT increased, hypoa boomuninaemia and pruritus. Grade 3 or higher TRAEs occurred in 25% patients. By the cut-off date of Jan 7 2019, among 135 evaluable patients, 3 partial responses and 40 stable diseases were observed for an objective response rate (ORR) of 25.2% and a disease control rate of 54.8%. PD-L1 expression results were obtained from 125 patients and 45.6% (57/125) were PD-L1+. PD-L1+ patients achieved higher ORR than PD-L1- patients, 29.8% versus 22.1%. In addition, a responder drop of 47 patients (31 partial responses and 14 stable diseases) was observed in responding patients, which typically proceeded the radiographic identification of clinical benefit. Conclusions: Toripalimab has demonstrated a manageable safety profile and encouraging clinical activity in the largest check-point blockade study in NPC to date. A change in plasma EBV DNA demonstrated a manageable safety profile and encouraging clinical activity in the largest check-point blockade study in NPC to date. A change in plasma EBV DNA level and other biomarkers will be correlated with clinical response. Patients will be continuously monitored for additional safety and survival readouts. Clinical trial information: NCT02915432.

6018 Poster Discussion Session: Displayed in Poster Session (Board #7), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Activity and tolerability of BLU-667, a highly potent and selective RET inhibitor, in patients with advanced RET-altered thyroid cancers. First Author: Matthew H. Taylor, Oregon Health & Science University, Portland, OR

Background: RET alterations are targetable oncogenic drivers in ~90% of advanced medullary thyroid cancer (MTC) and 20% of papillary thyroid cancer (PTC), yet no selective RET inhibitors are approved. BLU-667 is an investigational highly potent and selective RET inhibitor targeting oncogenic RET alterations including those that confer resistance to multikinase inhibitors (MKIs). We provide an update on the expanded experience of BLU-667 in RET-altered thyroid cancer from the registration-enabling ARROW study (NCT03037385). Methods: ARROW is a global DE (30-600 mg daily [QD or Bid]) and dose expansion (DX; 400 mg QD) study in pts with advanced solid tumors. Primary objectives are response rate (ORR; RECIST 1.1) and safety. Results: As of 19 Dec 2018, 60 pts with RET-mutated MTC (M918T [37], C634R/S/W [8], V804M [4], other/pending [11]) and 5 pts with RET-fusion+ PTC (NCOA4 [3], CDC2 [2]) received BLU-667 (37 DE, 28 DX). 58% had prior MKI therapy. Among 49 response-evaluable MTC pts, ORR is 47% (95% CI: 33, 62; 2 complete and 21 partial responses; PR; 4 PR pending confirmation; 25 stable disease; 1 progressive disease). 96% (22/23) of responding pts continue treatment; 15 with response duration ≥ 6 months. 2/4 evaluable PTC pts had PR; 41 enrolled PTC pts continue treatment at 8-11 months. Responses in MTC occur regardless of MI resistance (prior cabozantinib/vandetanib: 6/12 [50%]; 36% [12/33]; 3/8 [37%]). Responses in PTC regardless of MKI resistance and may significantly improve outcomes for pts with RET-altered thyroid cancers. Enrollment of the expansion is ongoing with registrational intent. Clinical trial information: NCT03037385.

6019 Poster Discussion Session: Displayed in Poster Session (Board #8), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Anlotinib treatment in locally advanced or metastatic medullary thyroid carcinoma: A multicenter, randomized, double-blind, placebo-controlled phase IIb trial. First Author: Dapeng Li, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Anlotinib (AL3818) is a novel multi-target TKI, inhibiting tumor angiogenesis and proliferative signaling. Our previous single-arm phase 2 AL3818 trial (Clinical trial ID: NCT02586350) has demonstrated durable antitumor activity with a manageable adverse event profile in locally advanced or metastatic medullary thyroid carcinoma (MTC). Here we report results of the phase IIb trial (ALTER1031, NCT02586350) of anlotinib for locally advanced or metastatic MTC with a larger samples. Methods: Between September 2015 and September 2018, 91 patients were enrolled in China. Eligible patients have diagnosed as phase IV MTC with relapsed and measurable disease and without antiangiogenic target therapy. The patients were randomly assigned in a 2:1 ratio to receive anlotinib or a matched placebo. The primary endpoint was progression-free survival (PFS). Results: 91 patients were randomized 62 to anlotinib arm and 29 to placebo arm. Until the data cutoff date (1 Feb 2019), median PFS was 20.67 months (95%CI: 14.03-34.63) in anlotinib arm vs 11.07 (95%CI: 5.82-14.32) months in placebo arm (HR 0.53, p = 0.0289). The OS data were not sufficiently mature for analysis. Considerable improvement in ORR was observed over the two arms (48.39% vs 3.45%, p < 0.0001). The adverse events (AEs) were 100% in anlotinib arm and 89.66% in placebo arm. The most common AEs in anlotinib arm were hand-foot syndrome, hypertension, hyperglycemia and diarrhea. Conclusion: ALTER1031 set its primary endpoint of PFS shows that anlotinib treatment is effective and well tolerated. The safety profile was consistent and no new adverse events were identified. These data potentially extend the role of anlotinib monotherapy as a new therapy strategy for MTC patients. Clinical trial information: NCT02586350.

6020 Poster Discussion Session: Displayed in Poster Session (Board #9), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Alliance A091404: A phase II study of enzalutamide (NSC# 766085) for patients with androgen receptor-positive salivary cancers. First Author: Alan Loh Ho, Memorial Sloan Kettering Cancer Center, New York, NY

Background: A subset of salivary gland cancers (SGCs) express the androgen receptor (AR). This phase II trial evaluated the anti-androgen enzalutamide (Astellas) for patients with AR+ SGCS. Methods: Locally advanced/unresectable or metastatic AR+ SGCS are enrolled in this multi-center, open-label, phase II trial with AR-targeted drugs was allowed. Enzalutamide 160 mg orally once daily was given (1 cycle= 28 days). The primary endpoint was confirmed response (RR) according to RECIST v1.1 within the first 8 cycles. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety. A Simon-Optimal two-stage design was used to detect a 20% RR (vs. 5%) (alpha = 5%, beta = 90%). >1 response(s) in the first 21 would trigger accrual to 41; >4 responses would be considered promising. Results: 46 eligible patients (pts) were enrolled (40 M, 6 F; median age 65) in 22 months. In the first 21 pts, we initially had 2 confirmed PRs allowing for full study accrual, though one was later changed to stable disease. Among the 46 pts, 7 had PR as best response, though only 2 were confirmed within the first 8 cycles (4% (95% CI: 0.5-15%). Two other PRs did not count towards the primary endpoint due to 1 development beyond 8 cycles (cycles 12-18) and 2 a confirmatory scan completed <4 weeks apart. The other 3 pts with unconfirmed PR developed progression of disease (PD) after the first PR scan, 24 pts had stable disease; 15 pts PD as best response. Among 11 pts previously treated with AR-targeted therapy, best responses were 1 confirmed PR, 7 SD, 3 PD. With a median follow-up of 11.7 months (mo), OS at 12 mo was 66% (95% CI: 52-83%), PFS at 12 mo was 24% (95% CI: 14-42%), and median PFS was 5.5 mo (95% CI: 3.7-7.3). Conclusions: This is the first prospective trial evaluating an androgen alone for AR+ SGCS. The failure to meet the protocol-defined measure of success was due in part to the lack of durability of initial responses. The clinical activity observed suggests the AR-dependence of AR+ SGCS, even among those previously treated with other hormonal therapies. Support: U10CA138088, U10CA138082; Access: American Society of Clinical Oncology; Clinical trial information: NCT02749903.
Background: Liquid biopsies have the utility for detecting minimal residual disease in several cancers, but its clinical utility for real-time treatment adaptation remains limited. We adopted Epstein-Barr virus (EBV)-associated nasopharyngeal carcinoma (NPC) as a model to investigate this hypothesis. We characterize longitudinal response of circulating EBV DNA to induction chemotherapy (IC) and concurrent chemoradiotherapy (CCRT) in locally advanced NPC (LA-NPC), and investigate the association of complete biological response (cBR) with clinical outcomes.

Methods: The medical records of 673 LA-NPC cases with serial EBV DNA measurements (pre-treatment, after each IC cycle, post-CCRT) were extracted. Cox regression and landmark analyses were used for survival analyses.

Results: Four distinct phenotypes were identified based on their longitudinal EBV DNA B3 response: 1) Early responders (200/673 [29.7%]) achieved cBR post-IC; 2) Intermediate responders (332/673 [49.3%]) included patients with cBR post-IC<sub>2</sub> and cBR post-CCRT after 2 IC cycles or following a temporary bounce (detectable reading following initial cBR); 3) Late responders (75/673 [11.2%]) achieved cBR only post-CCRT after 3-4 IC cycles; 4) Treatment-resistant (66/673 [9.8%]) patients demonstrated non-cBR post-IC-CCRT. These phenotypes were identified significant differences in EBV DNA level and adjusted for pre-treatment EBV DNA load, N-category and chemotherapy de-intensification and intensification strategies based on the four phenotypes, which could shape the individualized treatment of LA-NPC. Our study highlights the feasibility of liquid biopsy for real-time therapeutics adaptation.

Conclusions: Digital ELISpot for EBV DNA and complete biological response (cBR) may predict immunotherapy response and provide novel strategies for patient-specific treatment guidance.
In our trial, randomized phase II trial comparing TPF with TP and Cetuximab (C) replacing F. Selectable stage III or IV squamous cell carcinoma of the head and neck (SCCHN). The (T) is a therapeutic option in patients suffering from locally advanced or unresectable disease.
Hyperprogressive disease (HPD) in head and neck squamous cell carcinoma (HNSCC) patients treated with immune checkpoint inhibitors (ICI). First Author: Salvatore Alfieri, Head and Neck Cancer Medical Oncology 3 Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: HPD was described in 9% of cancer patients (pts) treated in phase I trials, in 13.8% of advanced non-small cell lung cancer and 29% of HNSCC pts upon ICI. A better definition of the hallmarks and survival outcomes of HPD pts in a larger cohort of HNSCC is still lacking. Methods: We retrospectively analyzed all advanced HNSCC pts treated with ICI at our Institution between October 2014 and December 2018. Three scans, performed before ICI, at baseline and at first evaluation during ICI, were assessed according to RECIST 1.1. Tumor Growth Kinetics (TGK) and first radiological evaluation and TGKpost were ≥2. Correlation between HPD and clinical characteristics was performed by Fisher or t-student test. Median overall survival (mOS) and progression free survival (mPFS) were estimated using the Kaplan-Meier method and compared between HPD and non-HPD using the log-rank test. Results: Ninety pts were eligible: 18% were female, 4% had ECOP Q5 2, 73% smoking history, 37% oropharyngeal cancer (61% HPV+), 65% locoregional disease (89% previously irradiated), 54% received combined immunotherapy, 75% in ≥2nd line. Two out of 90 pts had TGKpre = 0 and were not evaluable for TGK ratio. HPD was observed in 7.9% (788 of 90 pts. HPD pts were significantly younger compared to non-HPD pts (median age 53 ± 3.7 vs 63.3 ± 0.9 years, p = 0.002) and had a significantly higher median neutrophil-lymphocyte ratio (NLR) (11.5 ± 3.5 vs 6.6 ± 0.4, p = 0.004). Overall, mOS and mPFS were 7.5 (95% CI: 4.2-10.8) and 2.2 months (95% CI: 0.9-3.4), respectively. At a median follow-up of 20.9 months (95% CI: 19-22.8), HPD pts had a significantly worse mPFS compared to non-HPD pts (1.8 vs 95% CI: 1.5-2.2 vs 3.5 months, p = 0.001). HPD correlated with a not significant 3.72 fold increase in lower mOS compared to non-HPD pts (95% CI: 4.1-12.5 vs 8.3 months, p = 0.348). Three (43%) out of 7 HPD pts early switched to chemotherapy after PD to ICI having a mOS of 8.1 months (range 3.7-25.3). Excluding these 3 pts, HPD correlated with a significantly worse mOS compared to non-HPD (2.6 vs 95% CI: 1.9-3.3 vs 8.3 months, p = 0.006). Conclusions: HPD was identified in 7.9% of HNSCC and correlated with younger age and higher NLR. HPD pts who did not receive a subsequent treatment had poorer mPFS and mOS. The assessment of HPD in a control cohort of advanced HNSCC upon standard chemotherapy is ongoing.

Apatinib for locoregionally recurrent or metastatic nasopharyngeal carcinoma after failure of first-line chemotherapy: A multicenter, phase II trial. First Author: Wei Jiang, Affiliated Hospital of Quillin Medical University, Quillin, China

Background: Concordant programs for patients with nasopharyngeal carcinoma (NPC) who failed to first-line chemotherapy after locoregional recurrence or metastasis are not yet available. Here, we investigated the efficacy and safety of apatinib as an second-line treatment in these patients. Methods: In this multicenter, phase II trial, patients of NPC with disease progression after failure of first-line chemotherapy were treated with apatinib (200mg PO bid). The primary endpoint of this study was objective response rate (ORR), secondary endpoints included progression free survival (PFS), overall survival (OS) and toxicity. Results: Between January and December 2017, 33 patients were finally enrolled onto the analysis from three centers in China. The baseline characteristics were summarized in Table. Of the 12 patients achieved a partial response and no complete responses were observed, yielding an ORR of 36.3%. Additionally, 6 patients (18.2%) experienced stable disease of at least 5 months in duration, and the disease control rate was 54.5%. At a median follow-up time of 14 months (range 1-22), median PFS was 5.0 months (95% CI: 2.3 to 7.7). The median OS had not reached, and the 1-year OS rate was 83.1%. The most common adverse events (grade 1 to 2) related to apatinib were hypertension (42.4%), hand-foot syndrome (54.5%), proteinuria (12.1%) and oral ulcer (24.2%). Conclusions: Apatinib showed a well therapeutic effect and a manageable safety profile for patients of advanced NPC after previous chemotherapy. Further study in combination chemotherapy and other targeted agents in patients with NPC is warranted. Baseline demographic and disease characteristics. Clinical trial information: NCT03130270.

Preclinical efficacy of copanlisib in cetuximab sensitive and resistant tumors of HNSCC. First Author: Konrad Friedrich Klinghammer, Charite Comprehensive Cancer Center, Berlin, Germany

Background: Copanlisib is a highly selective, pan-class I PI3K inhibitor with preferential activity against the p110α and p110δ isoforms that lead to downregulation of PI3K signaling. Copanlisib has been approved for the treatment of follicular lymphoma in the US. Here, we explored the anti-tumor activity of copanlisib in head and neck squamous cell carcinoma (HNSCC), where PI3K signaling has been identified as alternate signaling in cetuximab resistant tumors. Further, TCGA data show up to 56% of HNSCC display either PI3K signaling has been defined as alternate signaling in cetuximab sensitive and resistant tumors of HNSCC: Interim analysis on 199 patients—The TOPNIVO study on behalf of the GORTEC and the Unicancer Head & Neck Group. First Author: Caroline Even, Gustave Roussy, Villejuif, France

Background: In the randomized phase III Study CA209141, Nivolumab (N) demonstrated significant overall survival (OS) benefit with favorable safety profile for platinum refractory R/M SCCHN and is now approved for these patients (pts). The objectives of the study are to provide additional insight into the frequency of high-grade AEIs related to N and the efficacy of N in real life. Methods: Between August and December 2017, 203 pts were included in the multicenter, non-controlled phase II TOPNIVO. The main inclusion criteria were patients with platinum refractory R/M SCCHN with progressive disease, ECOG 0-2. Pts received N 3mg/kg every 2 weeks intravenously over 30 minutes. Four pts did not receive N. We report here the safety during the first 6 months (mo) after inclusion and OS results on the first 199 treated pts. Results: Median age was 62 yr, 83% were male, 84% were ECOG 0-1, 16% 2. The primary site of cancer was oral cavity 26%, oropharynx 38%, larynx 16%, hypopharynx 21%, 33% had loco regional relapse, 32% metastatic disease and 35% both. 49% had received one prior line of chemotherapy and 30% two prior lines. 157 (79%) pts ended their treatment within the first six mo: 5 for AE related to N (pneumonitis 3 pts, hepatitis 1 pt, diarrhea 1 pt), 107 for progression, 33 for death (24 related to progression, 9 to intercurrent disease), 12 other. 132 pts (66%) experienced at least 1 AE grade ≥3. On the 226 AE grade 3-4, 21 (mainly pneumopathy, lipase increase and asthenia) were related to N and occurred in 18 pts. On the 51 AEs grade 5, 3 were considered related to N (2 pneumonitits, 1 cardiac arrest). The median OS was 7.7 mo (CI 95%: 6.0; 9.5) in the whole population; 9.2 mo (6.8; 12.1) in the 167 pts with ECOG 0-1, 3.0 mo (1.1; 6.0) in the 32 pts with ECOG ≥2.1 mo, 7.2 mo (7.6; NR) in the 64 pts with metastatic disease, 7.7 mo (5.0; 9.6) in the 66 pts with locorregional disease and 4.6 mo (3.1; 7.9) in the 69 pts with both. OS was similar in pts older or younger 70 yr. Conclusions: The interim analysis of the TOPNIVO study shows no additional toxicities of N compared to what has been described previously, confirms the previous results of OS and provides new survival data in subgroups of pts. Clinical trial information: NCT03226756.

A study of nivolumab in patients with recurrent and/or metastatic platinum refractory squamous cell carcinoma of the head and neck (R/M SCCHN): Interim analysis on 199 patients—The TOPNIVO study on behalf of the GORTEC and the Unicancer Head & Neck Group. First Author: Caroline Even, Gustave Roussy, Villejuif, France

Background: The TOPNIVO study shows no additional toxicities of N compared to what has been described previously, confirms the previous results of OS and provides new survival data in subgroups of pts. Clinical trial information: NCT03226756.
Efficacy and safety of immune checkpoint inhibitors in elderly patients

**Background:** Pembrolizumab (a humanized monoclonal antibody blocking programmed death receptor-1[PD-1]), and cetuximab (a chimeric monoclonal antibody inhibiting epidermal growth factor receptor) are both FDA-approved, second-line monotherapies for R/M HNSCC. This is the first trial to evaluate anti-tumor efficacy of dual therapy with pembrolizumab and cetuximab. Previously reported safety data demonstrated favorable toxicity. An interim futility analysis of cohort 1 (anti-PD-1/PD-L1 and cetuximab naïve) was completed per protocol. **Methods:** Patients (pts) with platinum-refractory/ ineligible, R/M HNSCC were treated with pembrolizumab 200mg IV on day 1 and cetuximab 400mg/m2 loading dose followed by 250mg/m2 weekly (21-day cycle). Primary endpoint: overall response rate (complete and partial responses) by 6 months (mo). Secondary endpoints: 12-mo progression-free survival (PFS) probability, overall survival, response duration, safety, correlational analyses. **Results:** 14 evaluable pts were enrolled March 2017-October 2018. Median age 70 years (range 47-86y), M:F 6:8, EGOG 0.1:2.2:1.4 mucosal primaries (9 oral cavity, 2 HPV-mediated oropharynx, 2 non-EBV-associated nasopharynx, 1 larynx). 11 pts (79%) had no prior lines of systemic therapy for R/M HNSCC (range 0-1.6). 6 pts (42.8%) had a partial response by 6 months, meeting pre-planned criteria for trial continuation. 4 pts (28.6%) had stable disease and 4 (29.4%) had progressive disease. Median time to progression was 128 days (4.3 mo). Median duration of response was 160.5 days (5.4 mo) for partial responders and 133 days (4.4 mo) for pts with stable disease. Disease control rate (partial + stable) was 71.4%. There were 7 grade 3 treatment-related toxicities. 2 pts discontinued cetuximab due to toxicity, however, both continued pembrolizumab. 46% with pembrolizumab plus cetuximab is potentially active for platinum-refractory/ ineligible pts with R/M HNSCC. These results meet protocol specifications for trial continuation. Final results will include PD-L1 expression data. Clinical trial information: NCT03082534.

**Conclusions:** Elderly pts treated with ICI had significantly higher PFS but not OS compared to younger pts; Grade 3 irAEs (36% vs 14%, p = 0.007). Conclusions: Elderly pts treated with ICI had significantly higher PFS but not OS adjustment. Grade ≥3 irAEs were associated with significantly higher ORR to ICI in the whole population.
Metformin treatment of locally advanced head and neck squamous cell carcinoma (HNSCC) patients induces an anti-tumorigenic immune response. First Author: Athleka Kansara, University of Cincinnati, Cincinnati, OH

Background: Metformin is a biguanide, widely used oral hypoglycemic agent. Metformin has also shown to inhibit tumor growth and progression in a wide variety of cancers including Head and Neck Squamous Cell Carcinoma (HNSCC). Metformin activates AMP protein kinase (AMPK) related pathways leading to inactivation of mammalian target of rapamycin (mTOR) and suppression of its downstream effectors. In addition, metformin is postulated to alter immune regulation in the tumor microenvironment leading to increased tumor cell killing. Here, we report our findings on the impact of metformin on T cells, NK cells and cytokines from patient peripheral blood mononuclear cells (PBMCs) from a phase I open-label single site dose escalation study combining metformin and chemoradiation (CRT) in HNSCC (NCT02325401).

Methods: In this study, we evaluated the immune cell phenotypes and cytokine profiles of peripheral blood in patients before and after metformin treatment on trial by using flow cytometry and cytokine magnetic bead assays (Luminex). Cytokine profiles were further studied in co-culture experiments combining PBMCs, HNSCC cell lines, and metformin. Results: Patients who received metformin developed expanded NK cell populations, increased NKG2D expression, and a shift in their CD8+ T-cell memory phenotypes. Patient serum ELISA examination revealed increased anti-tumorigenic cytokine profiles. Metformin treatment of HNSCC cell lines in vitro as well as HNSCC PBMCs, HNSCC cell lines, and metformin. ELISA examination revealed increased anti-tumorigenic cytokine profiles. Metformin treatment of HNSCC cell lines in vitro as well as HNSCC PBMCs ex vivo resulted in downregulation of STAT3 compared to healthy controls. Metformin treatment of locally advanced head and neck squamous cell carcinoma (HNSCC). Metformin activates AMP protein kinase (AMPK) related pathways leading to inactivation of mammalian target of rapamycin (mTOR) and suppression of its downstream effectors. In addition, metformin is postulated to alter immune regulation in the tumor microenvironment leading to increased tumor cell killing. Here, we report our findings on the impact of metformin on T cells, NK cells and cytokines from patient peripheral blood mononuclear cells (PBMCs) from a phase I open-label single site dose escalation study combining metformin and chemoradiation (CRT) in HNSCC (NCT02325401).

Results: This study, we evaluated the immune cell phenotypes and cytokine profiles of peripheral blood in patients before and after metformin treatment on trial by using flow cytometry and cytokine magnetic bead assays (Luminex). Cytokine profiles were further studied in co-culture experiments combining PBMCs, HNSCC cell lines, and metformin.

Conclusions: Here we show evidence that metformin treatment has a direct effect on the innate immune system in patients with HNSCC, inducing an anti-tumorigenic immune response suggesting that metformin continues to be a good candidate to yield improved clinical outcomes in patients with advanced stage HNSCC. Clinical trial information: NCT02325401.

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Predictors of early immunotherapy response in head and neck cancer: Per partitioning analysis (RPA) and adjusted hazard ratio (AHR) methods were used. Conclusions: Our data suggests patients with HPV-positive R/M head and neck squamous cell carcinoma (HNSCC), First Author: Kedar Kirtane, Moffitt Cancer Center, Tampa, FL Background: Human papillomavirus status is known to be prognostic for patients with HNSCC. Current data suggests that HPV-positive HNSCC tumors exhibit increased infiltration of immune cells and higher levels of T-cell exhaustion markers compared with HPV-negative tumors, possibly suggesting a difference in response patterns to immunotherapy. We evaluated whether HPV status is associated with duration of response in patients receiving anti-PD-1 inhibitors. Methods: We performed a retrospective chart review of 54 patients at Moffitt Cancer Center who received either pembrolizumab (N = 32) or nivolumab (N = 22) from February 2016 to July 2018. Results: Per-protocol analysis showed a significant difference in median time to progression (TTTP) between HPV-positive and HPV-negative patients (TTTP: 9.3 months vs. 7.0 months; P = 0.04). Multivariate analysis with the Cox proportional hazard model confirmed that HPV status was significantly associated with TTTP (HR: 2.40; 95% CI: 1.13-5.11; P = 0.02). Conclusions: HPV status is an independent predictor of TTTP in patients with HNSCC treated with anti-PD-1 inhibitors. Future studies are needed to validate our findings and further clarify the value of integrating the indicators with current clinical strategies in improving survival of NPC patients.
2007 – 2015 who received curative IMRT according to approved guidelines in the Canadian cohort of LA-NPC. Patients (Pts) with WHO type II and III LA-NPC were excluded with concurrent IMRT with high-dose CDDP and adjuvant CDDP/Carboplatin and 5-FU (maximum total/adjuvant CDDP-Dosh/300 mg/m²) between 2003-2016 were analyzed. EBER status was tested by ISH. Staging was classified by UICC/AJCC⁷ edition TNM. Kaplan-Meier 5-year (5y) for overall survival (OS) and recurrence-free survival (RFS) was calculated and compared by log-rank test between stage, adj chemo (yes vs no) and total CDDP-D (≥300 vs <300 mg/m²). Multivariable analysis (MVA) identified survival predictors. Results: A total of 312 pts were evaluated: median age = 49.8 (range 17.4–75.9); EBER+) (67%) vs (33%); stage III/IV= 26%/51%/47%; T4= 36%; N3= 17%; adj chemo = 83% (21% switched to carboplatin); median total/adjuvant CDDP-D=380/160 mg/m²; median follow-up 7.6 years (range 0.6-14.9). 5y OS differed by stage II-III IV (95% vs 80%; p < 0.001) and total CDDP-D > 300 vs ≤300 mg/m² (89% vs 83%; p = 0.02). Adj chemo and total CDDP-D impacted 5y OS in stage IV (table). 5y RFS was higher in stage IV with total CDDP-D > 300 vs ≤300 mg/m² (74% vs 59%; p = 0.03), with a trend in locoregional control (LCR) (91% vs 80%; p = 0.05) but not significant on distant control (DC) (78% vs 72%, p = 0.36). Conclusions: Total CDDP-D > 300 mg/m² impacts OS in the overall cohort. The benefit of adj chemo and total CDDP-D on OS and RFS is significant in stage IV but not stage II-III LA-NPC, mainly due to higher LRC rather than OS. 5y OS and MVA by stage.

### 6048 Poster Session (Board #37), Sat, 1:15 PM-4:15 PM

**Impact of tobacco smoking on radiotherapy outcomes in 1875 HPV-positive oropharynx cancer patients.**

First Author: Pernille Lassen, Department of Experimental Clinical Oncology, Aarhus, Denmark

**Background:** This study investigates the impact of smoking on radiotherapy (RT) outcome and survival in a population-based cohort of HPV+ oropharynx cancer (OPC). **Methods:** We identified all OPC with positive p16 staining from 2007 – 2015 who received curative IMRT according to approved guidelines in two oncology groups. Associations between smoking and locoregional control (LCR) and distant control (DC) were estimated by competing risk regression. Disease free survival (DFS) and overall survival (OS) were estimated by proportional-hazards regression model. Multivariable analyses (MVA) adjusted for age, gender, performance status (PS), T- and N-category, and treatment regimen. **Results:** A total of 1875 patients were included. Median age was 59.2 (31.3-86.8); 79% (1481) were males; 96% (1481) had PS 0-1. Smoking status had no impact on the association of BGLAP with OS, which has not been evaluated in multiple clinical trials. We assessed circulating protein biomarkers in HNSCC patients prior to treatment to better understand pathways related to clinical outcomes and relevant for targeting in combination with durvalumab. **Methods:** Sixty-six selected serum proteins were measured by multiplex immunoassay at baseline in HNSCC patients receiving durvalumab treatment: 106 patients with high PD-L1 (>25% tumor cells; SP263 assay) in phase II HAWK trial and 52 patients with low PD-L1 in phase II CONDOR trial. **Results:** Multivariate Cox modeling demonstrated that higher baseline concentrations of angiogenic, pro-inflammatory, and myeloid-associated proteins (ANGPT2, CRP, IL6, S100A12) were associated with shorter overall survival (OS), while higher concentration of a bone formation marker and immunostimulatory hormone (BGLAP) correlated with longer OS in 158 durvalumab-treated HNSCC patients (P < 0.05). The 5 proteins remained significantly associated with OS in a multivariate model including PD-L1, EOCG, tumor size, and neutrophil count. Bone metastases status had no impact on the association of BGLAP with OS, which has not been reported before in HNSCC. Interestingly, ANGPT2 level above median showed the highest hazard ratio (HR = 2.2, P < 0.001) among all evaluated variables. Furthermore, higher levels of WVF, an angiogenesis-related protein, correlated with shorter OS by univariate survival analysis (P < 0.001). **Conclusions:** Our results suggested an important role of angiogenesis in the resistance of HNSCC patients to durvalumab treatment, and ANGPT2 may have predictive utility for durvalumab combination with an anti-angiogenic agent. The predictive value of BGLAP remains to be evaluated in a randomized clinical study. **Clinical trial information:** NCT022077530; NCT02319044.
Phase 1b study of chemoprevention with green tea polyphenol E (PPE) and epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor ( Erlotinib) in patients with advanced premalignant (AP) lesions of the head and neck.

First Author: Dong Moon Shin, Emory Winship Cancer Institute, Atlanta, GA

Background: Based on the strong synergistic effects between green tea polyphenol E (PPE) and EGFR-TKI in preclinical studies (Int J Cancer, 2008; Cancer Prev Res, 2009; JCO, 2009), we conducted a phase 1b study with PPE and erlotinib combination for APL (mild-, moderate-, severe dysplasia or carcinoma in situ [CIS]) of the oral cavity and larynx from 2/2011 to 11/2011 at the Emory Winship Cancer Institute.

Methods: All pts were enrolled after they signed the IRB approved informed consent form. Tissue biopsy before and at 6 months (6-M) treatment was mandatory, and cytobrushed samples of the APL and normal buccal mucosa at 3-, 6-, and 12-M were obtained for biomarker studies. Treatment included fixed dose of PPE (200 mg, P.O., TID) and dose escalation of erlotinib P.O., (50mg level 1), 75mg (level 2) and 100mg (level 3) for 6-M. The primary endpoint was safety and toxicity, and secondary endpoints were evaluation of pathologic responses, cancer free survival (CFS) and biomarker modulation.

Results: Out of 27 enrolled pts, 6 control subjects for biomarker studies, 2 ineligible, and 19 were treated with PPE and erlotinib for 6-M. Clinical characteristics of treated patients included median age 63 yrs, (range,33-78); 9 M/10 F; 10 former or current smokers/9 never smokers; 15 severe dysplasia or CIS, 2 moderate dysplasia, 2 mild dysplasia; 13 had surgical resection; 17 oral cavity primary; and 2 at larynx. 3 pts were treated at dose level 1, 4 at level 2, and 12 at level 3. Toxicity (G0 or G1 included) were: skin rash (1 G3, 1 G2), reduction in skin thickness (1 G2), epistaxis (1 G2), and hypertension (2 G3, 1 G2). Skin rash (associated with erlotinib) may be DLT and MTD has not been reached. The recommend doses for phase 2 or 3 studies will be PPE 200mg TID plus erlotinib 100mg QD. 17 pts were assessed for pathologic responses at 6-M: pCR 7/17 (41%), pPR 2/17 (12%), pSD 5/17 (29%) and pPD (3/17 (18%). The median follow up was 32 months. Median CFS has not been reached. 16 pts are alive at the time of data analyses and 1 pt died (by noncancerous reason). Biomarker studies are ongoing for tissues and/or cytobrushed samples.

Conclusions: The treatment of the combination of green tea PPE plus erlotinib for 6-M was well tolerated in pts. All pts showed evidence of the histopathological changes, including epidermal hyperplasia, increased Ki-67 labeling indices, and increased Ki-67 labeling indices were significantly inversely correlated with CTGF gene expression (r = -0.18 and -0.51, p < 0.05). 1843 DEGs were found at FDR < 0.05 as a function of CTGF-M. Pathways mapping to tissue remodeling were significantly enriched for among downregulated genes in CTGF hypermethylated tumors. Increased CTGF methylation was inversely correlated with the mesenchymal subtype mRNA gene signature (r = -0.21, p = 0.0026) and correlated with the atypical subtype (r = 0.32, p = 0.000002). Conclusions: Implementation of CTGF-M in routine diagnostic is feasible and correlates well with CTGF gene-expression levels and activation of tissue remodeling pathways. Therefore, CTGF-M might be instructive for stratifying HNSCC patients for CTGF targeting therapies. CTGF emerges as a promising prognostic marker independently of HPV status.

Pre-treatment obesity prolongs survival in elderly patients (>65 years) with head and neck cancer (HNC).

First Author: Parth Anj Desai, UT Health Southwestern, Dallas, TX

Background: Pre-treatment Body mass index (BMI) is an important prognostic factor in HNC with variable survival benefit reported till date. Despite increasing incidence of HNC in geriatric patients there is limited information on prognostic variables in this group. Methods: This is a single center, retrospective cohort study of patients with HNC treated between 2012 and 2017. Patients were stratified by BMI (Class 1- BMI < 25 kg/m²; normal), Class 2- BMI: 25-29.9 kg/m² (overweight), Class 3- BMI > 30 kg/m² (obese). Various variables were collected & appropriate statistical analysis was done. Results: 186 elderly HNC patients with non-metastatic disease were stratified into three BMI groups (Table & figure) to have equally distributed co-variates. The Mean OS was significantly higher in class 3 patients (53 months) compared to class 1 (21 months) (p = 0.02). In multivariate analysis, class 3 was an independent good prognostic indicator (Hazard ratio = 0.44, Range-0.21-0.90, p=0.03). Stage, CCI score & gastrostomy tube were adverse prognostic factors in the study. Conclusions: Obese elderly HNC patients have survival benefit over normal/underweight patients. Predicitive modeling of integrating BMI with other prognostic factors is needed to determine appropriate management in these patients.
6053 Poster Session (Board #42), Sat, 1:15 PM-4:15 PM

Association of single nucleotide polymorphisms within genes in NF-kB, TGF-β, and JNK signaling pathways with the risks of nasopharyngeal carcinoma in Chinese Han. First Author: Hanyi Zhang, Sichuan Cancer Hospital, Chengdu, China

Background: Nasopharyngeal Carcinoma(NPC) is an Epstein-Barr virus(EBV) associated malignancy with remarkable ethnic and geographical distribution. The EBV oncoprotein latent membrane protein 1 (LMP1) is the primary oncogene of EBV infection through its signaling cascade and its connections to other pathways including NF-kB, TGF-β and JNK signaling, which plays an important role in the pathogenesis of NPC. In GWAS.Genome-wide association studies) these pathways were also identified. Single nucleotide polymorphisms (SNPs) in the regulatory regions may regulate the expression of genes in these pathways, or affect the function of the coded protein. Methods: Altogether 149 SNPs were covered by the 15 SNPs in the TRAF2, TRAF3, NFKBA, MAP2K4, and CHUK genes were genotyped in a hospital-based case-control study of 350 NPC cases and 587 healthy controls from the Chinese Han. The observed genotype frequencies in the controls were tested for Hardy-Weinberg equilibrium (HWE) using the chi-square test. Odds ratios (ORs) and 95% confidence intervals (95% CI) for associations between genotypes and NPC risk and tumor characteristics were calculated by logistic regression, and they were adjusted for multiple testing using the SNP spectral deposition (SNPSpD) approach for multicollinear results. Results: We found one NFKBA SNP was associated with NPC risk after adjustment for multiple comparisons. Minor allele carriers of the NFKBA had an increased risk of NPC (P<0.05). The analyses were adjusted for age and gender. For a SNP with a minor allele frequency between 10% and 50%, the study had greater than 90% power to detect an OR of 1.50 at a significance level of 0.05 (PS—software for power and sample size calculation, http://biostat.mc.vanderbilt.edu/wik/bin/view/Main/PowerSampleSize). The other genotyped SNPs were not associated with NPC. Conclusions: Our data suggests that genetic variation especially in the NFKBA may be a useful biomarker for NPC screening and further studies are warranted.

6055 Poster Session (Board #44), Sat, 1:15 PM-4:15 PM

Immune signatures associated with response to neoadjuvant PD-1 blockade in oral cavity cancer. First Author: Hannah Knochelmann, Medical University of South Carolina, Charleston, SC

Background: PD-1 inhibition therapy has revolutionized clinical medicine as it can mediate durable responses in a small cohort of patients. Yet, it remains incompletely understood why these patients respond. To address this question, we studied patients with oral cavity squamous cell carcinoma (OCSCC) to elucidate immune signatures associated with response to nivolumab. Methods: We defined the immune profile from the blood and tumor of patients on neoadjuvant nivolumab. We tested if tumor-infiltrating lymphocytes (TIL) could be preferentially expanded ex vivo from nivolumab-responsive patients versus those who were either non-responsive or had never received nivolumab. During the course of therapy, we comprehensively profiled a number of surface markers on patients’ T cells to define their activation status, cytotoxic capacity and memory phenotype. Moreover, the immune profile of the peripheral blood was assessed pre- and post-nivolumab using high dimensional mass cytometry. Results: Regardless of PD-1 therapy, TIL were successfully expanded from 11 of the 12 patients. TIL were comprised of both CD4+ and CD8+ T cells. Additional investigation revealed that the frequency of CD4+ T cells and effector memory T cells in TIL correlated with disease progression (CD4: p = 0.04, r = 0.74, effector memory: p = 0.046, r = 0.74). TILs from responders expressed higher CD26 (p = 0.007, r = -0.88) and Tim3 (p = 0.045, r = -0.74) while PD-1, Lag3, and Oxa4 were not differentially expressed based on response. Spearman correlation and Mann Whitney U test were used to assess phenotypic differences. Conclusions: We demonstrate, for the first time, that TIL can be reliably expanded from OCSCC patients on neoadjuvant nivolumab. Moreover, individuals who were responsive to PD-1 blockade had TIL expressing high levels of CD26 and Tim3. Future studies will explore if these markers are predictive of responses and if they contribute to treatment outcome.

6054 Poster Session (Board #43), Sat, 1:15 PM-4:15 PM

A phase II randomized control trial of erlotinib in combination with celecoxib in patients with operable oral squamous cell carcinoma (OSCC). Erol-Kib Slahi, First Author: Sudhir Vasudevan Nair, Tata Memorial Centre, Mumbai, India

Background: When combined with COX-2 inhibitors, the EGFR tyrosine kinase inhibitor Erlotinib has shown a better antitumor response in pre-clinical studies. Since high volume hospitals in many countries usually have a longer waiting period for surgery, neoadjuvant targeted therapy may be helpful in reducing disease progression and downstaging oral squamous cell carcinoma. Methods: Sixty-four treatment-naïve operable oral cancer patients were randomized into a four-arm window of opportunity study consisting of treatment with erlotinib 150mg daily, celecoxib 200mg twice daily, the combination of both or observation alone (NCT02748707). Since the regular wait period for surgery at our hospital was four to five weeks, we planned a 21-day drug treatment versus observation followed by definitive surgery in the fourth week. MRI scans and biopsies were done before and after drug treatment. Post-operative adjuvant treatments were given as per the standard guidelines used for regular patients. Results: There were 10 females and 54 males with a median age of 44 and 45 years respectively. Taking a 20% reduction in the maximum tumor dimension after drug treatment (assessed clinically and radio logically) as partial response, the combination arm had a 60% partial response and a 25% stable disease. Whereas, 60% in the control arm had disease progression. The ratio of the longest tumor dimension at day 21 versus day 0 (Clinical & MRI assessment) also showed a significant difference between the observation vs erlotinib arms (p < 0.001) using Mann-Whitney Test. Grade II/III rashes was the commonly observed toxicity predominantly in the combination arm. Though not powered for survival analysis, a significant difference (p = 0.048) was observed for two-year overall survival for celecoxib + control (50%) versus erlotinib + combination (86%) using Kaplan Meier Estimator. Bio marker analysis (transcriptome sequencing and IHC) is being done on pre and post-treatment tumor specimens and the final results will be presented. Conclusion: Preoperative targeted therapy with erlotinib and celecoxib combination can arrest disease progression and downstage tumors with possible impact on survival. The identified biomarkers can further refine a future cohort for effective neoadjuvant targeted therapy in oral cancers. Clinical trial information: CTRI/2012/07/002828.

6056 Poster Session (Board #45), Sat, 1:15 PM-4:15 PM

Risk of mortality varies by type of fat consumed in a longitudinal cohort of head and neck cancer patients. First Author: Hania M. Too, Department of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign, Urbana, IL

Background: Dietary interventions have promise for improving cancer outcomes, but remain an understudied area of cancer care. The relationship between head and neck squamous cell carcinoma (HNSCC) mortality and dietary fat intake has not yet been examined. The objective of this study was to determine how pre-treatment dietary intake of different types of fats was associated with disease-specific and all-cause mortality in adults diagnosed with HNSCC. Methods: Our sample included 472 newly diagnosed HNSCC patients recruited into the University of Michigan Head and Neck Specialized Program of Research Excellence (HN-SPRE) between 2008 and 2012. Participants completed pre-treatment and post-treatment Food Frequency Questionnaires (FFQs) and health surveys. Multivariable Cox Proportional Hazards models were used to test the associations between both the type and quantity of fat intake (categorized into tertiles: low, medium and high intake) and time to mortality, after adjusting for relevant covariates. Fat types included animal, vegetable, medium-chain-fatty-acids (MCFA), long-chain-fatty-acids (LCFA), unsaturated, saturated, and trans. Results: During the study period, there were 144 total deaths and 97 cancer-specific deaths. In considering pre-treatment dietary intake, compared to low intake levels of LCFA, high intakes of unsaturated-fats were associated with a reduced risk of HNSCC-specific mortality compared to low intake (HR 0.52; 95% CI: 0.29–0.93). Considering post-treatment dietary variables, medium (HR: 0.21; 95% CI: 0.08–0.49) and high (HR: 0.41; 95% CI: 0.21–0.78) total fat intakes were associated with reduced risk of all-cause mortality compared to low intake. Medium (HR: 0.25; 95% CI: 0.08–0.67) and high (HR: 0.26; 95% CI: 0.09–0.67) total fat intakes were associated with reduced risk of HNSCC-specific mortality compared to low intake. Conclusions: Our data suggest that HNSCC prognosis may vary depending on both the type and quantity of fats consumed, specifically total fat and long chain fatty acids. Clinical intervention trials are needed to further examine this hypothesis.
Identifying adverse molecular features of HPV+ head and neck cancers using patient-derived models. First Author: Devraj Basu, The University of Pennsylvania, Philadelphia, PA

Background: Advancing therapy for human papilloma virus-related (HPV+) head and neck squamous cell carcinoma (HNSCC) is hindered by inadequate preclinical models and risk stratification tools. This study addresses both barriers by characterizing a panel of patient-derived xenografts (PDXs) that includes nine new models of HPV+ disease. Methods: Exome-sequenced genetic features of the PDXs were compared to their growth properties and the outcomes of their patients of origin. Genetic traits with potential prognostic utility were validated in multiple retrospective patient cohorts.

Results: The HPV+ PDXs avoided known artifacts in HPV+ cell lines, including 3q amplifications and loss of PIK3CA mutants, while enriching for alterations in H3K4 methyltransferases and Notch pathway genes. A positive association emerged between PDX tumor mutational burden (TMB) and their prognostic utility were validated in multiple retrospective patient cohorts. These features have potential for application to risk stratification, biomarker development, and trial design.

Prophylactic gabapentin decreases fatigue and swallowing difficulty in patients undergoing concurrent chemoradiation (CCR) for head and neck cancer (HNC): Interim results from a randomized controlled trial. First Author: Barbara A. Murphy, Vanderbilt University Medical Center, Nashville, TN

Background: Preliminary data suggest that gabapentin (G) administered during HNC radiation may decrease treatment associated pain. To confirm this, we undertook a prospective, randomized trial in HNC patients undergoing CCR. Primary outcomes: pain severity (scale of 0-10) and opioid use. Exploratory outcomes: local and systemic symptoms measured by the Vanderbilt Head and Neck Symptom Survey version 2 and the general symptom survey (VHNSSv2/GSS). We report results of the exploratory endpoints from the interim analysis. Methods: Measures: VHNSSv2 - 50 items, demonstrated reliability/validated, captures acute/chronic local HNC specific symptoms; GSS - 11 item checklist, demonstrated content validity, captures acute/chronic systemic symptoms. Population: HNC patients (≥ stage 2) undergoing primary or adjuvant CCR. Procedures: Randomized to standard pain management (SPM) or SPM + G dose escalated to 900mg tid. VHNSSv2/GSS completed weekly during treatment beginning week 1 and ending the last week of radiation therapy. Results were analyzed using a mixed-effects regression analysis adjusting for baseline levels of each symptom. Results: 71 patients completed a mean of 5.5 surveys. Patients on G experienced a reduction in overall systemic symptoms as measured by the GSS (11-items, p = 0.0073), fatigue (two-items, p = 0.013) sleep disturbance (five items, p < 0.0001), neurosensory eating (3 items, p = 0.026), phlegm-related symptoms (4 items, p = 0.004), and trend to better smell (2 items, p = 0.055). No impact on swallow, xerostomia, voice, dental or musculoskeletal symptoms was noted. Conclusions: This exploratory analysis suggests that G may moderate neurological and neuropsychiatric toxicities in HNC patients undergoing CCR. Further studies are warranted.
Prognostic impact of baseline circulating tumor cells (CTCs) detected by the isolation by size of epithelial tumor cells (ISET) in locally advanced head and neck squamous cell carcinoma (LAHNSCC): Results of a prospective study. 
First Author: Thiago Bueno Oliveira, A.C. Camargo Cancer Center, Sao Paulo, Brazil

Background: The prognostic impact of CTCs in LAHNSCC is yet to be determined, with conflicting results in previous trials, the majority utilizing cytokeratin dependent techniques for identification and counting of CTCs. The primary objective of this study is to determine the detection rates using the ISET method, and the prognostic role of CTCs in LAHNSCC patients (pts) treated with a curative intent. Methods: In this prospective study, peripheral blood samples of pts with non-metastatic LAHNSCC, stages III/IV, were analyzed for CTCs using the ISET method, in two scenarios: curative surgical resection and adjuvant radiotherapy (CTCs before RT) and candidates for a non-surgical strategy (unresectable or organ preservation) either with upfront RT concurrent with chemotherapy (CT) or cetuximab (CTCs before RT), or preceded by induction CT (CTCs before IRT). Results: Eighty-three pts were included, the majority males (83%), with oropharynx primary (50%) and submitted to IRT (40%). The detection rate of baseline CTCs was 94% (78/83), and CTCs counts were significantly correlated with survival. For each week increase of 1 CTC at baseline there was a relative increase of 18% in the risk of death (HR = 1.18; 95%CI: 1.06-1.31; p < 0.001), 16% in the risk of progression (HR = 1.16; 95%CI: 1.04-1.28; p = 0.004) and a reduction of 22.9% for CTCs sought to determine biomarker predictors of outcome to Nivo in M1 HNSCC.

Safety and efficacy of docetaxel combined with cisplatin as induction chemotherapy followed by cisplatin concurrent chemoradiotherapy plus gemcitabine as adjuvant chemotherapy in locally advanced nasopharyngeal carcinoma: A prospective and multicenter phase II trial. First Author: Zhi Hui Wang, The Fifth Hospital Of Sun yat-sen University, Zhuhai, China

Background: Radiation therapy is the only curative treatment modality for nonmetastatic nasopharyngeal carcinoma (NPC). Concurrent chemoradiation (CCRT) is the standard treatment strategy for NPC in locally advanced stages. However, the results after such treatment are suboptimal. Clearly, novel treatment strategies are needed to further improve patients' survival rates. This trial aimed to determine the safety and efficacy of a new treatment strategy. Methods: Patients with stage III – IVa-NPC received TP (docetaxel 75 mg/m², cisplatin 75 mg/m² every 3 weeks for 2-3 cycles) followed by cisplatin chemotherapy concurrently with 3-dimensional conformal radiation therapy or intensity-modulated radiation therapy plus gemcitabine (1000mg/m² every 2 weeks for 2 cycles) as adjuvant chemotherapy. Objective response rates and acute toxicity were assessed based on RECIST (1.1) and CTCAE v.4.0, respectively. Kaplan-Meier analysis was used to calculate survival rates. This trial is registered with the Chinese Clinical Trials Registry, number ChiCTR-OIC-17011464. Results: From July 2010 to July 2017, 20 eligible patients with nonmetastatic stage III-IVb NPC were enrolled. The objective response rates were 90% (3 complete responses [CRs] and 15 partial responses [PRs]) after two or three cycles of induction chemoradiation (ICT) and 100% (17 CRs and 3 PRs) after CCRT plus gemcitabine adjuvant chemotherapy, respectively. With a median follow-up time of 41 months, the 3-year overall survival rates were 90% (18/20,95% confidence interval [CI], 76.9%-100%). The 3-year progression-free survival, distant metastasis-free survival, and local progression-free survival rates were 80% (16/20,95% CI, 62.5%-100%), 85% (17/20,95% CI, 64.9%-100%) and 99% (19/20,95% CI, 85.4%-100%), respectively. The most frequent grade 3–4 toxicities were neutropenia (3/20,15%) and nausea (2/20,10%) after ICT and thrombocytopenia (6/20,30%) and leukopenia (6/20,30%) after CCRT plus gemcitabine adjuvant chemotherapy. Conclusions: Neoadjuvant TF followed by concurrent chemoradiation plus gemcitabine as adjuvant chemotherapy is an effective and produced promising outcomes in patients with LA-NPC in this hypothesis-generating study. The authors concluded that randomized controlled trials are warranted to definitively confirm this aggressive and potentially efficacious strategy. Clinical trial information: ChiCTR-OIC-17011464.
6068 Poster Session (Board #55), Sat, 1:15 PM-4:15 PM
A randomized trial of laryngeal organ preservation evaluating two cycles of induction chemotherapy with platinum, docetaxel, and a novel Bcl-xL inhibitor. First Author: Paul Swiecicki, University of Michigan Rogel Cancer Center, Ann Arbor, MI

Background: Laryngeal bio-selection with induction chemotherapy (platinum + 5-FU infusion; PF) has been demonstrated to result in impressive rates of survival and organ preservation with moderate toxicities. We sought to reduce the toxicity of PF by substituting docetaxel (T) for 5-FU and improve the tumor response rate with the addition of the Bcl-xL inhibitor AT-101.

Methods: PF with advanced stage laryngeal cancer were treated with 1 cycle of T 75 mg/m2 + platinum (P) (cisplatin 100 mg/m2 or carboplatin AUC 6) and were randomized 2:1 to the addition of AT-101. Patients with a CR proceeded to chemoradiation (CRT) with concurrent weekly P. All pts with PR or NR underwent a second cycle of induction with PF + AT-101. Pts with a >50% response (CR or PR) after the second cycle of induction chemotherapy underwent CRT. Pts with a <50% response (NR) underwent laryngectomy.

PET-CT was performed 12 weeks after CRT. Pts with residual disease underwent salvage laryngectomy (SL). Results: 54 eligible pts were enrolled; 46 M, 8 F; median age 59; 26 T4; stage IV 38; site: 2 hypopharyngeal, 39 supraglottic, 11 laryngeal, 2 subglottic. After cycle 1 of induction, 28/44 (64%) died prior to assessment by DL and 2 were removed from protocol due to adverse events (AEs). 29/50 pts (58%) had >50% response, 3 of which had CR; 2 proceeded to CRT & 1 received a 2nd cycle of IC. 21/50 pts (42%) had <50% response. A total of 48 pts received cycle 2 of IC. After the 2nd cycle, a total of 39/50 pts (78%) had >50% response & received CRT. No difference in response was seen with the addition of AT-101.

Conclusions: AT-101 did not improve responses to P. Treatment with 2 cycles of IC with PT produced similar response rates to our institutional controls, but organ preservation was somewhat less following treatment with weekly P + RT. Toxicities were overall improved with this treatment strategy. Clinical trial information: NCT01633541.

6067 Poster Session (Board #56), Sat, 1:15 PM-4:15 PM
Impact of smoking cessation in locally advanced head and neck cancers undergoing radiation. First Author: Ruth Lauren Sacks, MD Anderson, Houston, TX

Background: Multiple studies have highlighted the negative outcomes associated with smoking during radiation (XRT) for locally advanced head and neck cancer. However, there has been little research investigating the potential benefit of smoking cessation prior to XRT and the effect on response rates, relapse, distant metastases, secondary malignancies, and overall survival. Methods: From 2005-2012 with locally advanced head and neck cancer undergoing XRT. 127 were referred to the Tobacco Treatment Program (TTP) based on provider referrals, self-referrals, or screening. Of those referred and retrospectively reviewed, 89 were identified as current smokers and 41 of them participated in the TTP for smoking cessation. Among these 89 patients, 50 patients (18 participated in the TTP) quit smoking prior to XRT and 29 patients (19 participated in the TTP) continued to smoke, which are referred to as Quitters and Smokers, respectively. 10 patients (2 participated in the TTP) had incomplete data and were excluded from further analysis. Results: Quitters had 100% complete response (CR) on initial assessment following XRT. 7/50 (14%) developed relapsed disease with 4 local recurrences (LR) and 3 distant metastases (DM). 6/50 (12%) developed secondary malignancies. By contrast, Smokers had 96.5% CR on initial assessment following XRT. 8/29 (27.5%) developed relapsed disease with 6 LR and 2 DM. 6/29 (20.6%) developed secondary malignancies. The median follow ups for Quitters and Smokers were 57.5 and 54 months with overall survival rates of 82% and 79%, respectively.

Conclusions: Current smokers that achieved smoking cessation prior to XRT demonstrated lower rates of relapse, DM, and secondary malignancies compared to those that continued to smoke. Thus, smoking cessation is an integral part of head and neck cancer treatment and needs to be further incorporated in cancer care to improve cancer treatment outcomes. As a future direction, a comparable group of patients who did not smoke from the same time range will be compared for response rates, LR, DM, secondary malignancies, and survival.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Conclusions: (5-yr 90% vs 72% and 10-yr 86% vs 61%; p = 0.004). By HPV status, no difference in RFS suggests non-cancer-related causes of death in the WC and HC groups compared to the RT alone group. Method: Phase I study of NBTXR3 in head and neck squamous cell carcinoma (HNSCC) patients enrolled: 3 at 5%, 3 at 10%; 5 at 15% and 8 at 22% with no observed DLT or limiting toxicities (DLT) were primary endpoints of phase I. Absence of NBTXR3 leakage and preliminary efficacy using RECIST 1.1 principles were also evaluated. Results: The dose-escalation is complete. Nineteen patients were enrolled: 3 at 5%, 3 at 1%; 5 at 15% and 8 at 22% with no observed DLT or SAE related to NBTXR3 or IT injection. One grade 1 NBTXR3-related AE (asthenia at 22%) and four IT injection-related AEs (grade 2 oral pain; grade 1 dyspnea at 10%; grade 1 arthralgia at 22%) were reported. RT-related toxicity was as expected with IMRT. RP2D has been determined to be 22%, CT-scan assessment between 24h and 7 weeks post-IT injection demonstrated absence of NBTXR3 leakage in the surrounding tissues. Among 13 evaluable pts treated at doses >10%, 9 achieved a complete response of the injected lesion. Conclusions: These results show that NBTXR3 activated by RT is safe and well tolerated at all dosages with preliminary encouraging efficacy results. It thus represents a promising future treatment for frail and elderly pts with locally advanced HNSCC with limited treatment options. Expansion phase has started at the RP2D. Clinical trial information: NCT01946867.

Methods: Data from a published retrospective study (Geiger Oral Onc 2013) of HC vs WC in resected HNSCC was updated. Overall survival (OS) and recurrence-free survival (RFS) data were analyzed by Kaplan-Meier method for all pts and by HPV status. Multivariate analyses were performed to assess impact of HPV status, smoking, age, HC vs WC, and cumulative cisplatin dose ( < 200mg/m2 vs ≥ 200mg/m2). Results: 51 patients (pts) received HC and 53 WC. Median follow-up was 87.7 months (6.9-13.7). For the whole cohort, HC had significantly improved OS over WC (p = 0.0095; 5- and 10-year OS 84% and 70% vs 82% and 61%). No OS benefit for HC was seen in pts with HPV+ HNSCC (5- and 10-year OS 75% and 70% for HC vs 72% and 61% for WC; p = 0.75). For HPV-negative HNSCC, HC had borderline significance with HC vs WC (5- and 10-year OS 73% and 68% vs 65% and 44%; p = 0.06). For the whole cohort, there was no difference in 5- and 10-year RFS (78% and 74% for HC vs 72% and 62% for WC; p = 0.32). When analyzed by HPV status, there was no difference in RFS with HC or WC for either HPV+ (p = 0.43) or HPV-negative HC (p = 0.97). On multivariate analyses of OS for all pts, only HPV status was significant (p = 0.0095; HR 0.78, CI 0.60-0.991; 11.6% 5- and 10-year OS 84% and 72% vs 82% and 61%; p = 0.004). By HPV status, cumulative dose had no significant effect on OS. Conclusions: OS is better with HC and with cumulative dose >200 mg/m2 in unselected patients. The benefit of cisplatin is likely higher for non-HPV HNSCC. A difference in OS with no difference in RFS suggests non-cancer-related causes of death in the WC cohort. Ability to receive HC could be a surrogate marker of comorbidity.

Original study cohort characteristics.

<table>
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<td>T, N-stage, primary site</td>
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Safety of nivolumab and ipilimumab in combination with radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN). First Author: Jennifer Maria Johnson, Thomas Jefferson University Hospital, Philadelphia, PA

Methods: We enrolled a Phase II study, the primary endpoint being 3+ months progression-free survival (PFS) for newly diagnosed patients with locally advanced head and neck cancer treated with radiotherapy and immunotherapy. Preliminary results with this non-platinum-containing RT plus 10 regimen are encouraging. Longer follow-up is needed for assessment of late effects and efficacy. Enrollment is ongoing in the expansion cohort. This study is supported by BMS. Clinical trial information: NCT03162731.
6073 Poster Session (Board #62), Sat, 1:15 PM-4:15 PM

Safety and disease control achieved with the addition of nivolumab (Nivo) to chemoradiotherapy (CRT) for intermediate (IR) and high-risk (HR) locally-advanced, advanced head and neck squamous cell carcinoma (HNSCC): RTOG Foundation 3504. First Author: Maura L. Gillison, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Nivo, which inhibits the programmed death-1 (PD-1) receptor, improved survival for pts with platinum-refractory recurrent/metastatic HNSCC. A clinical trial evaluated the safety of adding nivo to 4 standard intensity modulated (chemo) radiotherapy (RT) regimens (see table) for pts with newly diagnosed IR/HR HNSCC. Methods: Eligibility included IR (p16+ oralopht, oxorganoph, op, T1-N2b-N3/T3-4N0-3, >10 year pack-years, or T4N0-T3/N1-3N3, ≤10 yrs) or HR HNSCC (oral cavity, larynx, hypopharynx, p16+ op, T1-N2a-N3/T3-4N0-3), 10 pts/arm (8 evaluable; 0-2/8 DLTs acceptable). Nivo (dose & schedule varied per arm) started 2 wks pre-RT & continued 3 months post-RT. Feasibility of administering nivo months 3-12 post-RT defined as ≤4 of 8 pts/arm received 7 doses. Arm 4 limited to age ≥70, Zubrod performance status (PS) 2, CCI ≤50 mL/min, grade ≥2 hearing loss or ≥ grade 3 neuropathy. Results: Characteristics of 39/40 treated pts: median age 62, 79% male, 49% PS0, 38% HR, 67% p16+, 72% T3-4, 85% N2-3, Grade ≥3 niv-related, AEs: dehydration-3%, anemia-2%, fatigue-3%, nausea, vomiting, lipase increase-6%, amylase increase-2%, lymphoocyte/neutrophil WBC decrease-4%, hyponatremia-3%, anorexia, macula-papular rash, SAE in 4/5, 4.9/5, 4/10, 4/10. DLTs: adjuvant chemofeasibility, median follow-up (mo), progression or death events per arm shown in table. Conclusion: Nivo concomitant with all (chemo)RT regimens was safe for pts with newly diagnosed IR/HR HNSCC but nivo unsafe for high-dose cisplatin or in cisplatin-ineligible pts (NCT02764593). Preliminary data on progression/death is provided. Acknowledgements: Support for this study was provided by Bristol-Myers Squibb Company. Clinical trial information: NCT02764593.

Cost-effectiveness analysis of chemoradiation compared to radiation alone in the treatment of non-metastatic oropharyngeal cancer. First Author: Husam Albarmawi, University of Maryland School of Pharmacy, Baltimore, MD

Background: Using concurrent chemoradiation (CRT) to treat oropharyngeal cancer (OPC) has increased since 2000. However, there is limited information regarding the cost-effectiveness of CRT compared to radiation alone (RT) especially given the approval of cetuximab (cetux) in 2006. We conducted a cost-effectiveness analysis to compare the platinum-based CRT compared to RT and cetuximab plus RT (cetux-CRT) compared to RT to determine the value of CRT over time. Methods: In this retrospective cohort study, we identified non-metastatic OPC patients aged 66 years or older diagnosed between 2000-2011 using the linked Surveillance, Epidemiology and End Results-SEER-NCH dataset. We divided all cohorts based on the diagnosis period. 2000-2005 (Cohort I) and 2006-2011 (Cohort II). Cetux-CRT was added in Cohort II only. We matched the platinum-based CRT and cetux-CRT groups to the RT groups using propensity score models that included age, race, marital status, income, Charlson Comorbidity Index and stage at diagnosis. The outcomes were incremental cost, incremental life-year gained (LYG) and incremental cost-effectiveness ratio (ICER) during the 3 years after diagnosis. Costs were estimated from the Medicare perspective and using 2017 USD. Results: 2,646 OPC patients were eligible for the study. The estimated parameters with the corresponding 95% confidence intervals (CI) are shown in the table. Conclusions: From 2000-2005, platinum-based CRT was a cost-effective option compared to RT. From 2006-2011 and compared to RT, platinum-based CRT provided a survival benefit at higher costs while cetux-CRT patients incurred higher costs with no survival benefit.

6074 Poster Session (Board #63), Sat, 1:15 PM-4:15 PM

Is there a benefit of adding surveillance imaging to frequent history and physical examination in patients treated definitively for head and neck squamous cell carcinoma? First Author: Jeffrey Chi, Northwell Health, Lake Success, NY

Background: In head and neck squamous cell carcinoma (HNSCC) patients (pts) who completed curative-intent definitive treatment (tx), close surveillance is important. Across all centers, pts are closely monitored for symptoms and undergo frequent dedicated head and neck evaluation. Role of surveillance imaging after the initial 12 week post-treatment PET/CT has been a matter of less clear. Our institutional practice is to follow pts with regular interval imaging for two years after treatment. However this carries a financial cost, and risk for false positives and unnecessary biopsies. Methods: This is a retrospective chart review of pts treated definitively for HNSCC at our institution from 2012 to 2016. Pts who had a biopsy (bx) post-tx due to suspicion for recurrence were included. Pts belonged to 3 groups: In the first group (A), biopsy was prompted by findings on surveillance imaging (SI); in the second (B), biopsy was prompted by symptom triggered imaging (STI) and in the third (C), biopsy was based on physical exam (PE). We recorded the aggregate results of bx in each group and calculated the positive predictive value (PPV) for each. Results: Of 353 HNSCC pts, 66 underwent post-tx bx for suspected recurrence of which 46 were positive. Of the 30 pts in group A, 21 had positive bx (PPV = 70%). Within this group, PPV was highest with PET/CT (81.82%) followed by magnetic resonance imaging (66.67%) and CT (62.5%). 20 out of 20 pts in group B had bx proven recurrence (PPV = 100%). In group C, 36 pts in 36 pts in group C (PPV = 75%). While there was no overlap between groups A and B, there was some overlap between groups A and C; and B and C. 45.45% of all recurrences were captured because of SI. When both imaging and PE were performed simultaneously, 54.35% of recurrences were detected first by PE and 45.65% by imaging alone. BX triggered by SI had the highest PPV. SI has the lowest PPV, but 45.65% of recurrences were diagnosed because of SI alone. Our study suggests that routine SI for at least two years post-treatment for HNSCC pts may add to the surveillance value of frequent PE but larger studies are needed to determine the optimal frequency and type of SI modality.

6075 Poster Session (Board #64), Sat, 1:15 PM-4:15 PM

Analysis of hydration and anti-emetics policies in preventing cisplatin-related gastrointestinal and renal toxicities in low-risk human papillomavirus positive-oropharyngeal cancer (HPV+OPC) patients undergoing chemoradia- tion in De-ESCALaTE trial. First Author: Anthony Hee Kong, University of Birmingham, Birmingham, United Kingdom

Background: The De-ESCALaTE trial confirmed the superiority of cisplatin over cetuximab in combination with radiotherapy for the treatment of low-risk human papillomavirus positive oropharyngeal cancer (HPV+OPC). The most common serious adverse events (SAEs) for cisplatin were due to vomiting and nausea, in contrast with oral mucositis and vomiting for concurrent cetuximab. In this study, we examined the efficacy of different hydration and anti-emetic policies in preventing cisplatin-related gastrointestinal and renal toxicities as well as related SAEs in the cisplatin arm of the De-ESCALaTE trial. Methods: This was a post-hoc pre-specified analysis of data collected within the De-ESCALaTE trial including pre-hydration, diuretics, the amount of intravenous (IV) fluids before, during and after chemotherapy, whether oral fluid hydration was advised and type of antiemetici regimen prescribed, if any, after chemotherapy administration, including if a triple antiemetic regimen with a NK1 receptor antagonist, steroids and a serotonin 5-HT3 antagonist was given before and after chemotherapy. The primary outcome was number of SAEs per patient; secondary outcome was number per patient of cisplatin-induced severe toxicity events of interest: nausea, vomiting, dehydration or renal toxicity. Results: 166 (mean age 57 yrs; 132 m, 34 f) patients received cisplatin. Hydration and anti-emetics policies for cisplatin treatment are significantly correlated with the rate of SAEs and acute severe nausea, vomiting, dehydration or renal toxicities. Using stepwise backwards multivariable ordinal logistic regression in the presence of baseline characteristics, use of a triple anti-emetics regimen (OR 0.41, p = 0.032) and 2.5 to 3L IV fluids before and after cisplatin chemotherapy (OR 0.161, p = 0.009) as well as oral fluids advised post chemotherapy (OR 0.365, p = 0.03) were associated with a significantly lower incidence of SAEs and severe toxicities of interest. We will also present data on relative cost-effectiveness of the different regimens. Conclusions: Based on our results, we recommend the use of a triple anti-emetics regimen, as well as hydration of 2.5 to 3L before and after chemotherapy as well as advising patients to take oral fluids advised to reduce cisplatin toxicities related to nausea, vomiting, dehydration and/or renal injury. Clinical trial information: ISRCTN33522080.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Concomitant chemoradiotherapy (CT/RT) is the standard treat-
ment for locally advanced non-resectable squamous cell carcinoma of the head
and neck. Acute side effects can be serious and late effects important. Patients
with HPV+ tumors carry a better prognosis than other patients. De-escalation
studies are explored with respect to RT, dose, fractionation, target volume
and adjuvant pharmacotherapy, with encouraging results. However, several patients
still recur locoregionally, also in high dose RT volumes. Some patients have
distant metastases, often with massive tumor burden and late during follow up (FU).
Purpose of the study: 1. To evaluate the effect of induction chemothera
ypy (IC) of (a) progression free survival (b) distant metastases as first site of failure (c)
locoregional failure (d) pattern of tumor response, spatial and temporarily, exploring
the possibility to reduce RT dose and/or target volume(s) in future protocols. To
address the impact of high dose RT for bulky disease, T4/T4 given concuręnt with cis etuximab (E). Methods: Patients had previously untreated stage IIIIV
(>80 % int IV, T3N 7ii), MO disease, WHO 0-1, unresectable squamous cell
carcinoma of the head and neck, HPN positive as evaluated with p16 and/or
PCR. Pts were randomised between 2 arms. Pts in arm A were scheduled for 2
tycles of TPF: T (docetaxel) 75 mg/m2 day 1, P (cisplatin) 75 mg/m2 day 1 and F
(Fluorouraci) 1000 mg/m2 over 24 hours day 1-4. RT was delivered to IMRT
at 3.3 Gy in 6 weeks for T4/T4 tumors, 7.6 Gy in 6 weeks for T3/T4 tumors. 76 Gy in 6
weeks for E given once week before and weekly during RT. Tumor response was
evaluated according to RECIST with CT, MRI or PET/CT after IC, at 6-8 weeks, 1
and 2 years FU. Results: From January 2011 to February 2016, 152 consecutive
pts were enrolled, 77 in arm A. All pts had oropharyngeal cancer. In arm A, 7 pts had
toxicities. Only 13/636 pts (2%) received an out of 36 evaluable pts. At 2 years FU 70/77
(91%) were alive in arm A, 69/75 (92%) in arm B. Distant metastases as first site of failure
was 3 (3.9%) in arm A and 7 (9.3%) in arm B. Adverse events grade 3-
4, ever registered, were seen in 71 pts in arm A and 63 in arm B, were transient,
most often related to RT. Conclusions: Survival and locoregional control at 2
years were similar and similar in both arms. Distant metastases as first site of failure
was more than doubled in arm B, not having induction chemotherapy (IC). Clinical trial information: EuDrCT number: 2009-013438-26.

Background: Cis is the gold standard radiosensitizer for CRT to treat head
and neck cancer. Prospective trials have required that cis be administered
early in the week (Mon/Tues) to optimize radiosensitization without evidence
to support this practice. This retrospective analysis considers the impact of cis
administration over a week. Dosed FTC were evaluated on their administration (DOW) and its
impact on OPSCC pt outcomes. Methods: We reviewed OPSCC cases treated with primary CRT at
our center. Pts treated with non-cis or induction chemotherapy were excluded.
Data collected includes age, DOW (Mon/Tues vs Wed/Thurs/Fri), smoking status, total dose (TD) of cis (=200mg/m2 vs >200 mg/m2), single dose (SID) (100mg/m2 x 1 day) vs split dose (SpD) [50mg/m2 x 2 days],
administration, T stage (0-2b vs 2c-3), N stage (0-2b vs 2c-3), overall survival (OS) (from start of RT), local/regional/distant failure, KPS and HPV/
p16 status. Univariate Cox proportional hazards regression was used to
evaluate the effect of cisplatin dose, DOW (Mon/Tues vs Wed/Thurs/Fri), smoking status,
total dose of cisplatin. DFS was significantly better with higher cisplatin dose (HR =
0.95 per 100 mg/m2 increase in cisplatin). Administration schedule of cis-
platin (weekly versus high dose) was not significantly associated with DFS.
In univariate analysis, age, N stage, T stage, KPS and HPV/p16 status were
significantly associated with OS, while DOW, TD, and SpD were not. In
multivariate analysis (MVA), none of the associations between cis dosing and
OS were significant (although MVA was limited by low number of events and
total variables included). Conclusions: This retrospective analysis suggests that
the DOW cis is given has no impact on CRT outcomes for OPSCC pts. SpD cis
despite the alternative administration approach.

Impact of antiviral prophylaxis in HPV positive patients treated with concurr
ten chemoradiotherapy for head and neck cancer. First Author: Nathalie
Lelarte. Centre de recherche du Centre hospitalier de l'Université de Montréal (CIRCHUM), Montréal, QC, Canada

Background: Chemoradiotherapy used for the treatment of locally advanced
head and neck cancer (HNC) causes a high incidence of mucositis that may be
accentuated by a reactivation of herpes simplex virus (HSV). To date, no study has evaluated the impact of antivirals used as prophylaxis to prevent
mucositis or their severity. Methods: This is a retrospective observational study
involving patients who received at least one cycle of concurrent chemoradiotherapy for the treatment of head and neck cancer between January 2014 and June 2017 at the Centre hospitalier de l'Université de Montréal (CHUM). HSV negative patients were excluded. After approval by the IRB, we compared the incidence and severity of mucositis in HSV positive patients who started an antiviral prophylaxis before cycle 1 or 2
(prophylaxis group) to HSV-unknown HSV positive patients who did not receive
antiviral prophylaxis (control group). Emergency visits and hospitalizations
related to mucositis were collected. Mucositis were assessed regularly by
radiation oncologists during the treatment. Results: Of 482 patients who received
concurrent chemoradiotherapy for HNC, 75 were HSV negative and 407 were included in this study. In the group with (n = 94) and without
prophylaxis (n = 313), patients received carboplatin and 5-FU (77% vs 62%)
and cisplatin (23% vs 38%) with concurrent radiation respectively. The rate
of all grade mucositis in patients with and without prophylaxis (95% vs 96%;
p = 0.19) was not statistically significant. The rate of grade 3/4 mucositis was
(42% vs 49%; p = 0.29), the rate of emergency visit (29% vs 28%; p = 0.91)
and hospitalization (9% vs 8%; p = 0.80) were not statistically significant
between each group. However, in a subgroup of patient receiving carboplatin
and 5-FU, antiviral prophylaxis seems to decrease significantly the rate of
grade 3+4 mucositis (p = 0.04). Conclusions: The addition of antiviral
prophylaxis in HSV positive in patients undergoing concurrent chemora
diotherapy for locally advanced HNC didn't decrease the rate of all grade
mucositis. In the subgroup of patients receiving carboplatin and 5-FU mainly
of oropharynx origin, HSV prophylaxis decreased the severity of mucositis.

Outcomes of postoperative treatment with concurrent chemoradiotherapy
(CRT) in high-risk resected oral cavity squamous cell carcinoma (OCSCC)
A multi-institutional collaboration, First Author: Jessica Lyn Geiger, Cleveland Clinic,
Cleveland, OH

Background: Adjuvant CRT with high-dose cisplatin remains standard treat
ment for OCSCC with high risk pathologic features of positive surgical margins
(SM+) and/or extranodal extension (ENE). High-dose cisplatin is associated
with significant toxicities, and alternative dosing schedules or treatments are
used. We evaluated outcomes associated with different systemic therapies
concurrent with RT and the effect of cumulative dosing of cisplatin. Methods: An IRB-approved collaborative database of patients (pts) with pri
mary OCSCC (Stage I-IVB AJCC 7th edition) treated with primary surgical
resection between 1/1/2005 and 1/1/2015 with or without adjuvant therapy
was established from 6 academic institutions. Pts were categorized by sys
temic therapy received, and resultant groups compared for demographic data,
pathologic features, and outcomes by t-test and Chi-squared tests. Kaplan-Meier
curves, log-rank p-values, and multivariate analysis (MVA) for disease
free survival (DFS) and freedom from metastatic disease (DM). Results: From
a total sample size of 1282 pts, 196 pts were identified with high risk features
(SM+, ENE) who were treated with adjuvant CRT. Median age was 56 years,
63.3% of pts were men, 81.1% were Caucasian, 70.9% had significant to
bacca history. 35.7% of pts had SM+, 82.7% ENE, 65.3% with perineural invasion (PNI), 49% had lymphovascular space invasion (LVS
). There was a trend associating higher cisplatin dose delivered with improved locoregional control, DM, and overall survival (OS) (p-values 0.131, 0.084, and 0.187,
respectively). DFS was significantly better with higher cisplatin dose (HR = 0.95 per 100 mg/m2 increase in cisplatin). Administration schedule of cis
platin (weekly versus high-dose) was not significantly associated with DFS.
On multivariate analysis, age, N stage, T stage, KPS and HPV/p16 status were
significantly associated with OS, while DOW, TD, and SpD were not. In
multivariate analysis (MVA), none of the associations between cis dosing
and OS were significant (although MVA was limited by low number of events and
total variables included). Conclusions: This retrospective analysis suggests
that the DOW cis is given has no impact on CRT outcomes for OPSCC pts. SpD cis
despite the alternative administration approach.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
6081 Poster Session (Board #70), Sat, 1:15 PM-4:15 PM
Influence of tumor size and Eastern Cooperative Oncology Group performance status (ECOG PS) at baseline on patient (pt) outcomes in lenvatinib-treated radiodine-refractory differentiated thyroid cancer (RR-DTC). First Author: Lori J. Wirth, Massachusetts General Hospital Cancer Center, Harvard University, Boston, MA

Background: In SELECT, lenvatinib significantly improved progression-free survival (PFS) of pts with RR-DTC versus placebo (18.3 v 3.6 months; hazard ratio [HR]: 0.21 [99% CI: 0.14, 0.31]; P<0.001). Here we examine the treatment of RR-DTC with lenvatinib in relation to tumor size (sum of all largest lesions) and ECOG PS. Methods: In this post hoc analysis of SELECT with pts randomized to receive lenvatinib, Kaplan-Meier estimates of time to ECOG PS ≥ 2 were calculated for subgroups of pts according to baseline ECOG PS or tumor size. Objective response rate (ORR) and Kaplan-Meier estimates of overall survival (OS) and PFS according to ECOG PS (0 or 1) at baseline were calculated. Correlations between ECOG PS at baseline (0 or 1) and maximum tumor shrinkage were calculated using one-way analysis of variance. Results: Pfs with ECOG PS 0 or 1 at baseline had similar demographic and disease characteristics. ORR was 78.5% and 51.0% for pts with ECOG PS 0 and 1 at baseline, respectively (odds ratio [95% CI]: 3.508 [2.018, 6.097]). Mean maximum percent decrease in tumor size was significantly greater in pts with baseline ECOG PS 0 (46.13%) versus pts with ECOG PS 1 (-37.16%; P=0.001). For pts with ECOG PS 1 at baseline, time to ECOG PS ≥ 2 was numerically shorter with tumor size > 60 mm versus tumor size ≤ 60 mm (HR [95% CI]: 1.450 (0.708, 2.967)). Additional results are summarized in the table. Conclusions: Among pts with RR-DTC, FFS, OS, ORR, and time to ECOG PS ≥ 2 were generally better for patients with lower ECOG PS or smaller tumor size at baseline. These results may indicate that it is beneficial to start lenvatinib in pts with RR-DTC early, before ECOG PS worsens and tumor size increases. Clinical trial information: NCT01321554.

<table>
<thead>
<tr>
<th>Time to ECOG PS ≥ 2</th>
<th>Tumor size*</th>
<th>OS</th>
<th>PFS</th>
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<tr>
<td>ECOG PS 0 or 1</td>
<td>≤ 35 mm</td>
<td>45</td>
<td>85</td>
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<tr>
<td></td>
<td>&gt; 35 – ≤ 60 mm</td>
<td>25</td>
<td>60</td>
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<td></td>
<td>&gt; 60 – ≤ 92 mm</td>
<td>20</td>
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</tr>
<tr>
<td></td>
<td>&gt; 92 mm</td>
<td>15</td>
<td>35</td>
</tr>
</tbody>
</table>

*Sum of all targeted lesions at baseline.

6083 Poster Session (Board #72), Sat, 1:15 PM-4:15 PM
NISCANH: A phase II, multicenter nonrandomized trial aiming at evaluating nivolumab (N) in head and neck (H&N) cancers. First Author: Jerome Fayette, Centre Léon Bérard, Medical Oncology, Lyon, France

Background: SGCHN are rare tumors including adenoid cystic carcinoma (ACC) and non-ACC, with no standard systemic treatment for R/M pts. We evaluated N monotherapy in R/M SGCHN pts. Methods: R/M SGCHN pts (ACC or non-ACC) not eligible to local treatment were included in this phase II study. The primary endpoint was progression-free survival (PFS) in the first stage. Secondary endpoints included ORR, PFS, OS, and safety. Considering that N would be uninteresting if NFRen ≥ 20% and promising if ≤ 40% and using a Fleming’s single-stage design (α: 5% unilateral, power: 90%), at least 14 successes/42 evaluable pts were required for each cohort to be positive. Results: 46 ACC and 52 Non-ACC pts (median age 61 yrs [range 29-81], 43.9% female, 51.5% PS1 and 2.0% PS2) were enrolled and received at least one dose of N. Median treatment duration was 5.5 mo (ACC) and 3.3 (Non-ACC). Median FU was 10.8 mo (ACC) and 8.3 mo (Non-ACC). 95 pts were evaluable for the primary endpoint. NFRen was 15/45 pts (33.3%, 90%CI [21.8; 46.6]) and 7750 pts (14.0%, 90%CI [6.8; 24.7]) for ACC and non-ACC pts respectively. 4 (8.7%) partial responses (PR) and 26 (56.5%) stable diseases (SD) were observed in ACC cohort while 2 (3.8%) PR and 22 (42.3%) SD were observed in non-ACC. Median PFS was 4.9 mo (95%CI = 3.4; 5.6) in ACC pts and 1.8 mo (95%CI = 1.7; 3.5) in non-ACC pts. The most common related adverse events (AE) (> 10% by cohort) were asthenia, hypothyroidism, diarrhea, rash, pruritus, and hyperglycemia. 298 pts (71.1%) presented 1 or more related adverse events (AE). 34 Grade 3-4 (mainly hepatic) and 9 pts (9.2%) prematurely discontinued Nivolumab due to toxicity. Conclusions: Limited efficacy was observed with N in R/M SGCHN pts. N in combination might be of interest and deserves exploration in ACC pts. Clinical trial information: NCT03132038.

6082 Poster Session (Board #71), Sat, 1:15 PM-4:15 PM
A randomized phase II study of pembrolizumab with or without radiation in patients with recurrent or metastatic adenoid cystic carcinoma. First Author: Jonathan S. Daniel Schiffer, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Adenoid cystic carcinoma (ACC) is a salivary gland malignancy characterized by a high rate of distant recurrence. Systemic therapy has generally failed to produce durable benefit. Radiation (RT) is used for localized disease and as directed treatment for metastases. Here, we report the safety and efficacy of pembrolizumab (pembro) administered with or without hypofractionated RT in a phase II randomized study. Methods: Eligible pts (pts) have recurrent or metastatic ACC with evidence of progressive disease (PD) within the last 12 mos and ≥ 1 measurable non-CNS lesion, along with 1-5 additional lesions deemed appropriate for RT to 30 Gy in 5 fractions. Pts were randomized to pembro alone (200 mg IV q3 weeks) or in combination with RT given within 7 days of cycle 1, day 1. The primary endpoint was objective response rate (ORR) outside the RT field by RECIST 1.1. Using a parallel two-stage design, if ≥1 response out of 10 was observed in either arm, 10 more pts would be enrolled to that arm. If ≥3 responded, the null hypothesis (ORR=5%) would be rejected in favor of a 25% ORR. Predefined secondary endpoints included progression free survival (PFS) and toxicity. Analyses of tumor growth rate (TGR) excluding RT lesions and immune biomarkers were exploratory. Results: Ten pts per arm were randomized into the trial’s first stage with median age 65 (45-79). No objective responses were seen. Stable disease (SD) was observed in 13 pts; 6 had PD as best response, 1 was unacceptable. Median PFS was 7 mos (95% CI: 3-13 mos), with 9 pts without progression at 6 mos. More pts remain on study treatment (range 11-31 mos). In pts with SD, TGR decreased by >25% in 7 of 12 pts and by >75% in 4 pts. There was no difference in likelihood of SD or PFS between arms. Treatment related AEs (TRAEs) occurred in 18 pts but there were no G3-5 TRAEs. Among 8 biopsies analyzed, PD-L1+ tumor/immune cells ranged from 12-52%. Conclusions: Pembro alone or with hypofractionated RT was well tolerated. We observed no objective responses, but 65% of pts with PD prior to study entry achieved SD, the majority with decreased TGR, and 15% had prolonged SD. Additional strategies are needed to further delay progression and effect response. Clinical trial information: NCT03087019.

6084 Poster Session (Board #73), Sat, 1:15 PM-4:15 PM
A phase II trial cohort of nivolumab plus ipilimumab in patients (Pts) with recurrent/metastatic adenoid cystic carcinoma (R/M ACC). First Author: Vatche Tchekmedyan, Memorial Sloan Kettering Cancer Center, NY, NY

Background: R/M ACC is a malignant neoplasm most commonly of salivary gland origin with no standard treatment. The impact of combined PD-1/CTLA-4 checkpoint blockade in R/M ACC is unknown. Methods: In a two-stage minmax phase II trial, pts with progressive R/M ACC (non-salivary primaries allowed) were enrolled and treated with nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (1 cycle = 6 weeks). Imaging, using RECIST v1.1 response assessment, was scheduled to be performed approximately every 12 weeks. The primary endpoint was overall response rate (ORR = complete response [CR]+partial response [PR]) per RECIST v1.1. To detect a difference between an unacceptable ORR of 5% and a desirable ORR of 20% (one-sided type I error of 10%, power of 90%), at least 1 in the first 18 pts required an observed response. At least 4 responses of 32 total pts were needed to meet the primary endpoint. Treatment beyond progression of disease (PD) was allowed at the discretion of the investigator. A second cohort of pts with non-ACC salivary cancer is still accruing for separate analysis. Results: From 6/12/2017-6/20/2018, 32 pts were enrolled and evaluable for the primary endpoint. There was 1 confirmed PR in the first 18 pts, therefore enrollment of the second stage continued. ORR was 6% (2/32). One additional pt had an unconfirmed PR (~31% regression before CNS PD). From 6/20/2018-6/20/2019, another 2 pts were enrolled and evaluable for the primary endpoint. There were 2 PRs, 15 SD, and 11 PD. Four pts never reached a first disease assessment; 3 due to death from clinical PD and 1 was removed for toxicity. Six pts discontinued the trial for toxicities (Grade 4 [G4] neutropenia/sepsis and G3 adrenal insufficiency (1), G2 hypophosphatosis (2), G3 arthrosis > 7 days (1), G3 colitis (1), and G3 hepatitis/G4 creatinine kinase (CK) elevation (1)). The 2 confirmed PRs consisted of ~73.1% and ~58.4% regressions, with a duration of therapy of 18.4 and 7.8 months, respectively (treatment ongoing for both). Conclusions: The study did not meet its primary endpoint, though the responses observed were dramatic. Paired biopsy and peripheral blood samples will be analyzed to elucidate insights into mechanisms of response and resistance to dual checkpoint blockade. Clinical trial information: NCT03172624.
Development and validation of a prediction-score model for distant metastases in major salivary gland carcinoma. First Author: Jelena Lukovic, Department of Radiation Oncology, Princess Margaret Cancer Center, Toronto, ON, Canada.

**Background:** We developed and validated a prediction-score for distant metastases (DM) in major salivary gland carcinoma (SGC). Methods: Patients with SGC treated with curative-intent surgery +/- postoperative radiation therapy (PORT) at 4 tertiary cancer centers were divided into discovery (institution A&B) and validation (institution C&D) cohorts. Multivariable analysis using competing risk regression was used to identify predictors of DM in the discovery cohort and create a prediction score. The optimal score cut-off for high vs low-DM risk was determined using a minimal p-value approach. The results were subsequently evaluated in the validation cohort. The cumulative incidence and Kaplan-Meier methods were used to analyze DM and overall survival (OS), respectively. Results: 1035 patients were included (Table). In the discovery cohort, DM predictors (risk score coefficient): were: positive margin (0.6), pT3-4 (0.7), pN+ (0.7), lymphovascular invasion (LV; 0.8), and high risk histology* (1.2). High DM-risk SGC was defined by sum of coefficients greater than 2. In the discovery cohort, the 5-year cumulative incidence of DM for high vs low risk SGC was 50% vs 8%; p < 0.01; these results were similar in the validation cohort (44% vs 4% at 5 years; p < 0.01). In the combined cohorts, this model predicted distant-only failure (40% vs 6%; p < 0.01) and late (>2 yr post surgery) DM (22% vs 4%; p < 0.01). Patients with high DM-risk SGC had a decreased incidence of DM in the subgroup receiving PORT (46% vs 8%; p < 0.01) or concurrent chemotherapy (71% vs 34%; p < 0.01). The 5 yr-OS for high vs low risk SGC was 48% vs 92% (p < 0.01). Conclusions: This validated prediction score model may be used to identify SGC patients at increased risk for DM and select those who may benefit from prospective evaluation of treatment intensification and surveillance strategies. Baseline characteristics:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Discovery (n=932)</th>
<th>Validation (n=442)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Median follow up, yrs</td>
<td>5.3</td>
<td>5.1</td>
<td>0.18</td>
</tr>
<tr>
<td>Median age, yrs</td>
<td>56</td>
<td>57</td>
<td>0.19</td>
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<tr>
<td>Gender, male</td>
<td>518 (56%)</td>
<td>329 (79%)</td>
<td>0.17</td>
</tr>
<tr>
<td>LVI</td>
<td>6 (2)</td>
<td>7 (1.6)</td>
<td>0.61</td>
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<tr>
<td>Positive margin</td>
<td>285 (30.5%)</td>
<td>150 (33%)</td>
<td>0.6</td>
</tr>
<tr>
<td>High risk histology*</td>
<td>372 (40%)</td>
<td>224 (50%)</td>
<td>0.04</td>
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<tr>
<td>pT3-4</td>
<td>224 (36)</td>
<td>129 (31)</td>
<td>0.09</td>
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<tr>
<td>pN+</td>
<td>145 (25)</td>
<td>89 (21)</td>
<td>0.45</td>
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<tr>
<td>PORT</td>
<td>215 (35)</td>
<td>158 (38)</td>
<td>0.6</td>
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<tr>
<td>5-yr DM (95% CI)</td>
<td>20% (17-24%)</td>
<td>14% (11-18%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*High risk histology: adenoid cystic carcinoma, salivary duct carcinoma, carcinosarcoma, undifferentiated carcinoma

Genomic landscapes of FNAs positive for medullary thyroid cancer (MTC) and potential impact on systemic therapy. First Author: Lori J. Witch, Massachusetts General Hospital Cancer Center, Harvard University, Boston, MA

**Background:** Systemic therapies targeting specific genomic alterations in advanced MTC are available or under investigation. The Afirma Genomic Sequencing Classifier (GSC) uses RNA sequencing to assess FNA specimens from cytologically indeterminate thyroid nodules, which are also tested for specific molecular aberrations associated with thyroid cancer via a suite of highly accurate malignancy classifiers. This suite can be applied independently to Bethesda V VI nodules. The Afirma Xpression Atlas (XA) is an additional test that can be combined with Afirma GSC to report nucleotide variants and fusions across 511 cancer-associated genes. Here we report the prevalence and genomic landscape of MTC classifier positive (MTC+) FNA samples. Methods: All Afirma GSC and malignancy classifier tests run in the Veracyte Clinical Laboratory between July 2017 and January 2019 were deidentified and examined for MTC+ cases. Afirma XA was run on all such cases, and all variants and fusions were tabulated. Results: Examination of 29,895 FNAs revealed 90 MTC cases. Of 22,793 Bethesda III cases, 32 (0.14%) were MTC+. Of 5,491 Bethesda IV cases, 33 (0.60%) were MTC+. Provider-ordered testing was done on an additional 16 and 9 MTC cases from Bethesda V and VI nodules, respectively. 58% of all MTC+ samples harbored a RET variant (+/- others), 9% contained a KRAS variant (+/- others), 6% included an HRAS variant, 1% had a BRAF fusion, 1% demonstrated other fusions, and 26% held no variant/fusion. Conclusions: In our cohort, Afirma XA identified a variant or fusion in 74% of MTC+ FNAs. Currently approved or investigational therapies exist for cancers with RET, BRAF and HRAS alterations, suggesting that 64% of our series might be eligible for treatment based on current FDA approval guidelines. In advanced MTC, noninvasive FNA sample collection at the time of diagnosis may ultimately impact on targeted therapy selection, with the option to repeat FNA testing should the disease progress. Future studies may investigate how finding a genomic alteration by FNA can inform the management of MTC and, in the case of progressive disease, improve our understanding of the mechanisms of disease progression and drug resistance.

Genomic landscape of FNAs positive for medullary thyroid cancer (MTC) and potential impact on systemic therapy. First Author: Lori J. Witch, Massachusetts General Hospital Cancer Center, Harvard University, Boston, MA

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Pilot study combining PD-L1 antibody durvalumab (D) with CTLA-4 antibody tremelimumab (T) and stereotactic body radiotherapy (SBRT) to treat metastatic anaplastic thyroid cancer (ATC). First Author: Eric Jeffrey Sherman, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** ATC is a rare and aggressive cancer with very limited treatment options. The thyroid is one of the most immunogenic organs in the body and PD-L1 is commonly expressed on ATC tumor cells and PD-1 in the inflammatory cells in the ATC microenvironment. However, antibodies to PD-1 as single agents did not produce an "abscopal" effect. Major inclusion criteria: Metastatic ATC; ECOG PS 0-2; No prior immunotherapy; Last anti-cancer treatment > 7 days prior to starting study. Primary objective 1-year overall survival with target of ≥ 2 out of 12 patients. Results: 12 patients were accrued. Male – 50%; Median PS 1; Median Age – 71 (49-82); Prior radiation to neck (75%); Prior chemotherapy (75%). MSI-High was noted in 2/11 subjects. BRAFV600E mutation in 3/12 subjects. There were 0 confirmed responses and only 1 subject with SD for 4 cycles or longer. Median time on treatment was 11 weeks (1-28+ weeks). MSI status did not affect treatment response. MSI-High patients were on treatment before progression for 8-14 weeks. Median overall survival was 14.5 weeks with only one patient alive past 1 year. Neither the presence of a BRAF or p53 mutation appeared to affect either outcome. Conclusions: T/D with SBRT was not active in metastatic ATC. Future studies looking at other novel immunotherapy combinations in ATC should be evaluated. Biopsies done on study are being analyzed. Clinical trial information: NCT03122496.
TPS6089
Poster Session (Board #78a), Sat, 1:15 PM-4:15 PM
A multicenter, randomized, double-blind, placebo-controlled phase III study of anlotinib or placebo in combination with gemcitabine and cisplatin (GP) as first-line therapy for recurrent or metastatic nasopharyngeal carcinoma (R/M NPC). First Author: Yunpeng Yang, State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine; Sun Yat-sen University Cancer Center, Guangzhou, China

Background: GP is the standard first-line chemotherapy for R/M NPC. However, the outcome of patients who are refractory to first-line chemotherapy is poor. There remains an unmet need for more effective first-line treatment. Overexpression of vascular endothelial growth factor (VEGF) is common in NPC, and the higher expression is related to lower OS. This feature makes NPC potentially suitable for antiangiogenic treatment. Anlotinib is a novel multi-target tyrosine kinase inhibitor that targets VEGF R 1 to 3, fibroblast growth factor receptor 1 to 4, and platelet-derived growth factor receptor α and β. Our phase I study of anlotinib in R/M NPC patients who failed from standard treatment had shown a manageable safety profile and promising antitumor activity with an ORR of 25%. This phase 3 trial aims to compare the efficacy and safety of anlotinib versus placebo in combination in GP with patients in R/M NPC in the first-line setting. Methods: Key eligibility criteria of this study are that the patient has metastatic disease after curative radiotherapy or is primarily metastatic; has an ECOG PS of 0 or 1; has adequate organ function; and has at least 1 measurable lesion according to RECIST 1.1. Eligible patients will be randomized in a 1:1 ratio to receive intravenous gemcitabine at 1 g/m² on days 1 and 8, cisplatin at 75 mg/m² on day 1, plus anlotinib or placebo $14 every 3 weeks as follows: $12 orally daily on days 1–14 followed by anlotinib or placebo 12 mg daily on days 1–14 every 3 weeks as maintenance therapy. The primary endpoint is PFS. Secondary endpoints include OS, ORR, quality of life and safety profile. Independent Data Monitoring Committee and Independent Review Committee will be used in this study. Study participants will be followed in anlotinib group and 7 mos in placebo group. To detect a 3-month improvement of PFS in anlotinib group at a two-sided significant level of 0.05 and power of 0.8, allowing for a dropout rate of 10%, a total of 336 patients will be enrolled. From August 2018, 58 patients have been enrolled. Clinical trial information: NCT03601975.

TPS6090
Poster Session (Board #78b), Sat, 1:15 PM-4:15 PM
KEYNOTE-689: Phase 3 study of adjuvant and neoadjuvant pembrolizumab combined with standard of care (SOC) in patients with resectable, locally advanced head and neck squamous cell carcinoma (LA HNSCC). First Author: Ravindra Uppaluri, Dana-Farber Cancer Institute and Brigham and Women’s Hospital, Boston, MA

Background: Evidence of efficacy and pathological response at the time of surgery was reported in two phase 2 studies (NCT02296684 and NCT02641093) of preoperative pembrolizumab in patients with high-risk, resectable, locally advanced (LA) head and neck squamous cell carcinoma (HNSCC). The randomized, open-label, phase 3 KEYNOTE-689 trial (NCT03765918) will evaluate efficacy and safety of pembrolizumab as neoadjuvant and adjutant therapy in combination with SOC (radiotherapy ± cisplatin) in patients with previously untreated, resectable LA HNSCC.

Methods: Patients with newly diagnosed LA HNSCC will be randomly assigned 1:1 to two treatment arms. Patients in arm A will receive neoadjuvant pembrolizumab (200 mg Q3W for two cycles) followed by surgical resection then SOC plus adjuvant pembrolizumab (15 cycles). Patients in arm B will undergo only surgical resection followed by adjutant SOC. Eligibility criteria will include age ≥18 years; newly diagnosed, resectable, stage III/IVA HNSCC (AJCC Cancer Staging Manual, 8th edition); and ECOG performance status 0-1. Randomization will be stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx), tumor stage (III vs IVA), and HPV p16 status (oropharynx p16 positive vs oropharynx p16 negative or larynx/hypopharynx/oral cavity). Treatment will continue until disease progression, unacceptable toxicity, patient refusal or patient decision to withdraw. Patients in arm A will undergo the first diologic imaging assessment after two cycles of neoadjuvant pembrolizumab and before surgery. In both arms, postoperative imaging will be performed 12 weeks after SOC, then every 3 months until the end of year 3, and then every 6 months until the end of year 5. Dual primary end points are major pathological complete response, defined as 20% or greater invasive single tumor cells within resected primary tumor and sampled regional lymph nodes per blinded central pathology, and event-free survival. Secondary end points include overall survival, pathological complete response, and safety and tolerability. Recruitment is ongoing and will continue until ~600 patients are enrolled. Clinical trial information: NCT03769318.

TPS6091
Poster Session (Board #79a), Sat, 1:15 PM-4:15 PM
EACH: A randomised phase II study evaluating the safety and anti-tumour activity of the combination of abemaciclib and cetuximab relative to cetuximab monotherapy in recurrent/metastatic head and neck squamous cell cancer. First Author: Martin David Forster, University College London Hospitals, London, United Kingdom

Background: Patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) have low response rates to licensed second line therapies, including PD-1 inhibitors nivolumab and pembrolizumab, and represent an area of unmet clinical need. The chimeric IgG1 epithelial growth factor receptor (EGFR) monoclonal antibody cetuximab potentiates the activity of radiotherapy in locally advanced HNSCC and chemotherapy in R/M HNSCC and is also licensed with modest activity as a single agent. Cetuximab initiates Natural Killer (NK) cell antibody-dependent cell-mediated cytotoxicity (ADCC), resulting in an anti-tumour immune response and the potential to augment the activity of PD-1/PD-L1 inhibition. EACH aims to examine the safety and efficacy of the potentially synergistic interaction between cetuximab and abemaciclib, a fully human IgG1 anti-PD-L1 monclonal antibody in R/M HNSCC. Methods: EACH is a randomised phase II trial preceded by a safety run-in phase. Eligible patients have histologically or cytologically confirmed measurable recurrent or metastatic squamous cell carcinoma of any site in the safety run-in phase, and HNSCC in phase II, that is considered incurable by local therapies. The safety run-in has a single arm de-escalating design, aiming to establish the safety of cetuximab with abemaciclib and determine the optimal dose of cetuximab within this combination. The safety run-in has a dosing schedule of abemaciclib (10 mg/kg) + cetuximab (500 mg/m²) intravenously every 2 weeks, with de-escalation of cetuximab to 400 mg/m² and 300 mg/m² if necessary. The safety run-in phase commenced recruitment in July 2018 and is ongoing. The phase II component will randomise 114 HNSCC patients between either abemaciclib + cetuximab at the dose determined by the safety run-in phase or abemaciclib (10 mg/kg) alone. Treatment will be in 4-week cycles for up to one year. The primary endpoint in the safety run-in phase is the occurrence of dose limiting toxicities, and in phase II is Disease Control Rate at 24 weeks, using iRECIST. Blood and fresh tissue will be collected for exploratory translational studies, which will focus on the identification of potential novel predictive biomarkers for response. Clinical trial information: NCT03494322.

TPS6092
Poster Session (Board #79b), Sat, 1:15 PM-4:15 PM
Tableceulin in combination with pembrolizumab (Pembro) in platinum-pretreated, recurrent/metastatic Epstein-Barr Virus (EBV)-positive nasopharyngeal carcinoma (EBV+NPC). First Author: Lillian L. Siu, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Background: Approximately 25% of patients (pts) with NPC develop RM disease, which has a poor prognosis (median overall survival [mOS]: 12–16 mo), despite standard treatments with radiation and/or chemotherapy. NPC is an EBV-associated cancer in which programmed cell death ligand 1 (PD-L1) expression is upregulated upon EBV activation. Pembrolizumab showed antitumor activity in a phase 1b study of pts with RM-NPC (objective response rate [ORR]: 26%; mOS: 16.5 mo) (Hsu, J Clin Oncol 2017;35:4050-56). Targeting RM EBV+ NPC with tab-cel immunotherapy (off-the-shelf, allogeneic EBV-specific T cells) in pts has also shown promise, with 2-yr OS rates of 84% (Prockop, ASCO 2016;34:3012). The favorable safety profile of tab-cel offers the opportunity for combination immunotherapy with pembrolizumab for increased efficacy. Methods: This multicenter, open-label, single-arm phase 1b/2 study evaluates safety and efficacy of tab-cel in combination with pembrolizumab. Study participants are ≥12 yrs of age with incurable, locally recurrent or metastatic EBV+ NPC previously treated with platinum-containing therapy. Pts are checkpoint-inhibitor naïve (phase 1b/2) or refractory to anti-PD-1 or anti-PD-L1 therapy (phase 1b). Tab-cel is selected from a bank based on matching ≥2 HLA alleles, including ≥1 restricting HLA allele, between pts and donors. Tab-cel will be administered intravenously (IV) on days 1, 15, and 15 of a 21-day cycle. Initial tab-cel dose is 2x10⁶ cells/kg and the de-escalated tab-cel dose (if needed) is 1x10⁶ cells/kg. Pembro is administered at 200 mg IV Q3W in adults and 2 mg/kg IV Q3W in pts aged 12 to 17 yrs. Primary outcomes of phase 1b are to characterize dose-limiting toxicities, identify the maximum tolerated dose (MTD) or in the absence of MTD, the recommended phase 2 dose, and assess safety. Primary outcomes for phase 2 are ORR and safety. Secondary endpoints include progression-free survival, OS, and duration of response. Enrollment is ongoing for 12-24 participants in the phase 1b portion of the study with a 6+6 design. Phase 2 is expected to enroll 36 pts. Clinical trial information: NCT03769467.

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**TPS6093**  
Poster Session (Board #80a), Sat, 1:15 PM-4:15 PM

Comparative effectiveness trial of transoral head and neck surgery followed by adjuvant radiochemotherapy versus primary radiochemotherapy for oropharyngeal cancer (TopROC). First Author: Chia-Jung Busch, Department of Otorhinolaryngology and Head and Neck Surgery, University Medical Center Hamburg Eppendorf, Hamburg, Germany

**Background:** For locally advanced, transorally resectable oropharyngeal cancer (OPSCC), both, surgical resection and risk-adapted adjuvant (chemo) radiotherapy or definitive chemoradiotherapy with or without salvage surgery are considered the current standard of care. To date, these two different therapeutically approaches for transorally resectable OPSCC have not been compared head to head in a randomized trial yet. The goal of this study is to compare primary transoral surgery followed by adjuvant treatment with definitive chemoradiation for resectable OPSCC, especially with regards to loco-regional control as well as organ function. **Methods:** TopROC is a prospective, two-arm, open label, multicenter, randomized controlled comparative effectiveness study. Eligible pts. are ≥18 years old with treatment-naive, histologically proven OPSCC (T1, N2a-c, M0; T2, N1-2c, M0; T3, N0-2c, M0 TNM 7th ed.) which are amenable to transoral resection, ECOG PS ≤2 and no distant metastasis. p16 immunohistochemistry by local pathology or FFPE tissue must be available for central diagnostic. 280 pts. will be randomly assigned (1:1) to surgical treatment (arm A) or chemoradiation (arm B). Standard of care treatment will be done according to daily clinical practice. Arm A consists of transoral surgical resection with neck dissection followed by risk-adapted adjuvant (chemo)radiation. Pts. treated in arm B receive standard chemoradiation with residual tumors only be subject to salvage surgery. Follow-up visits are planned until three years after treatment. Primary endpoint is time to local or loco-regional failure or death from any cause (LRF). Secondary endpoints include overall and disease-free survival, toxicity, patient reported outcomes and cost-effectiveness analysis. Approximately 20 centers will be involved in Germany. This trial is supported by the German Cancer Aid and accompanied by a large scientific support program. Recruitment started in January 2018. Clinical trial information: NCT03691441.

**TPS6094**  
Poster Session (Board #80b), Sat, 1:15 PM-4:15 PM

A global phase III multicenter, randomized, double-arm, open label trial of ASP-1929 photodynamic therapy versus physician’s choice standard of care for the treatment of patients with locoregional, recurrent head and neck squamous cell carcinoma (HNSCC). First Author: Merrill A. Bieil, Rakuten Aspiyan Inc., San Diego, CA

**Background:** HNSCC commonly affects local or regional sites and is associated with considerable morbidity and mortality. Outcomes of these patients remain poor with limited curative treatment options and low response rates. New modalities that are targeted, minimally invasive, and provide improved tumor response and control while having limited systemic side effects are needed. Photodynamic therapy (PIT) is a new cancer-targeted platform technology. It is a combination drug and device treatment that utilizes monochromatic antennas conjugated to a dye (IRDye 700DX) that is photoactivated using nonthermal red light to induce rapid and selective tumor cell death. The objective of this phase 3 study is to evaluate the efficacy and safety of ASP-1929 (EGFR-directed antibody cetuximab-IRDye700 conjugate) PIT treatment as a monotherapy in patients with locoregional HNSCC. **Methods:** A global, multicenter phase 3, randomized, double-arm, open-label, controlled trial of ASP-1929 PIT vs physician’s choice standard of care (SOC) for the treatment of locoregional, HNSCC in phase 3 trial in patients who have failed or progressed on or after at least two lines of therapy, of which at least one line must be systemic therapy, is currently underway. Primary endpoints of the study are PFS and OS and the key secondary endpoint is ORR. Key inclusion criteria include: disease not amenable to curative therapy; tumor(s) accessible for PIT light treatment and measurable by CT or MRI; male or female ≥18 yrs old; treatment failure defined as disease progression at any site of metastasis. 276 pts will be randomized (2:1) into 2 arms and approximately 10 centers in Germany will be involved. Standard of care (arm II) consists of surgical resection followed by risk-adapted adjuvant (chemo)radiation. The experimental arm I receives neoadjuvant N 3mg/kg. Treatment will be done according to daily clinical practice. Arm I consists of transoral surgical resection with neck dissection followed by risk-adapted adjuvant (chemo)radiation. Pts. treated in arm II receive standard chemoradiation with residual tumors only be subject to salvage surgery. Follow-up visits are planned until three years after treatment. Primary endpoint is time to local or loco-regional failure or death from any cause (LRF). Secondary endpoints include overall and disease-free survival, toxicity, patient reported outcomes and cost-effectiveness analysis. Approximately 20 centers will be involved in Germany. This trial is supported by the German Cancer Aid and accompanied by a large scientific support program. Recruitment started in January 2018. Clinical trial information: NCT03700905.

**Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.**
A phase 3 (COSMIC-311), randomized, double-blind, placebo-controlled study of cabozantinib in patients with radioiodine (RAI)-refractory differentiated thyroid cancer (DTC) who have progressed after prior VEGFR-targeted therapy. First Author: Marcia S. Brose, Head and Neck Surgery, Radiology, University of Pennsylvania, Philadelphia, PA

Background: Treatment options are limited for patients with RAI-refractory DTC that is resistant to VEGFR-targeted therapy. Cabozantinib inhibits receptor tyrosine kinases including VEGFR2, MET, AXL, and RET, which are implicated in the development of DTC, and has shown clinical activity in early-phase studies of patients with RAI-refractory DTC. This study evaluates the efficacy and safety of cabozantinib in patients with RAI-refractory DTC who have progressed during or after prior VEGFR-targeted therapy.

Methods: This is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial (NCT03690388). The co-primary endpoints are progression-free survival and objective response rate evaluated by blinded independent radiology committee (BIRC) per RECIST v 1.1. Additional endpoints include safety, overall survival, quality of life, and changes in relevant biomarker levels (eg, thyroglobulin). Approximately 300 patients will be randomized in a 2:1 ratio to receive either cabozantinib (60 mg QD orally) or placebo. Randomization is stratified by prior treatment with lenvatinib and age (≥ 65 yrs vs > 65 yrs). Eligible patients must have a pathologic diagnosis of DTC and must have been previously treated with or deemed ineligible for treatment with iodine-131 for DTC. Patients must have received lenvatinib or sorafenib for DTC and progressed during or following treatment with a VEGFR inhibitor. Up to 2 prior VEGFR-targeting TKI agents are allowed. Patients randomized to placebo may be eligible for real time on-study crossover to cabozantinib based on BIRC confirmation of disease progression. Unblinded patients randomized to cabozantinib may continue on study treatment if there is clinical benefit per investigator. Key words: Radioiodine-refractory differentiated thyroid cancer, cabozantinib, VEGFR-targeted therapy, trial-in-progress. Clinical trial information: NCT03690388.

ACCURACY: phase (P) 2 trial of AL101, a pan-Notch inhibitor, in patients (pts) with recurrent/metastatic (R/M) adenoid cystic carcinoma (ACC) with Notch activating mutations (Notchact mut). First Author: Renata Ferrarotto, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Notch signaling plays a key role in tumorigenesis. Notch cleavage by γ-secretase frees the Notch intracellular domain, which promotes the expression of target genes involved in cancer. AL101, a small molecule, is a γ-secretase inhibitor that potently inhibits Notch1-4, resulting in robust antitumor activity in vivo (PMID 26005526), including ACC xenograft models with Notchact mut (Ferrarotto, AACR 2019, Abstr 4885). Three P1 trials tested AL101 as monotherapy or in combination regimens in > 200 solid/hematologic cancer pts. In the P1 trial of AL101 monotherapy, conducted in 94 pts with advanced/metastatic solid tumors refractory to standard therapies (Tx), AL101 was generally well tolerated, with manageable AEs, and the recommended P2 dose was 4 mg IV once weekly (QW; El-Khoueiry, ASCO 2018, Abstr 2515). 4 pts had objective responses, 2 of those had Notchmut (1 of which had ACC). ACC, a rare cancer that most commonly develops in the major salivary glands, but can also arise in minor salivary glands in the trachea, lacrimal gland, and other sites, is refractory to chemotherapy, with a high recurrence rate. Notchact mut are found in a subset of ACC pts (11%–22%), with particularly aggressive disease and poor prognosis. There is no proven active treatment for R/M ACC pts (PMID 27870570). Methods: ACCURACY (NCT03691207) is an open-label, single-arm, multicenter study of AL101 (4 mg IV QW) in pts with R/M ACC (bone-exclusive disease included) with known Notchact mut. Pts with disease progression within 6 months of enrollment or newly diagnosed metastatic pts are allowed; pts who received > 3 prior systemic Tx are excluded. Primary endpoint: ORR by RECIST v1.1 (or modified MDA bone criteria), by independent review committee (IRC). Secondary endpoints: ORR by investigator review (IR), duration of response by IRC and IR, PFS by IRC, OS, and safety. Per the Simon optimal design, 12 pts are enrolled in stage 1; if ≥2 pts respond, 24 additional pts are enrolled in stage 2. If ≥4 pts in stage 2 respond, the trial is deemed positive. This design yields 5% type I error rate and 80% power, if ORR is 25%. 4 of planned 36 pts have been enrolled as of 2/12/19. Clinical trial information: NCT03691207.
Comparison of normal saline versus heparin flush solutions for maintaining patency of central venous catheter in cancer patients. First Author: Amy Pai, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Published guidelines recommend normal saline (NS) flushes for maintaining patency of central venous catheters (CVCs) in cancer patients. The practice at a large oncology ambulatory facility was modified to use NS flushes instead of heparin for CVC maintenance (centrally inserted catheters and peripherally inserted central catheters, excluding implanted ports). The number of catheter occlusion events, pre- and post-implementation, was utilized to determine the effectiveness and safety of this practice change.

Methods: Retrospective data of patients aged 18 years and older who presented to the ambulatory centers were collected from the electronic health record (EHR). The number of alteplase instillations was used as a surrogate measure for occlusion events. Ambulatory line-days, defined as patients arriving for an appointment and with either an active CVC or a CVC placement, was the denominator. The numerator was the number of ambulatory line-days with a catheter line and alteplase dose(s) given. The pre-intervention CVC maintenance period using heparin flushes was March 2016 - April 2017. The post-intervention CVC maintenance period using NS flushes was May 2017 - September 2018. Results: 95,089 line-days and 4,452 unique patients were analyzed pre-intervention and compared to 115,194 line-days and 5,575 unique patients post-intervention. The baseline incidence rate of occlusion was 0.91% compared to the post-intervention incidence rate was 2.67% (p < 0.01). The increase started immediately within the first month of the practice change (2.26%) and continued throughout the implementation observation time.

Conclusions: In an ambulatory oncology-practice setting with a high volume of CVC utilization, an increase in line occlusions rate was observed after implementing the practice change of flushing CVCs from heparin to NS. This raises concerns regarding safety and additional burdens to patients and caregivers, and additional analyses are ongoing to evaluate the further impact of this evaluation.
6504  
**Oral Abstract Session, Fri, 2:45 PM-5:45 PM**  

Economic analysis of alternative pembrolizumab and nivolumab dosing strategies at an academic cancer center.  
*First Author:* Evan Thomas Hall, Stanford University School of Medicine, Stanford, CA  

**Background:** Pembrolizumab (P) and nivolumab (N) were initially investigated and FDA-approved with weight-based dosing strategies, but later the approval label was amended to a fixed dose administration. Giving increasing concerns about financial toxicity of cancer therapies, we hypothesize that weight-based dosing of P and N and allowing vial sharing among patients will result in substantial cost savings.  
**Methods:** We obtained IRB approval to retrospectively examine all outpatient doses of P and N given within Stanford Medicine infusion centers between July 1, 2018 and Oct 31, 2018 using the Stanford Medicine Research Data Repository (STARTR) database. We performed cost-minimization analysis modeling the impact of dosing strategies based upon patient weight versus fixed dosing (2 mg/kg vs 200 mg q3wks for P; 3 mg/kg vs 240 mg q2wks or 6 mg/kg vs 480 q4wks for N). “Dose-minimization” (DM) was defined as whichever dose was lower (weight-based or fixed dose). The impact of allowing vial sharing (considering commercially available vial sizes) between patients treated at the same site and on the same date was assessed. Average sales price (ASP) from Center for Medicare and Medicaid Services for Part B drugs was used for cost estimates.  
**Results:** A total of 1,029 doses of P or N were administered across a variety of cancer types. For most doses (N = 789, 77%), the calculated weight-based dose was less than the fixed dose. DM resulted in decreased usage and expenditures of both P and N, and a further decrease was observed with vial sharing. Total savings estimated with DM and vial sharing were $1,422,988 per million (Table). This amounted to savings of > 22,000 mg of P (112 fixed doses) and > 11,000 mg of N (47 fixed doses). Savings were greatest at the highest volume infusion center.  
**Conclusions:** Alternative dosing strategies of P and N would result in significantly less drug utilization and pharmaceutical expenditure without apparent impact on efficacy. Potential barriers to this approach include existing policies regarding vial sharing and drug vial sizes. **Table:**  

<table>
<thead>
<tr>
<th>Drug Name</th>
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6505  
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6507  
**Oral Abstract Session, Fri, 2:45 PM-5:45 PM**  

Quality of end-of-life care at minority-serving US cancer centers: A retrospective study of Medicare claims data.  
*First Author:* Garrett Wasp, Dartmouth-Hitchcock Medical Center, Lebanon, NH  

**Background:** Higher EOL treatment intensity is burdensome and has been defined as low-quality care. We explored cancer centers’ EOL quality outcomes among minority and white patients and evaluated whether minority-serving cancer centers had systematically lower EOL quality.  
**Methods:** We conducted a retrospective cohort study of Medicare beneficiaries with poor-prognosis cancers who died between April 1, 2016 and December 31, 2016. We identified 10,006 minority (black, Hispanic, Asian, other) and non-Hispanic white (white) patients within the same center and across centers, grouped by concentration of minorities served (low: <15%, medium: 15-30%, high > 30%).  
**Results:** Among 126,434 patients, 10,006 (21.4% minority) received treatment at one of 53 National Cancer Institute-designated and/or Comprehensive Cancer Network-affiliated cancer centers. Only 4/8 quality measures had sufficient sample size to calculate a minority-specific rate for 10 centers. Those measures showed high within-center correlation for minority and white patients (ICU admission: r = 0.79, p < 0.001; no hospice referral: r = 0.70, p < 0.001; life-sustaining treatment: r = 0.73, p = 0.004; palliative care: r = 0.78, p < 0.0001), but the mean adjusted rate for minority versus white patients was significantly worse for two measures: no hospice referral (40.2% vs. 37.2%; p < 0.02) and life-sustaining treatments (21.8% vs. 19.4%; p < 0.02). When grouped by concentration of minorities served (low: 12 centers, medium: 20, high: 11), 5/8 measures showed systematically lower quality as the concentration of minorities increased: more than 1 ED visit (6.0/8.5% vs. 7.7%; p = 0.002), ICU admission (29.1/27.3%; p = 0.004), no hospice referral (34.3/38.7% vs. 36.8% p = 0.005), and life sustaining treatments (14.8/ 16.7/17.9% p = 0.005).  
**Conclusions:** There were systematic differences in end-of-life quality measures at US cancer centers. For many measures, quality was lower at centers that served a greater concentration of minorities. However, EOL care quality for minority and white patients was similar for most but not all measures within any given center.
Multivariable negative binomial regression was used to compare between-group issues between visits, and patients received links to support self-management reports to guide their care, an email alert notified nurses of ongoing unresolved PROMPT-Care patients had 26% (95% CI 0.2%, 57%) fewer ED presentations had 30 ED presentations and PROMPT-Care patients had 21 ED presentations four assessments within the first six months on trial. On average, control patients (mean age 62, 58% female, 27% stage IV) participated and were sent at least formation: ACTRN12616000615482.

diverse population, with potential healthcare cost savings. Clinical trial in-

Results support its utility as an improved model for ongoing supportive care for a ment or are in follow-up, and patients with a wide range of tumor types. The

Background: While screening rates have improved among minorities, racial/ ethnic disparities in diagnosis and treatment persist. Many steps in the diagnostic pathway can delay tissue diagnosis, and in usual practice, biopsies are performed days to weeks after biopsy recommendation. The purpose of this study was to identify if racial/ethnic disparities exist in time from biopsy recommendation to biopsy, and if a same-day biopsy program (biopsy on the same day as the recommendation) eliminates these disparities.

Methods: After IRB approval, we identified all diagnostic mammogram and ultrasound exams leading to biopsy pre- (September 2016-March 2017) and post- (September 2017-March 2018) implementation of our same-day biopsy program. We compared the distribution of age, race, language, insurance type, days to biopsy and proportion of same-day biopsies in pre- vs. post-implementation groups using the Wilcoxon test (for continuous variables) and the Pearson’s chi-squared test (for categorical variables). Multivariable linear and logistic models were estimated in pre and post periods to assess if days from biopsy recommendation to biopsy (linear) and having a same-day biopsy (logistic) were associated with age, race, language, and insurance type. Results: 663 and 482 exams were analyzed pre- and post-implementation, respectively. Age, race, language, and insurance type were similar between time periods. For all patients, the same-day biopsy program decreased mean time from diagnostic examination to biopsy by 8 (IGR: 4.13) to 0 (IGR: 0-4) days (p < 0.001). During the pre time period, non-white patients and having government insurance were associated with longer days to biopsy (non-white aCoef: 2.30 (95% CI: 0.58-4.03); insurance aCoef: 1.67 (95% CI: 0.02-3.32); p < 0.05), and increasing age and having government insurance were significantly associated with decreased odds of having a same-day biopsy (age aOR: 0.97 (95% CI 0.96-0.98); insurance aOR: 0.35 (95% CI 0.14-0.88); p < 0.05), after adjustment. During the post time period there was no evidence of these disparities. Conclusions: A same-day biopsy program eliminated racial/ethnic disparities in time from biopsy recommendation to biopsy to recommend.

Phase III non-randomized controlled trial of PROMPT-Care, an eHealth interven-
tion utilizing PROMT-Care, an eHealth intervention utilizing patients’ reported outcomes in oncologic clinical care: Impact of pre- and post-implementation department presentations. First Author: Afaf Girgis, Centre for Oncology Education and Research Translation (CONCERT), Ingham Institute for Applied Medical Research and University of New South Wales, Sydney, Australia

Background: The significant impact of routine assessment and clinical utili-

tion of patient-reported outcomes (PRO) on patient and survival outcomes and reduced emergency department (ED) presentations has been demonstrated in specific patient populations (e.g. advanced cancer). This controlled trial evaluated the impact of an eHealth system, PROMPT-Care, on ED presentations in a diverse population of cancer patients from four oncology treatment centers. Methods: All adult patients receiving cancer care (including adjuvant therapy and follow-up) were eligible, excepting those with a diagnosis of a hematological malignancy, insufficient English literacy or no internet access outside of the clinic. Intervention (PROMPT-Care) patients completed monthly online assessments comprising 61 items of distress, common symptoms and unmet needs, with PRO results electronically transferred into the electronic medical record (EMR). In “real-time”, the care team accessed patients' PRO summary reports to guide their care, an email alert notified nurses of ongoing unresolved issues between visits, and patients received links to support self-management. Control group patients (n = 2,288) comprised the general cancer patient population receiving usual care at the participating cancer therapy centers. Multivariable negative binomial regression was used to compare between-group differences. Results: From April 2016 to March 2018, 345 eligible patients (mean age 62, 58% female, 27% stage IV) participated and were sent at least four assessments within the first six months on trial. On average, control patients had 30 ED presentations and PROMPT-Care patients had 21 ED presentations per person completing at least one ESAS assessment during the study were considered to have ESAS.

Conclusions: A same-day biopsy program eliminated racial/ethnic disparities in time from biopsy recommendation to biopsy to recommend.

Longitudinal toxicity analysis with novel summary metrics of lenalidomide manage-

ment in follicular lymphoma in ECOG-ACRIN 2408. First Author: Gita Thanarajasingam, Mayo Clinic, Rochester, MN

Background: Conventional adverse event (AE) analysis (ToxC) focuses on incidence of grade (gr) 3+ toxicities, and fails to capture AE time profile. Novel metrics that reflect chronic low gr and overall AE burden are needed. We applied the Toxicity over Time (Toxt) approach to ECOG-ACRIN 2408 to depict time-dependent toxicity of lenalidomide (L) with rituximab mainte-

nance (MR) in follicular lymphoma (FL), and we developed a novel summary metric of symptomatic AE burden, the maximum gr over time (MGTOT). Methods: In E2408, high risk FL patients (pts) were randomized (1:2:2) to: A) bendamustine-rituximab (BR) x 6 then MR x 2 years (yrs) vs B) BR-

bortezombi x 6 then MR x 2 yrs vs C) BR x 6 then MR x 2 yrs + L x 1 yr (MRL). Analysis included 3 laboratory and 5 symptomatic AEs of highest incidence during maintenance on arms A and C. Treatment-related AEs of any gr were analyzed by ToxC and Toxt. Repeated measures, time-to-event (TTE) and area under the curve (AUC) analyses capture trends over time in Toxt; MGTOT combines the 5 symptomatic AEs. Results: 104 randomized pts (30 MR, 74 MRL) were included. For the laboratory AEs, by ToxC, neutropenia incidence was significantly higher in MRL (84%) than MR (47%, p < .001). Toxt additionally shows neutropenia does not worsen over time (10/14/20% gr 1/ 2/3+ at c1, 6/21/12% gr 1/2/3+ at c12). For the symptomatic AEs, ToxC indicates 2 gr 3+ GI AEs. However, gr 1-2 GI AEs are more common on MRL (59%) than MR (26%, p < .001). ToxT AUC captures a higher burden of GI AEs over time on MRL(2.8) vs MR(1.4, p < .002). TTE depicts sooner GI AE onset in MRL (10% vs 0% gr 2+ GI by day 50, p = 0.03). Bar charts of incidence and grade by cycle illustrate this improves over time (34/74/4 gr 1/2/3+ at c1, 13/0/0 gr 1/2/3+ at c12). Toxt MGTOT analyses demonstrate earlier time to gr 2+ symptomatic AEs on MRL vs MR (63% vs 31% by day 50, p < .001) and suggest that overall AE burden over time is higher for patients on MRL(AUC 18.2) than MR(11.8, p < .001). Conclusions: Toxt depicts AE time profile and can guide AE interventions. Summary metrics suggest that symptomatic AEs occur earlier and their burden over time is higher on MRL. We are implementing ToxT in patient-reported AE data to better characterize pt tolerability.

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Population-based cohort of prostate cancer patients on active surveillance (AS): guideline adherence, conversion to treatment and decisional regret. First Author: Satunina Pettersson, University of North Carolina School of Medicine, Chapel Hill, NC

Background: AS is recommended for early-stage prostate cancer, for which overtreatment has been widely described. In published studies from large academic institutions and/or controlled clinical trials, where patients are monitored rigorously, AS is safe and results in low rates of cancer-specific mortality. However, active surveillance in the community setting has not been previously examined. Methods: In collaboration with the North Carolina state cancer registry, 346 men with newly-diagnosed low- or intermediate-risk prostate cancer throughout the state from 2011–13 who pursued active surveillance were enrolled in an observational cohort; medical records and patient-reported outcomes (validated measures of prostate cancer anxiety (MAX-PC) and Clark’s prostate cancer decision regret) were collected prospectively. Guideline-adherent monitoring during active surveillance was assessed using contemporary NCCN guidelines: PSA testing every 3–6 months and prostate biopsy within 18 months of initial diagnosis. Results: 58% of patients received adequate PSA testing and 45% prostate biopsy; overall, 32% of patients received guideline-adherent monitoring. Urology follow-up in Year 1 was 97% but dropped to 67% in Year 2. Within the first 2 years, 16% of patients converted to treatment. Multivariable analysis showed MAX-PC scores (OR 1.8, p = 0.008) and younger age were significantly associated with conversion; no other sociodemographic (race, education, marital status, rural/urban) or diagnostic variable (risk group) was associated. At 2 years, 94% expressed no regret. Conclusions: In a non-controlled setting of patients pursuing AS in the community, adherence to guideline-recommended monitoring was only 32%. Few patients expressed decisional regret. Conversion to treatment was likely driven by patient anxiety but not disease-related factors. While there are continued efforts to increase AS uptake, these results highlight the importance of behavioral interventions during active surveillance to reduce anxiety and improve monitoring adherence. Whether AS in non-controlled settings is safe and effective requires further study.

The use of optimal evidence-based chemotherapy (chemo) regimens in physician offices versus hospital outpatient facilities. First Author: Michael Jordan Fisch, AIM Specialty Health, Chicago, IL

Background: The proportion of infused chemo administered in hospital outpatient facilities (HOF) increased from 6% in 2004 to 43% in 2014. The average annual cost for patients receiving chemo was significantly higher in HOFs than in physician offices (POs). One option to explore differences in the quality of care between these two settings is to examine the use of chemo regimens, which, based on their efficacy, toxicity, and costs, have been designated as “on-pathway.” This study compared on-pathway rates among patients receiving infused chemo administered in POs vs. those in HOFs.

Methods: Using administrative claims data, we identified 61,496 breast, lung, or colorectal cancer patients receiving chemo from 2013 to 2018. Chemo regimens were considered “on-pathway” when they were on payer’s program list of optimal regimens when administered. Generalized linear models examined the association between site of service and on-pathway prescribing rates, and costs of care. Models adjusted for age, sex, year, rural status, cancer type and setting, and comorbidities, with fixed effects for providers.

Results: Percentage of infused chemo administered in HOFs increased from 44.2% in 2013 to 54.7% in 2018. After adjustment, on-pathway prescribing rate did not differ significantly between HOFs and POs (50.1%, 95% CI: 48.6%-51.5% vs. 49.8%, 95% CI: 48.3%-51.3%; p = 0.05), 6-month chemo cost ($56,885, 95% CI: $54,364-$59,924 vs $53,240, 95% CI: $38,929-$63,605, p < 0.001) and 6-month medical cost ($114,280, 95% CI: $110,716-$117,960 vs $79,455, 95% CI: $77,089-$81,893, p < 0.001) were significantly higher in HOFs vs. POs.

Conclusions: Quality of care as measured by use of optimal chemo regimens was similar in hospital and office setting. Cost continues to be significantly higher in hospital setting. These findings provide a strong basis for site-neutral reimbursement policies.

Clinical benefit of breakthrough cancer drugs approved by the United States Food and Drug Administration. First Author: Consolacion Molto, Hospital de Sant Pau, Barcelona, Spain

Background: The Breakthrough Therapy program was established in July 2012 to expedite drug development and approval by the FDA. We compared the characteristics of clinical trials leading to FDA approval as well as the magnitude of clinical benefit and value framework scores of breakthrough-designated and non-breakthrough-designated cancer drugs. Methods: We searched the Drugs@FDA website for cancer drug approvals from July 2012 and December 2017. For each indication, we applied the ASCO Cancer Research Committee (ASCORC) value frameworks and used thresholds of high clinical benefit developed by American Society of Clinical Oncology Value Framework version 2 (ASCO VF v2; scores ≥45), the ASCO Cancer Research Committee (OS) gains ≥2.5 months PFS gains ≥3 months), the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS v1.1; grade of A or B for trials of curative intent and A or B for those of non-curative intent), and the National Comprehensive Cancer Network (NCCN) Evidence Blocks (scores of 4 and 5). Trial characteristics and value framework scores were compared using Chi squared or Mann Whitney U tests.

Results: We identified 106 pivotal trials supporting the approval of 52 individual drugs for 96 indications. Of trial indications, 38 (40%) received breakthrough designation. Compared with trials for non-breakthrough drugs (n = 62), trials for breakthrough drugs (n = 44) had smaller sample size (median 373 vs 612, P= .03), were less often randomized (57% vs 86%; P= .001) and more likely to be open-label (84% vs 53%, P< .001). Trials for breakthrough drugs were more likely to demonstrate high clinical benefit using ASCO VF v2 (82% vs 51%, P= .002) and NCCN Evidence Blocks (86% vs 56%, P< .002). A similar proportion of trials supporting breakthrough and non-breakthrough drugs demonstrated high clinical benefit using the ASCO Cancer Research Committee (82% vs 68%, P= .25) and ESMO-MCBS (35% vs 33%; P= .87) frameworks.

Conclusions: In patients with advanced solid tumors, cancer drugs approved under breakthrough therapy designation were more likely to demonstrate high clinical benefit as defined by the ASCO VF and NCCN value frameworks. A similar proportion of approved breakthrough and non-breakthrough therapy drugs met the high benefit thresholds using the ASCO Cancer Research Committee and ESMO-MCBS frameworks.

Integrating psychosocial care into routine cancer care: A stepped-wedge design cluster randomized controlled trial (SWD-RCT) to evaluate effectiveness of the HuCare Quality Improvement Strategy (HQIS) on health-related quality of life (HRQoL). First Author: Rodolfo Passalacqua, Oncology Unit, Oncology Department, ASST of Cremona, Cremona, Italy

Background: Cancer patients (pts) often do not receive evidence-based psychosocial care. We evaluate the effects of an implementation strategy we previously demonstrated feasible, which includes communication skill training for all physicians and nurses; four support visits at the centers by an improvement team to assist staff in identifying obstacles, finding solutions, and strengthening motivation; screening for distress and social needs; individualized pts’ education with a referring nurse; use of a question prompt list.

Methods: Multicenter incomplete SWD-RCT with 3 clusters of 5 centers each. Consecutive outpatients requiring medical treatment and diagnosed in the previous 2 months were eligible. Primary endpoint: difference of at least one of the 2 domains of HRQoL emotional or social functions, at 3 months from baseline, in pts of the centers that implemented the HQIS vs standard of care (SoC). Secondary endpoints include: patient mood, long-term effect, overall HRQoL. Analyses were performed using a beta-binomial regression model.

Results: 762 pts were enrolled. At baseline, 41% showed high anxiety (HADS-A >7), and 88% had at least one psychosocial need. 299 health professionals attended 3-day courses (84% of all clinical staff). 647 pts (85%) were available for analysis. The 315 pts who received HQIS exhibited better quality of life for the emotional domain than those assigned to SoC (OR=1.15, p=0.016). Pts who showed the greatest improvement were the older (OR=1.003, p=0.035), had lower anxiety basal levels (OR=0.853, p<0.001), and social needs were met (OR=1.182, p<0.001). The difference was not significant for the social domain (OR=0.955, p=0.353). The HQIS’s long-term effect was confirmed for the emotional domain at 12 months. No effect on mood (HADS-D) and overall HRQoL was observed.

Conclusions: To our knowledge this is the first RCT demonstrating the effectiveness of a psychosocial care implementation strategy on cancer patients’ emotional well-being. Clinical trial identification: NCT03008993.
Randomized trial of text messaging (TM) to reduce early discontinuation of aromatase inhibitor (AI) therapy in women with breast cancer: SWOG S1105.

First Author: Dawn L. Herreshoff, Columbia University Medical Center, New York, NY

Background: Non-adherence to AIs for breast cancer is common and increases risk of recurrence. Text messaging (TM) has been shown to increase adherence to medications for chronic conditions. We conducted a multicenter randomized trial to evaluate if TM reminders improve AI adherence.

Methods: Patients taking an AI for >30 days and having >36 mos of planned therapy were eligible. Patients were randomly assigned to TM or NO-TM twice a week for 36 mos. Randomization was stratified by length of time on prior AI therapy (< 12 (64%) vs. ≥12-24 mos (36%)) and AI class (anastrozole, letrozole, exemestane). Content themes of the 36 TMs focused on overcoming barriers to adherence. Patients were assessed for discontinuation of AIs every 3 mos for 36 mos. The primary outcome was time to non-adherence, where non-adherence was defined as urine AI metabolite assay results satisfying the following: < 10 [units], undetectable, or no submitted specimen. A stratified Log-rank test was conducted. Multiple sensitivity analyses were performed using Cox regression.

Results: In total, 724 patients were registered between May, 2012 and September, 2013, among whom 696 (338/360 (93.9%) on TM and 338/364 (92.9%) on NO-TM) were eligible and adherent at baseline. Observed (time-independent) adherence at 36 mos was 55.4% for TM and 55.4% for NO-TM. The primary analysis showed no difference in time-to-adherence failure between patients on the TM and NO-TM arm (HR = 0.89, 95% CI: 0.76,1.05 p = .18). An analysis of negative urine tests alone resulted in similar non-significant results. With missed appointments not counted as failures, time to self-reported discontinuation (89.6% vs. 89.7%; HR = 1.17, 95% CI:0.69-1.98, p = .57) and site reported discontinuation (78.1% vs. 81.1%; HR = 1.31, 95% CI:0.86-2.01, p = .21) were also similar between the two groups. Conclusion: Patients receiving an AI were randomized to an intervention aimed at improving AI adherence, we found high rates of AI discontinuation. Bi-weekly text reminders did not improve adherence to AIs compared to usual care. Improving—long-term adherence will likely require sustained behavioral interventions and support.

Clinical trial information: NCT01515800.

Impact of Electronically Accessible Pathways (EAPathways) on clinical trial enrollment at a large multisite cancer center.

First Author: Jeryl Jean Villalold, Levine Cancer Institute, Charlotte, NC

Background: Clinical pathways streamline evidence-based treatment decisions and provide consistent, high-quality, value-based care. A high-quality clinical pathway should enhance screening and access to clinical trials. Our healthcare system utilizes EAPathways to allow providers to select treatment regimens vetted by section experts, inquire about clinical trials, and refer to relevant programs (e.g. palliative medicine) or testing (e.g. genomics) at a main cancer center and 22 regional sites. With over 400 clinical trials, our goal is to provide access regardless of where a patient lives or receives treatment. We aim to explore the impact of EAPathways on clinical trial enrollment at our healthcare system.

Methods: This study is a retrospective review to compare clinical trial inquiries through EAPathways and clinical trial enrollment using Oncore between 1/1/2017 and 7/31/2018. The primary outcome is the success rate reported as the total number of inquiries that resulted in clinical trial enrollment. Other outcomes include a comparison of inquiries and enrollments for hematology and solid tumor oncology, cancer treatment and non-treatment (e.g. specimen collection), and our main cancer center and regional sites. The number of and reason for opting out of treatments or trials was also analyzed.

Results: A total of 29.1% (740/2539) of clinical trial inquiries through EAPathways resulted in clinical trial enrollment. Success rates for the following settings were reported: 39.5% (223/564) in hematology, 27.0% (594/2203) in treatment trials, and 36.7% (407/1115) in non-treatment clinical trials. The majority of clinical trial enrollments were at our main cancer center compared to regional sites. A total of 39.7% (3356/8453) of patients were enrolled into an opt-out pathway due to reasons such as performance status, organ dysfunction, or hospice.

Conclusions: Clinical pathways can provide access to clinical trial enrollment in a variety of settings. These baseline metrics will help assess process improvement needs to increase clinical trial enrollment success rates and address reasons for opt-out.

The financial impact of fractionation scheme and treatment planning method for rectal cancer in the United States.

First Author: Assaf Moore, Tel Aviv University, Tel Aviv, Israel

Background: Preoperative long-course chemoradiotherapy (CRT) and short-course radiotherapy (SCR) for locally advanced rectal cancer (LARC) were found to have equivalent outcomes in three randomized trials. SCR may have lower acute toxicity and the down-staging following CRT is more well-established. At present, SCR is frequently used in Europe but has not been widely adopted in the United States (US). It is standard to deliver radiotherapy by 3D planning, while the use of intensity-modulated radiotherapy (IMRT) is controversial. In recent years there has been an increasing focus on understanding the cost and value of cancer care. In this study we aimed to assess the economic impact of fractionation scheme and treatment planning method for rectal cancer in the United States.

Methods: We performed a population-based analysis of the total cost of radiotherapy for LARC in the US annually. The national annual target population of patients was calculated using the Surveillance, Epidemiology, and End Results (SEER) database. Treatment costs for various fractionation schemes were based on billing codes and 2018 pricing by Medicare’s Hospital Outpatient Prospective Payment System (OPPS). The cost of chemotherapy was based on the Payment Allowance Limits for Medicare Part B Drugs by Centers for Medicare and Medicaid Services (CMS).

Results: We estimate that 12,945 patients with LARC are treated with radiotherapy annually in the US. The cost of CRT with 3D or IMRT is $15,881.76 and US$ 23,744.82 per patient, respectively. With 3-D CRT the cost is US$ 5,457 per patient. The use of SCR would lead to 64-77% annual savings of US$ 125,701,387 - US$ 236,727,934 in the US compared with 3-D and IMRT based CRT, respectively. IMRT based planning increases the total cost of CRT by 49% and if adopted widely would lead to an excess cost of US$ 101,787,312 annually.

Conclusions: As the first large long-term randomized trial to evaluate if TM reminders improve AI adherence, we found high rates of AI discontinuation. Bi-weekly text reminders did not improve adherence to AIs compared to usual care. Improving—long-term adherence will likely require sustained behavioral interventions and support. Clinical trial information: NCT01515800.

Quantification of the financial burden of antineoplastic agent price increases.

First Author: Michail Alevizakos, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Antineoplastic medication prices are overall increasing yet this phenomenon is not limited to new medications but can also be observed in already established medications. Methods: We accessed the yearly payment files from Medicare Part B for injectable antineoplastic agents (codes J9999-J9999) for the years 2010-2017 and all costs were adjusted to 2017 USD to adjust for inflation. We then calculated the price-per-dose for every medication and compared that price with the price-per-dose that the medication would have if its initial price was only affected by inflation. We subsequently multiplied the difference with the total doses of the medication administered in order to calculate the additional cost accrued by Medicare from medications whose price had increased more than the inflation rates. Only medications with total annual payments >10 million USD were included in the analysis. Notably, Medicare provides reimbursement based on average U.S. market prices. Results: Price increases were noted on average in 64.5% of already established medications (median 69.6%, range 45.4-74.1%), leading to an average additional extra cost of 243 million USD per year (range 140-330 million USD), for a total of 1.7 billion USD over the 7 years of observation. Rituximab (539 million USD), trastuzumab (221 million USD), and bevacizumab (178 million USD) accrued the highest extra costs. This extra cost represented 4.6-8.9% of the annual total Medicare Part B spending for antineoplastic medications (Table).

Conclusions: The majority of already established injectable chemotherapeutics demonstrate price increases that lead to substantial additional financial cost to Medicare and likely other U.S. markets as well. Price increases of Medicare Part B antineoplastic medications with cost >10 million USD/yr.
6520 Poster Discussion Session; Displayed in Poster Session (Board #211), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Trends in financial relationships between industry and individual medical oncologists in the United States from 2014 to 2017: A cohort study. First Author: Deborah Catherine Marshall, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Industry-physician financial relationships in medical oncology are common and introduce conflicts of interest. The Open Payments (OP) program collects and discloses data on industry payments to physicians, in part to discourage inappropriate relationships. However, the effect of OP on how oncologists engage with industry is unknown. Our aim was to evaluate trends in physician-level payments to test whether the implementation of OP has resulted in fewer physicians engaging with industry and has shifted the nature of interactions towards those considered more appropriate.

Methods: We performed a retrospective cohort study of US medical oncologists in 2014 from the National Plan and Provider Enumeration System. OP data for general (non-research) payments between 2014-2017 were matched to physician to evaluate receipt of payments over time. We calculated the percentage of physicians receiving payments, annual value and number of payments, and average annual trends over time, including by nature of payment. Results: From 2014-2017, medical oncologists received 1.4 million industry payments totaling $330.6 million. The absolute number of medical oncologists receiving payments decreased 4% on average annually (P<.006), and proportionally from 67.2% to 59.6% overall. The value and number of payments are not significantly different (though the absolute number of payments increased for accredited/certified CME (+821% and +209% annually) and decreased for non-accredited/certified CME (-18% and -25% annually). The value and number of food/beverage payments remained the same. The value and number of royalty/licensing payments increased significantly for oncologists receiving payments. We conclude that spending has not decreased suggesting that physicians are less likely to engage and industry is more selective. Increased payments for accredited CME suggest that less appropriate speaker's fees are being avoided. Food/beverage payments are not decreasing, thus these interactions may not be recapturing the price paid to industry. Increased payments are on-going scrutiny. Changes in physician payments since the inception of OP highlight the importance of transparency in policymaking.

6522 Poster Discussion Session; Displayed in Poster Session (Board #213), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Enhancing community capacity to improve cancer care delivery and the effect on patient-reported outcomes, healthcare utilization and total costs of care. First Author: Manali I. Patel, Division of Oncology, Department of Medicine, Stanford University School of Medicine, Stanford, CA

Background: To curbing rising expenditures and improve patient-reported outcomes (PROs), we designed an intervention with patient, caregiver, provider, and payer input. The intervention is based on prior work using a community oncology setting to assess advanced cancer patients' symptoms. In this study, we trained the LHW to refer patients to palliative care and/or behavioral health services in response to assessment advanced cancer patients

Methods: We conducted a comparative effectiveness study of adult non-metastatic cancer patients treated with curative intent with proton chemo-radiotherapy vs. photon chemo-radiotherapy from 2011-2016 at the University of Pennsylvania. Re-irradiation and disease sites treated with photon-only therapy were excluded. Data on adverse events and survival was gathered prospectively. Primary endpoint was 90-day adverse events associated with unplanned hospitalizations (CTCAEv4 grade ≥3 adverse events). Secondary endpoints included decline in ECOG performance status during treatment, 90-day grade ≥2 adverse events, disease-free survival (DFS) and overall survival (OS). Modified Poisson regression models with inverse propensity score weighting were fit for both outcomes. Propensity scores were estimated using an ensemble machine-learning approach. Results: 1,483 patients were included (391 proton/1,092 photon). Proton patients were significantly older (median 66 vs. 61), had less favorable Charlson-Deyo comorbidity scores (median lower in proton group vs. photon group: RR 0.31, 95%CI 0.15-0.66, p < 0.01); 90-day grade ≥2 adverse events (RR 0.78, 95% CI 0.65-0.93, p < 0.01); and decline in performance status during treatment (RR 0.51, 95%CI 0.37-0.71, p < 0.01). There was no difference in DFS or OS. Conclusions: In adults with locally advanced cancer, proton chemo-radiotherapy was associated with significantly lower relative risk of adverse events compared with photon therapy, and may be a solution to improve outcomes and the value of cancer care delivery and may be a solution to improve outcomes and overall survival.

6523 Poster Discussion Session; Displayed in Poster Session (Board #214), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Early case ascertainment and prospective multidisciplinary review for management of new melanoma diagnoses within an integrated healthcare system: The Kaiser Permanente Northern California experience. First Author: Thach-Giao Truong, Kaiser Permanente Northern California, Vallejo, CA

Background: Appropriate surgical treatment of early-stage melanoma yields a high cure rate, but this management can be nuanced. In particular, surgical management, including sentinel lymph node biopsy with nodal staging, is dependent on histologic assessment of thin melanomas. In this study, we assessed early-stage melanoma cases in our network to determine the proportion meeting nodal staging criteria and to investigate factors that influence nodal staging decisions. Methods: We performed a retrospective cohort study of adult non-metastatic cancer patients with thin melanomas ≤1.0mm. SLNB was performed in 9.8% of thin melanomas, and cT4 2%. Thin melanomas (50% of melanomas with high-risk features like lymphovascular invasion, high mitotic rate, positive deep margin, and ulceration. These recommendations were documented in the chart and communicated directly to the patient's care team. Results: From 1/1/2016 through 10/2018, our multidisciplinary committee reviewed 3626 patients with new melanoma from 22 sites in our integrated, regional hospital system. Median age was 66 (range 19-99); 60% were male. cT2N0 tumors comprised 7%, cT3 3%, and cT4 2%. Thin melanomas ≤1.0mm represented 71% of cases, of which 34% were ≤0.5mm. SLNB was performed in 9.8% of thin melanomas, and 18% were positive, much higher than historical positive rates of 3-4%. Conclusions: Early case ascertainment and prospective multidisciplinary review in a community oncology setting resulted in increased identification of high-risk thin melanomas, and consequently increased identification of nodal disease through SLNB. Positive SLNB triggered multidisciplinary case-conference following: thera...
6524 Poster Discussion Session; Displayed in Poster Session (Board #215), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Effect of exercise during adjuvant chemotherapy for breast cancer. First Author: Barbara K Haas, The University of Texas at Tyler, Tyler, TX

Background: In 2018, an estimated 266,120 women faced the challenge of living with breast cancer and approximately 40,920 died from their disease. Nearly 100% of these women experienced significant treatment related side effects that negatively impact quality of life (QOL). Exercise has repeatedly demonstrated to alleviate many of the side effects, improve QOL, and decrease cancer recurrence and mortality. In some trials, patients who do not maintain exercise during treatment for breast cancer. The purpose of this randomized controlled trial was to determine the effectiveness of exercising the day chemotherapy is administered on 1) the persistence with an exercise program, 2) side effects, and 3) QOL. Methods: Eligible women were randomly assigned to a control or experimental group. As part of their treatment plan, all participants were referred to one of 14 community-based exercise centers to exercise. Experimental group also exercised at one of two cancer centers each day chemotherapy was administered. Outcome measures include exercise retention and chemotherapy, completion; cancer-related fatigue, nausea/vomiting, peripheral neuropathy, weight gain, and QOL. Outcome measures were assessed prior to every second course of chemotherapy and 3- and 6-months post-chemotherapy. Results: 273 women with Stage I-III breast cancer receiving chemotherapy were enrolled in the study. The number of participants who withdrew from exercise was higher among those in the control group (n= 16; 12.4%) compared with those in the experimental group (n = 10; 6.9%). At cycle 5, those in the experimental group reported less motor peripheral neuropathy than those in the control group (p = .018) and higher physical well-being scores than those in the control group (p = .047). Conclusions: The highest impact of the intervention was on attrition from exercise. Since participants in both the control and experimental groups exercised throughout chemotherapy, it is not surprising that the groups performed comparably with regard to side effects and QOL. Given the positive effects exercise has demonstrated on persons receiving cancer treatment in numerous studies, having patients exercise in the cancer center on the day of chemotherapy is a significant step toward engaging persons receiving chemotherapy in an exercise program.

6525 Poster Discussion Session; Displayed in Poster Session (Board #216), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Clinical outcomes and cost-effectiveness of breast cancer screening for childhood cancer survivors treated with chest radiation: A comparative modeling study. First Author: Jennifer Yeh, Boston Children's Hospital and Harvard Medical School, Boston, MA

Background: Survivors of childhood cancer previously treated with chest radiation face elevated breast cancer risk similar to BRCA1 carriers. Children's Oncology Group (COG) guidelines recommend annual mammography with breast MRI, yet the benefits and costs of various screening strategies are uncertain. Methods: We used two breast cancer simulation models (Model 1 and 2) from the Cancer Intervention and Surveillance Modelling Network (CISNET) and data from the Childhood Cancer Survivor Study to reflect high breast cancer and competing mortality risks among survivors. We simulated 3 screening strategies: annual mammography with MRI starting at age 25 (COG25), annual MRI starting at 25 (MRI25), and biennial mammography starting at 50 (Mammo50). Performance of mammography+MRI was based on published studies in BRCA1/2 carriers who have similar cancer risk. Costs and quality of life weights were based on US averages and published studies. Results: Among a simulated cohort of 25-year-old survivors treated with chest radiation, the lifetime breast cancer mortality risk in the absence of screening was 10-11% across models. Compared to no screening, Mammo50, MRI25, and COG25 screening avert approximately 23-25%, 56-62% and 56-71% of deaths, respectively; averted deaths for COG25 compared to MRI25 were higher in Model 1 than Model 2 (9% vs. <1%). In Model 1, both MRI25 and COG25 were cost-effective; in Model 2, MRI25 was preferable (more effective, less costly than COG25). Conclusions: Compared to no screening, initiating annual screening at younger ages for at-risk survivors averts >50% of breast cancer deaths and is cost-effective. Additional data on test performance are needed to inform recommendations on screening modality.

6526 Poster Discussion Session; Displayed in Poster Session (Board #217), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Previsit breast cancer educational microlearning videos: Impact on patient satisfaction and engagement. First Author: Rachel M Hurley, Mayo Clinic Alix School of Medicine, Rochester, MN

Background: Most patients diagnosed with breast cancer turn to the Internet to learn about their diagnosis; however, information online is often generic, challenging to navigate, and not expert-curated. To facilitate patient education and outcome in our breast clinic, we piloted the implementation of pre-visit education via brief microlearning videos organized within an online platform. Methods: Seventeen videos of 2-4 minute duration were developed by multidisciplinary content experts. Videos covered a variety of educational topics relevant to breast cancer, including treatment options. Patients received a link via email to create an account, which provided access to the platform. Aggregate viewing data and optional patient surveys (online after viewing 3 videos and at the clinical appointment) were used to assess opt-in rates, engagement, and satisfaction. Results: Between September 2018 and January 2019, 57.4% (240/418) of women with biopsy proven breast cancer who were sent an email invitation registered on the platform. On average, patients watched 11 of the 17 videos, with 93.7% of users (225/240) viewing at least one. Overall, 85% (166/198) of women recommended the microlearning format for patient education. The most-viewed video topics included types of breast cancer, breast abnormality and biopsy, understanding biopsy results, tumor markers, and staging. Seventy-eight percent (154/198) of women reported that they planned to share the videos with family or caregivers, and 67% (133/198) felt that the educational content increased their satisfaction with their overall experience. Barriers to video access were emails marked as junk, not having an email address, and difficulties with video loading. Conclusions: The majority of patients participating in this pilot registered on the platform and watched pre-visit microlearning educational videos. These expert-curated videos contributed to high levels of satisfaction and engagement. Strategies to overcome barriers to access will be developed to expand the reach of this new valuable component of breast cancer care.

6527 Poster Discussion Session; Displayed in Poster Session (Board #218), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

Growth factor use and rate of neutropenic complications in breast cancer patients treated with dose-dense paclitaxel: A 5-year experience from a safety net hospital. First Author: Rachna Halawi, University of Texas Southwestern Medical School, Dallas, TX

Background: The NCCN guidelines recommend growth factor (G-CSF) support to reduce the risk of febrile neutropenia and maintain dose density in patients receiving dose dense chemotherapy. We retrospectively reviewed growth factor utilization with dose dense paclitaxel (ddT) in breast cancer patients treated at our institution. Methods: Electronic medical records of patients treated at Parkland Health and Hospital System between 2012-2017 for breast cancer with dose dense adriamycin and cyclophosphamide (ddAC) followed by ddT were reviewed. Data on patient characteristics as well as G-CSF use and neutropenic complications were collected. Results: Two-hundred sixty eight patients received a total of 1019 cycles of ddT. Only one physician in the practice routinely prescribed G-CSF after ddT. The majority of ddT cycles were administered without G-CSF support (781 vs 238 cycles). There were no episodes of neutropenic fever in either group. The rate of grade 3/4 neutropenia was 2.1 % with G-CSF support (all grade 3), and 2.7% without G-CSF support (85% grade 3), p = 0.61. Treatment delays were longer in patients who did not receive G-CSF support, but this difference was not statistically significant (mean of 4 vs 2.2 days, p = 0.07). The number of cycles needed to treat prevent 1 episode of grade 3/4 neutropenia was 167. Based on Medicare average sales price (ASP) for pegfilgrastim, routine use of G-CSF in our patient population would have added over $3.6M to the cost of care over the study period. Conclusions: Our results show a similarly low rate of neutropenic complications in patients receiving dose dense paclitaxel with or without G-CSF support. Therefore routine use of G-CSF with this regimen is not warranted. Judicious use of expensive medications such as G-CSF would reduce the cost of care and financial toxicity to patients, and promote high value care.
Improving time to initiation of bone modifying agents in patients with newly diagnosed multiple myeloma. First Author: Nathaniel Rosko, Cleveland Clinic, Cleveland, OH

Background: Current ASCO and IMWG guidelines recommend that all patients (pts) on active anti-myeloma therapy receive concurrent supportive care treatment with a bone modifying agent (BMA) to decrease the risk of skeletal related events (SRE). Unfortunately, recent data shows only 51% of Myeloma pts with myeloma received a BMA at 30 days, a failure of 80% as a risk factor.

Methods: To identify systemic barriers to BMA initiation, we conducted a cross-sectional, single center study. The primary goal of the study was to evaluate the association between the history of the providers who prescribed BMA and the start date of the medication.

Results: A total of 161 NDMM pts were evaluated between 2015 to 2018 at all sites. The average time difference between the start of anti-myeloma therapy and the start date of a BMA in NDMM pts was 10.5 weeks. Subset analysis based on whether pts were treated at MC vs affiliate sites was 10.6 weeks vs 9.1 weeks, respectively. During the first PDSA cycle, 14 NDMM pts were treated at MC, 86% (12/14) pts were treated with a BMA. The average time between cycle 1 day 1 of first line treatment and first dose BMA was 4.3 weeks (range 4-12 weeks). Conclusions: With increased physician education and awareness of a forthcoming baseline data, we achieved a 30% increase in BMA initiation and observed a significant improvement in time to initiation of BMA from 10.5 weeks to 4.3 weeks. Obstacles regarding effectiveness of communication with patients on the benefit of BMAs as well as need for dental clearance were barriers identified early on. We plan to incorporate BMAs guidelines in our institution's inpatient and outpatient care path with the goal to decrease time to initiation at all affiliated practices. Further mechanisms to ensure reinforcement of BMA initiation in NDMM patients is warranted to maintain therapeutic benefit.

Use, attitudes, and perceptions of tumor genomic testing: Survey of TAPUR physicians. First Author: Suanna S. Bruinooge, American Society of Clinical Oncology, Alexandria, VA

Background: This survey of Targeted Agent and Profiling Utilization Registry (TAPUR) Study physicians examined use, attitudes, and perception of tumor genomic testing (TGT), defined as any DNA test performed on tumor specimen/plasma. TAPUR is a multisite study of marketed agents targeting tumor genomics. Methods: 333 physicians at 54 TAPUR sites were surveyed (2016-2017). Survey domains included use of TGT, barriers to ordering TGT, and genomic confidence. Surveys included 3 scenarios for TGT ordering 1) pretreated advanced cancer patients (pts) without options, 2) newly diagnosed, untreated, metastatic pts and 3) early stage/potentially curable pts with standard options. Data were analyzed with descriptive statistics. Results: 112 physicians responded (33%). The table displays demographics and genomic confidence. Respondents reported a median of 25% of their pts had TGT in past 12 months for trials/routine care (range 0-85%). Barriers to testing included access to tumor specimen (86%), insurance coverage (67%), concerns that results will not be actionable (55%), and test issues (wait time, unsure which test/lab to use, test accuracy) (54%). TGT was ordered most often for scenario 1 (96%) and pts (70%). Few respondents (32%) would order testing in scenario 3. Of those who reported testing for scenarios 1 & 2, most told pts that results could inform treatment/prognosis/trials (97%) or may be uninformative (84%). In all scenarios, pt expectations of TGT results were discussed prior to testing. A minority reported frequently telling pts in advance that results could inform heritable cancer susceptibility (37%). Conclusions: Confidence in using TGT was high. TGT was performed most for pts with advanced cancer and few options. Availability of specimens was largest barrier reported, indicating the importance of blood-based tests. Findings informed the design of future therapeutic trial genomics.
6532 Poster Session (Board #223), Sat, 1:15 PM-4:15 PM
The effects of immunotherapy and novel therapies on medical oncology work load in a Canadian province. First Author: Ravi Ramjesingh, Division of Medical Oncology, Nova Scotia Cancer Center, Dalhousie University, Halifax, NS, Canada
Background: Both novel targeted therapies and immunotherapies have dramatically changed the landscape in a number of disease sites with previously limited treatment options. This has resulted in an impact on clinical workload for oncologists with sub specialty practices in the areas of non-small cell lung (NSCLC), melanoma (M), and gastrointestinal (GI) carcinoma. The aim was to investigate the effect of immunotherapy and these practices as compared to other disease sites within a single academic cancer center in Nova Scotia (NS), Canada. Methods: The NS Cancer Center is the academic cancer center for the province of NS providing care and oncology services to approximately 72% of provincial patients. We manually quantified appointment visits (new consultation, treatment and follow up visits) as well as telephone triage and chart checks from February 1 to April 30 across a 3-year interval (2016, 2017, and 2018) and then extrapolated this data to derive full year estimates. Disease sites most impacted by therapies that have changed treatment landscape (NSCLC, M and GI) were compared with the Breast and Gastrointestinal disease sites. Results: Clinical workload increased across all domains over the 3 year period but the majority of the increase is attributed to the 3 disease sites (Table). Conclusions: Medical oncology workloads are increasing over time and novel treatments (including immunotherapy) in disease sites with previously limited options likely account for a significant portion of that increase. New patient consultation metrics, taken in isolation, do not reflect current trends in medical oncology workload. Hiring practices, space allocation and use of physician extenders must take into account these shifting workload dynamics to mitigate physician burnout and potential impacts on quality and timeliness of care.

6534 Poster Session (Board #225), Sat, 1:15 PM-4:15 PM
Leveraging a conversational agent to support adherence to oral anticancer agents: A usability study. First Author: Bethany Mooney Berges, Hospital of the University of Pennsylvania, Philadelphia, PA
Background: Identifying effective, scalable strategies to ensure patient adherence to oral anticancer agents (OACAs) is a major challenge. Previous studies have shown widely variable rates of adherence, and suboptimal adherence is associated with decreased effectiveness and higher costs. A small yet to be rigorously tested in the context of OACAs.

Methods: A rapid cycle prototyping approach led to the development of 'Penny' — a bidirectional, conversational agent that engages patients via text messaging, and leverages natural language processing and machine learning to learn from clinical interactions. Core functionalities include: (1) real-time dosing instructions, (2) motivational reminders, and (3) symptom monitoring with self-management support. We conducted a four-month usability study between December 24, 2017 and May 1, 2018 in a large academic cancer center. At monthly intervals for the first 12 weeks of follow-up, research staff conducted qualitative interviews with participants to evaluate usability and acceptability. Results: 11 patients with gastrointestinal neuroendocrine cancer on capetitabine and temozolomide were approached regarding the study. Of these, 10 agreed to participate (ages 45- to 85-years old, overall, participants scored on the Net Promoter Score of 100. Reliability of Penny's algorithmic branching to provide accurate dosing information and symptom triage was also high: symptoms were accurately graded 100% of the time, and there was appropriate self-management advice or provider triage 100% of the time. Average daily adherence (based on self-report) was 98%. Participants reported that 3 emergency room visits were avoided during the study period. Conclusions: In preliminary testing, a mobile phone-based conversational agent was a usable and acceptable means of supporting OACA adherence. Expanded study testing patient safety and efficacy is underway.

6535 Poster Session (Board #226), Sat, 1:15 PM-4:15 PM
Risk stratification and daily symptom monitoring for oncology patients. First Author: Robert Michael Daly, Memorial Sloan Kettering Cancer Center, New York, NY
Background: Monitoring and managing patient reported outcomes (PROs) has been recommended for oncology patients on active treatment but can be time and resource intensive. Identifying patients likely to benefit and the optimal frequency of PRO capture is still under investigation. We tested the feasibility of monitoring patients with high risk markers and high-risk for acute care with daily symptom PROs.

Methods: Using data from our institution, we developed a model that employs over 400 clinical variables to calculate a patient’s risk of an emergency room visit within 6 months following the onset of treatment. From October 15, 2018 to January 23, 2019, we enrolled patients identified as high risk through a telehealth-enabled program to monitor and manage those patients’ symptoms. Enrolled patients entered PRO assessments daily via an online portal. Symptoms were monitored and managed by a centralized clinical team. Tiered notifications informed the team of concerning or escalating symptoms. We assessed how frequently patients completed symptom assessments and the frequency of symptom notifications. Results: During the pilot, 28 patients were identified as high risk and enrolled in the program (median age 65; 64% percent female). Disease types were: 15 (54%) thoracic, 7 (25%) gynecologic, 6 (21%) gastrointestinal. Median time in the program was 50 (9-98) days. Patients completed 840 of 1,350 assessments (62%). There were 328 assessments that triggered moderate alerts (39%) and 220 that triggered severe alerts (26%). The table describes the prevalence of symptoms at the patient-level. Conclusions: A model can be employed to identify high-risk patients in collaboration with clinicians. Our adherence rate with a daily symptom assessment was similar to those found in studies of less frequent PRO capture. Future work will expand to a larger patient population with other cancer types, evaluate impact on outcomes, and assess optimal frequency for PRO collection and alert thresholds.

Prevalence of symptoms reported at moderate or severe levels or more days % (n=28).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>36%</td>
<td>11%</td>
</tr>
<tr>
<td>Pain</td>
<td>75%</td>
<td>54%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>71%</td>
<td>54%</td>
</tr>
<tr>
<td>Nausea</td>
<td>50%</td>
<td>14%</td>
</tr>
<tr>
<td>Constipation</td>
<td>46%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>46%</td>
<td>6%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>43%</td>
<td>7%</td>
</tr>
<tr>
<td>Decreased oral intake</td>
<td>39%</td>
<td>11%</td>
</tr>
<tr>
<td>Emesis</td>
<td>21%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Colorectal cancer is an important health problem in Thailand; chemotherapy remains the most suitable treatment for metastatic patients. Chemotherapy treatment that was once delivered only in hospital environments is now administered at patient's home, helping patients to live normal lives during receiving chemotherapy. The chemotherapy regimens are based on a 48-hour 5-fluorouracil infusion regimen that combined with an oral medication. The regimen as FOLFIRI, FOLOTRI, and FOLFOX, 5-fluorouracil was in the elastomeric infusion pump and administered at the patients' home. Nurse coordinators followed up with the patients by phone. The FACT-G and FACT-C scale, patients' satisfaction and cost of treatment questionnaire were collected at time of enrolment, 2 months and end of treatment. Results: 156 patients were treated with AC and 45 patients treated with inpatient. 134 returned the questionnaire (response rate 86%). Intention to treat analysis revealed significantly improved in social wellbeing and FACT-G (p < 0.001) in AC group. Significant higher administration, service and overall satisfaction score in AC group. The AC reduced cost about 83% US dollars per cycle of chemotherapy. Conclusions: Ambulatory chemotherapy helps colorectal cancer patients to live normal lives and administer treatment at patients' home and results to significantly improve in quality of life especially in social wellbeing and more satisfaction. Moreover, ambulatory chemotherapy reduced cost of chemotherapy treatment.

6536 Poster Session (Board #227), Sat, 1:15 PM-4:15 PM
Evaluation of quality of life, satisfaction and cost of care in metastatic colorectal cancer patients receiving ambulatory chemotherapy. First Author: Princhai Chanrivong. Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Background: Colorectal cancer is an important health problem in Thailand; chemotherapy remains the most suitable treatment for metastatic patients. Chemotherapy treatment that was once delivered only in hospital environments is now administered at patient's home, helping patients to live normal lives during receiving chemotherapy. The chemotherapy regimens are based on a 48-hour 5-fluorouracil infusion regimen that combined with an oral medication. The regimen as FOLFIRI, FOLOTRI, and FOLFOX, 5-fluorouracil was in the elastomeric infusion pump and administered at the patients' home. Nurse coordinators followed up with the patients by phone. The FACT-G and FACT-C scale, patients' satisfaction and cost of treatment questionnaire were collected at time of enrolment, 2 months and end of treatment. Results: 156 patients were treated with AC and 45 patients treated with inpatient. 134 returned the questionnaire (response rate 86%). Intention to treat analysis revealed significantly improved in social wellbeing and FACT-G (p < 0.001) in AC group. Significant higher administration, service and overall satisfaction score in AC group. The AC reduced cost about 83% US dollars per cycle of chemotherapy. Conclusions: Ambulatory chemotherapy helps colorectal cancer patients to live normal lives and administer treatment at patients' home and results to significantly improve in quality of life especially in social wellbeing and more satisfaction. Moreover, ambulatory chemotherapy reduced cost of chemotherapy treatment.

6537 Poster Session (Board #228), Sat, 1:15 PM-4:15 PM
Proactive, multidisciplinary approach to supportive medicine: Improving health outcomes and care utilization. First Author: Thomas Jefferson University, Philadelphia, PA

Background: Evidence suggests that cancer patients who receive palliative care early in their disease have improved quality of life, decreased emergency department (ED) visits, and less aggressive end-of-life care. In 2017, the Sidney Kimmel Cancer Center at Jefferson established the Neu Center for Supportive Medicine and Cancer Survivorship (NCSMCS) as a model for integrated care in the outpatient setting for all cancer patients. A multidisciplinary team consisting of palliative care physicians, social work, psychology, and navigation conducts psychosocial screening and initiates a personalized care plan for each patient to clarify treatment goals and offer assistance. Objectives: To use biopsychosocial screening at specified time points to identify needs and evaluate the impact of supportive care as part of standardized oncology care regardless of stage. Methods: This assessment utilized Oncology Care Model (OCM) data for Jefferson Medicare patients between 7/1/16 to 7/31/18. Incidence of ED admits ED/Observation and admissions were evaluated as well as ICU utilization and advanced care planning. Poisson regression was used to generate incidence rate ratios (IRR) and 95% confidence intervals (CI) to facilitate the comparison of post- vs. pre-incidence rates of hospitalization. Results: The post-intervention hospital admissions decreased by 31% in NCSMCS (IRR 0.69, 95% CI 0.48-0.98) and by 10% in Non-NCSMCS (IRR 0.90; 0.84-0.96) and advanced care plans were more likely to be on file for NCSMCS (9.0% vs. 4.9%). The intensive care unit (ICU) admissions were decreased by 1.7%, among Non-NCSMCS (IRR 0.93; 95% CI 0.74-0.93). The utilization rates for ED admissions were not statistically different among both the groups. Conclusions: The preliminary data is promising and impact will be monitored as the intervention is expanded. Reducing admissions has benefits from both a cost savings as well as quality of life perspective. Future analyses will consider the impact of the intervention on a patient’s quality of life.

6538 Poster Session (Board #229), Sat, 1:15 PM-4:15 PM
Deployment and integration of a cognitive technology in China: Experiences and lessons learned. First Author: Tianle Li, Qingdao Baheal Intelligent Technology Co., LTD, Qingdao, China

Background: Cognitive technologies are rapidly being introduced in oncology for decision-support, prescribing therapy, predicting risk, reducing medical errors and for care management. Few studies have reported on successful approaches for clinical adoption. We report the early adopter experience of BahealIntelligenceTechnologyCo., Ltd. (Baheal), across China within a 2-year period (April 2017-January 2019). We also describe lessons and experiences of oncology users. Methods: Baheal developed collaborative agreements for use of IBM Watson for Oncology (WFO) in 96 hospitals across 8 provinces. Key opinion leaders who saw the potential for AI were recruited as champion advocates. A 29-item survey conducted included usability and integration within clinical workflow. 85 questionnaires were distributed to oncologists who were major WFO users; 51 were completed. All questionnaires were completed anonymously and de-identified prior to analysis. Results: As of January 31, 2019, 866 physicians have entered a total of 52,537 cancer cases into WFO. Most users approved of both the quality (44/51, 86.3%) and comprehensibility (45/51, 88.2%) of treatment options, rationales, and literature references. WFO was most frequently applied in the context of inpatient cases reviewed. 85 questionnaires were distributed to oncologists who were major WFO users; 51 were completed. All questionnaires were completed anonymously and de-identified prior to analysis. Results: As of January 31, 2019, 866 physicians have entered a total of 52,537 cancer cases into WFO. Most users approved of both the quality (44/51, 86.3%) and comprehensibility (45/51, 88.2%) of treatment options, rationales, and literature references. WFO was most frequently applied in the context of inpatient cases reviewed. Conclusions: Ambulatory chemotherapy helps colorectal cancer patients to live normal lives and administer treatment at patients' home and results to significantly improve in quality of life especially in social wellbeing and more satisfaction. Moreover, ambulatory chemotherapy reduced cost of chemotherapy treatment.

6539 Poster Session (Board #230), Sat, 1:15 PM-4:15 PM
Capacity to provide specialized care for older adults in community oncology practices: Results of the NCCORP Community Oncology Research Program (NCCORP) Landscape survey. First Author: Grant Richard Williams, University of Alabama at Birmingham, Birmingham, AL

Background: American Society of Clinical Oncology guidelines recommend that patients ≥65 years of age starting chemotherapy undergo a geriatric assessment (GA) to inform and guide management; however, little is known about resources available in community oncology practices to facilitate geriatric specialty care and implement these guidelines. Methods: Community oncology practices were electronically surveyed in 2017 regarding the availability of various providers, supportive services, and practice characteristics, as part of a larger survey of cancer care delivery research (CCDR) capacity at NCCORP sites. Designated CCDR leads provided information about their site. Descriptive statistics were used to report prevalence of resources available at each community practice. Results: Of the 925 NCCORP practice locations, 504 (54%) responded to the survey, representing 227 practice groups. Of respondents, 58% included a free-standing clinic or private/group practice and 82% included inpatient services. The median number of new cancer cases per year ≥65 years of age was 443 (Interquartile range [IQR] 220-903). The median number of medical oncology providers was 5 (IQR 3-11). Only 1.8% of practices had a dual fellowship trained geriatric oncologist on staff. Geriatricians were available for consultation or co-management for 34% of sites, but only 13% of those had availability within the oncology clinic. Among those with access to geriatricians, consultations were primarily outpatient (90%) versus inpatient (54%). Ancillary services that could support GA were variably available onsite: social work (83%), nurse navigators (78%), pharmacist (77%), dietitian (69%), supportive caregiver services (62%), rehabilitative medicine (57%), psychologist (51%), and psychiatrist (39%). Most sites utilized electronic health record systems (84%) and patient portals (98%). Conclusions: Availability of geriatric-trained providers is limited in community oncology practices. Use of primarily self-administered GA tools that direct referrals to available ancillary services may be an effective implementation strategy for guideline-based care.

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6542 Poster Session (Board #233), Sat, 1:15 PM-4:15 PM

Safety and outcomes of a cancer patient urgent care clinic. First Author: Jack S. Bovins, University of Texas Southwestern Department of Internal Medicine, Dallas, TX

Background: Several cancer centers describe cancer-patient dedicated urgent care clinic (UCC) that address commonly anticipated complaints of adults with cancer. UCC may be capable of preventing some ED visits, but little is known of the safety and outcomes for patients after a UCC visit. Methods: We identified UCC visits made by adults at our comprehensive cancer center between 2013-2016 and compared the cohort to patients who did not visit the UCC. We linked patients to tumor registry data and their electronic health record from the UCC visit, then tracked ED visits, inpatient and intensive care unit (ICU) admissions occurring within 24 hours of the UCC visit. Results: Between 2013-2016, 551 patients generated 772 UCC visits, compared to 17,496 who did not visit. UCC users had significantly (p<0.001) more advanced-stage cancer than non-UCC users (37.3% vs 18.9%), but there were no significant differences in mean age, race/ethnicity, or death within 180 days of diagnosis. The most common chief complaints accounted for nearly half of all UCC visits: (17.4%), URI symptoms/fever (12.6%), nausea/vomiting/diarrhea (7.8%), and fatigue/weakness (7.6%). After 10.0% of UCC visits, patients had an ED visit, while 12.3% were admitted to the hospital; only 5 UCC visits (0.7%) had an ICU admission. UCC users had significantly higher rates of ED visits and hospitalizations within 24 hours (Table). The median time from UCC visit to arrival ED visit was 3.0 hours, and 6.5 hours from UCC arrival to inpatient arrival. Conclusions: The majority of patients seen in UCC did not require ED or inpatient hospitalization. Patients with subsequent ED or inpatient visits had minimal delays in care. Findings suggest that triaging cancer patients to UCC is warranted. Continued collection of UCC data may result in high rates of mis-triaging or major delays in care. Patients with ED, Inpatient, or ICU visit after UCC, stratified by UCC visits per patient (2013-2016).

<table>
<thead>
<tr>
<th>UCC Visits/ Patient</th>
<th># of Patients (%)</th>
<th>ED within 24 hrs. (%)</th>
<th>Inpatient within 24 hrs. (%)</th>
<th>ICU within 24 hrs. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>417 (75.7)</td>
<td>43 (10.3)</td>
<td>50 (12.0)</td>
<td>4 (1.0)</td>
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<tr>
<td>2</td>
<td>81 (14.7)</td>
<td>16 (19.8)</td>
<td>19 (23.4)</td>
<td>4 (8.0)</td>
</tr>
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<td>3</td>
<td>30 (5.4)</td>
<td>10 (33.3)</td>
<td>11 (36.7)</td>
<td>1 (3.3)</td>
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<tr>
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<td>23 (4.2)</td>
<td>7 (30.4)</td>
<td>5 (21.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

6544 Poster Session (Board #232), Sat, 1:15 PM-4:15 PM

Delay in receipt of newly prescribed oral anticancer drugs. First Author: Daniel O’Neill, Columbia University Medical Center, New York, NY

Background: Oral anticancer drug (OACD) prescriptions require coordination between clinicians, payers, specialty pharmacies, and financial assistance (FA) groups, which may delay patient receipt of the drug. Factors associated with delay in receipt of OACDs are unknown. Methods: We prospectively collected data on all new OACD prescriptions (RXs) from the medical oncology practice at the Herbert Irving Comprehensive Cancer Center from 1/1/2018 to 12/1/2018. We collected patient demographic, insurance and clinical information; date of prescription; date of drug delivery; and staff interactions with payers and FA groups. Federal Drug Association (FDA) labels and Micromedex were reviewed for initial drug approval dates, approved indications and average wholesale price. We used multivariable linear and logistic regression to determine factors associated with number of days from prescription to receipt of OACD. Results: During the study period 510 OACD RXs were evaluated. Of these, 84 (16%) were never filled. The most common OACDs were capecitabine (90, 18%), abiraterone (45, 9%), palbociclib (35, 7%) and osimertinib (28, 6%). Of 426 filled RXs, the median time from prescription to receipt was 8 days (IQR 5-13), with 193 RXs (46%) received in ≤ 7 days, 145 (34%) in 8-14 days and 65 (15%) in >14 days. First Author: Izumi Okado, University of Hawaii Cancer Center, Honolulu, HI

Background: According to the IOM, effective coordination of care (CC) is a critical component of high-quality cancer care; however, there is a lack of reported measure limitations or current understanding of cancer care coordination. We examined psychometric properties and utility of a Care Coordination Instrument (CCI), a survey developed to assess cancer patients’ perceptions of care coordination. Methods: The 29-item CCI was administered to 200 patients receiving active treatment for cancer at private oncology practices and hospital-based facilities from Oct. 2018 to Jan. 2019. The CCI includes subscales that evaluate CC in 3 domains (Communication, Navigation, Operational) across 4 areas of CC (patient-physician; between health providers; during inpatient-to-ambulatory care transitions; during transitions across different phases of care). All items were rated on a 4-point Likert scale. Results: Psychometric analyses of the CCI demonstrated that it has good internal consistency reliability (α = .917) and the three-factor solution was an acceptable fit (CFI = .853, SRMR = .065). Overall, cancer types (leukemia, myeloma) and having an identified patient navigator significantly predicted higher patients’ ratings of CC (p < .05). Similar trends were found for Communication and Operation subscale scores (p < .05). Having an identified navigator predicted higher Navigation scores (p < .05). Marginally significant differences were found for practice setting, with patients receiving care in hospital-based facilities reporting better CC (p = .085). Item-level analyses revealed significant differences in specific aspects of CC (e.g., physician-patient communication) across cancer type, presence/absence of a patient navigator, and practice setting. Conclusions: The results demonstrate that the CCI is a reliable and valid instrument for measuring cancer patients’ perceptions of care coordination. Perceptions of CC correlated with the presence of a navigator, underlying cancer type and (trending) practice setting. Use of this instrument may reveal important information about cancer care coordination and may identify areas of targets for improvement in patient-centered cancer care delivery.
Results: The Virtual Cancer Care Network reduced non-standardization in cancer care remains to be a big problem in primary hospitals in China. Although limitation of WFO exists in the complex cases of certain tumor types, the rational use of WFO in the teaching and remote consulting could help and promote the standardized cancer treatment in China.

Conclusion:

Reference:

Non-standardization in cancer care remains to be a big problem in primary hospitals in China. Although limitation of WFO exists in the complex cases of certain tumor types, the rational use of WFO in the teaching and remote consulting could help and promote the standardized cancer treatment in China.
Minimizing drug wastage (DW) and cost of cabazitaxel used to treat metastatic castration-resistant prostate cancer (mCRPC). First Author: Di Mara Jiang, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Cabazitaxel is indicated for mCRPC, but is associated with substantial DW and financial strain on hospital budgets. It is only available in single-dose 60mg vials and has short reconstituted drug stability of < 24 hours. We aimed to determine feasibility of cost savings of an agressive batching strategy to facilitate vial sharing of Cabazitaxel. Methods: Our mitigation strategy was to administer Cabazitaxel 20mg/m² q3-weekly (without prophylactic G-CSF) on a single weekday whenever possible. Drug was prepared after patient (pt) arrival. Remaining amount from each vial was saved for subsequent pts on the same day. Amount administered, discarded and number of (#) vials used were obtained from pharmacy records. We estimated drug cost without batching by assigning 1 vial/treatment, and drug cost with batching as a composite of DWs and financial strain on hospital budgets. We evaluated 21,920 newly diagnosed patients in the National Cancer Database (NCDB) who received PBT between 2004 and 2016. Joinpoint analyses were used to evaluate the Annual Percent Change (APC) in the number and characteristics of patients treated with PBT. Results: The number of patients treated with PBT in NCDB facilities increased from 1,114 in 2004 to 3,173 in 2016 (APC = 8.78, p < .001), due mainly to increases in Group 1 cancers after 2010 (from 271 patients in 2010 to 1,124 in 2016, APC = 26.4, p < .001). The number of Group 2 patients treated with PBT increased slower (from 937 in 2004 to 2,049 in 2016, APC = 6.1, p < .05). Breast and prostate cancers were most common, although trends varied substantially by cancer site. Between 2010 and 2016, receipt of PBT increased for breast cancer patients from 40 in 2010 to 405 in 2016 (APC = 48.5, p < .001), but decreased for prostate cancer patients from 1,205 in 2011 to 680 in 2016 (APC = -14.06, p < .001). While most of Group 1 patients had private insurance coverage (59.3% of patients treated in 2016), Medicare was the most common primary insurance type among Group 2 patients (50% of patients treated in 2016). Conclusions: The number of newly diagnosed cancer patients treated with PBT has increased between 2004 to 2016 in the US, with a sharp increase for cancers with clinical indications for health insurance coverage since 2010. While most of these patients have private insurance coverage, the steady increase in the number of patients being treated with PBT for cancers with additional requirements for health insurance coverage is primarily in those with Medicare coverage.

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Poster Session (Board #243), Sat, 1:15 PM-4:15 PM

The diagnosis and outcomes when the outpatients receiving chemotherapy visited the emergency room: A tertiary referral center retrospective study of 734 cases. First Author: Takatsugu Ogata, Department of Clinical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan

Background: Today, the chemotherapy is performed in outpatient, but there is no research on the safety. This study aimed to determine the safety of outpatients receiving chemotherapy and the points to note when they visit the emergency room. Methods: We retrospectively collected data from July 2011 to October 2018 in tertiary referral center of outpatients receiving chemotherapy when they visited the ER within 3 months from the administration of chemotherapy. Results: Seven hundred and thirty-four cases (345 patients) were enrolled (median age, 71 years; male 410, female 324). The median days of the patients visiting the ER was 16 days after the administration of chemotherapy. The tumor types were gastrointestinal (226 cases), urological (199 cases), respiratory (112 cases), and the other (197 cases). The cytotoxic agents, antibody, or hormonal agents were 530 cases, 150 cases, or 173 cases, respectively. The median body temperature and systolic blood pressure were 36.8 °C and 130 mmHg, respectively. The median estimated glomerular filtration rate was 68. The cases of emergent admission were 296 cases. The tumor-associated disease was 184 cases and the chemotherapy-associated disease was 105 cases. The most frequent chemotherapy-associated disease was febrile neutropenia (FN) (35 cases). The admission of tumor-associated disease or chemotherapy-associated disease were 94 cases or 41 cases, respectively (p = 0.273). Conclusions: The outpatients receiving chemotherapy visited the emergency room because of their tumor-associated symptoms rather than chemotherapy-associated symptoms. It was safe that the chemotherapy is performed in outpatient. FN was the most frequent chemotherapy-associated disease. It is important to be careful that not only chemotherapy-associated symptoms but also tumor-associated symptoms when the outpatients receiving chemotherapy visited the ER.

Poster Session (Board #244), Sat, 1:15 PM-4:15 PM

A blinded evaluation of a clinical decision-support system at a regional cancer care center. First Author: Suthida Suwanvecho, Horizon Cancer Center, Bumrungrad International Hospital, Bangkok, Thailand

Background: Clinical decision-support systems (CDSS) such as Watson for Oncology (WFO) may reduce treatment variation in oncology, provided options offered by the system are at least as acceptable as expert, evidence-based options. Deviation from expert consensus in practice is not well documented. In this blinded study, WFO therapeutic options and treatment decisions made by individual oncologists at Bumrungrad International Hospital were evaluated by expert panel. Results: Treatments selected by BIH that were labeled as either “for consideration” or “not recommended” by WFO were evaluated by a panel of 3 oncologists in 2018. The panel evaluated WFO options and previous BIH treatments for prospective cases from 2016-2018, blinded to the source of treatment option. Consensus of panel rated treatment pairs as: identical; both acceptable and roughly equivalent; both acceptable, but one preferred; one is acceptable and the other, unacceptable; neither is acceptable. The results of 321 treatment choices for breast, lung, colon and rectal cancers were analyzed, and McNemar’s test, a modified pairwise chi-square, was applied to identify differences between pairs. Results: 71% of both BIH and WFO treatments across all 4 cancer types were considered acceptable or identical by the panel. In 18 cases (5.6%), WFO treatments were preferred; in 14 cases (4.4%), BIH cases were preferred. Unacceptable treatments by either BIH or WFO were identified in 15% and 23% of treatments, respectively. Statistical analysis of treatment pairs revealed no significant difference between BIH and WFO treatments for breast, colon and rectal cancer. Treatment for lung cancer differed significantly (p = 0.004); in 6% of cases, WFO was unacceptable and BIH acceptable; in 1% of cases, BIH was unacceptable and WFO was acceptable. Conclusions: This study is one of the first to compare therapeutic options from CDSS to treatment decisions made in practice, evaluated in a blinded fashion by an expert panel. 71% of treatments suggested by WFO CDSS were as acceptable as those selected by clinicians at the point of care, and some were considered superior. Decisions made in practice were unacceptable to the panel in 15% of cases, suggesting a role for CDSS.

Poster Session (Board #245), Sat, 1:15 PM-4:15 PM

A framework for building a clinically relevant risk model. First Author: Robert Michael Daly, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Acute care accounts for half of cancer expenditures and is a measure of poor quality care. Identifying patients at high risk for emergency department (ED) visits enables institutions to target resources to those most likely to benefit. Risk stratification models developed to date have not been meaningfully employed in oncology, and there is a need for clinically relevant models to improve patient care. Methods: We established and applied a predictive framework for clinical use with attention to modeling technique, clinician feedback, and application metrics. The model employs electronic health record data from initial visit to first antineoplastic administration for patients at our institution from January 2014 to June 2017. The binary dependent variable is occurrence of an ED visit within the first 6 months of treatment. The final regularized multivariable logistic regression model was chosen based on clinical and statistical significance. In order to accommodate for the needs to the program, parameter selection and model calibration were optimized to suit the positive predictive value of the top 25% of observations as ranked by model-determined risk. Results: There are 5,752 antineoplastic administration starts in our training set, and 1,457 in our test set. The positive predictive value of this model for the top 25% riskiest new start antineoplastic patients is 0.53. From over 1,400 data features, the most frequent differences between BIH and WFO treatments across all 4 cancer types were considered acceptable or identical by the panel. In 18 cases (5.6%), WFO treatments were preferred; in 14 cases (4.4%), BIH cases were preferred. Unacceptable treatments by either BIH or WFO were identified in 15% and 23% of treatments, respectively. Statistical analysis of treatment pairs revealed no significant difference between BIH and WFO treatments for breast, colon and rectal cancer. Treatment for lung cancer differed significantly (p = 0.004); in 6% of cases, WFO was unacceptable and BIH acceptable; in 1% of cases, BIH was unacceptable and WFO was acceptable. Conclusions: This study is one of the first to compare therapeutic options from CDSS to treatment decisions made in practice, evaluated in a blinded fashion by an expert panel. 71% of treatments suggested by WFO CDSS were as acceptable as those selected by clinicians at the point of care, and some were considered superior. Decisions made in practice were unacceptable to the panel in 15% of cases, suggesting a role for CDSS.

Poster Session (Board #246), Sat, 1:15 PM-4:15 PM

Reasons for discordance in treatment approaches between oncology practice and clinical decision support in China. First Author: Jun Liang, Peking University International Hospital, Beijing, China

Background: Therapeutic clinical decision-support systems (CDSS) are often evaluated by comparisons between CDSS options and actual practice decisions or expert opinions. Few such studies have carefully examined reasons for discordance. Methods: We reviewed 11 concordance studies from different hospitals across 8 provinces in China, published between 2017 and 2018. The studies compared IBM Watson for Oncology (WFO) therapeutic options to treatments selected by oncologists or a tumor board involved in review of cases for lung, colon, rectal, breast, gastric, and gynecological cancers. We identified given reasons for discordance and summarized themes across studies. Results: Of the 11 studies, 9 provided 1 or more reasons for discordance which could be analyzed. We found three major themes related to discordance: formulary restrictions, treatment-protocol differences, and physician or patient preferences (Table). Formulary differences between WIO and regional practices included off-label drug uses or unavailable therapies. Treatment-protocol differences included variations in regimens, such as simultaneous versus sequential treatments. Physician or patient preferences included factors such as the cost of treatment and logistics associated with various treatments. Conclusions: This study identified multiple reasons for discordance between an oncology CDSS option and oncologists’ treatment choices in China. Treatment differences arose from local formulary or protocol differences as well as provider and patient preferences. Future studies of CDSS should include reasons for discordance when assessing system performance in this manner.

Reasons for discordance.

<table>
<thead>
<tr>
<th>Source of Discordance</th>
<th>% of Studies Reporting</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulary restrictions</td>
<td>77 %</td>
<td>Off-label uses or availability of a therapy</td>
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<tr>
<td>Treatment protocol differences</td>
<td>33 %</td>
<td>Simultaneous versus sequential administration</td>
</tr>
<tr>
<td>Physician or patient preference</td>
<td>22 %</td>
<td>Cost of treatment or logistics associated with treatment</td>
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6556 Poster Session (Board #247), Sat, 1:15 PM-4:15 PM
Development of an artificial intelligence model to predict survival at specific time intervals for lung cancer patients. First Author: Smita Agrawal, Concerto HealthAI, Bengaluru, India.

Background: Survival prediction models for lung cancer patients could help guide their care and therapy decisions. The objectives of this study were to predict probability of survival beyond 90, 180 and 360 days from any point in a lung cancer patient’s journey. Methods: We developed a Gradient Boosting model (XGBoost) using data from 55k lung cancer patients in the ASCO CancerLInQ database that used 3956 unique variables including Dx and Rx codes, biomarkers, surgeries and lab tests from prior to to death date available in the Electronic Health Record was chosen at random for each patient. We used 40% data for training, 25% for hyper-parameter tuning, 20% for testing and 15% for holdout validation. Death date available in the Electronic Health Record was cross checked by linkage to death registries. Results: The model was validated on the holdout set of 8,468 patients. The Area Under the Curve (AUC) for the model was 0.79. The precision and recall for predicting survival beyond the three time points were between 0.7-0.8 and 0.8-0.9 respectively (see table). This compares favourably to other lung cancer survival models created using different machine learning techniques. (Jochems 2017, Dekker 2009). A Cox- PH model created using the top 20 variables also had a significantly lower performance (see table). Analysis of input variables yielded distinctive patterns for patient subgroups and time points. Tumor status, medications, lab values and functional status were found to be significant in patient sub cohorts. Conclusions: An AI model to predict survival of lung cancer patients built using a large real world dataset yielded high accuracy. This general model can further be used to predict survival of sub cohorts stratified by variables such as stage or various treatment effects. Such a model could be useful for assessing further be used to predict survival of sub cohorts stratified by variables such as stage or various treatment effects. Such a model could be useful for assessing.

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<tr>
<th></th>
<th>Precison</th>
<th>Recall</th>
<th>F1 score</th>
<th>Support</th>
<th>AUC</th>
<th>Cox PH AUC</th>
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<tbody>
<tr>
<td>Death in 90D</td>
<td>0.61</td>
<td>0.44</td>
<td>0.51</td>
<td>2235</td>
<td>0.79</td>
<td>0.69</td>
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<td>Alive after 90D</td>
<td>0.82</td>
<td>0.9</td>
<td>0.86</td>
<td>6233</td>
<td>0.79</td>
<td>0.69</td>
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<tr>
<td>Death in 180D</td>
<td>0.65</td>
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<td>3431</td>
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<td>0.70</td>
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<tr>
<td>Alive after 180D</td>
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<td>Death in 360D</td>
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<tr>
<td>Alive after 360D</td>
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<td>0.75</td>
<td>4395</td>
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6558 Poster Session (Board #249), Sat, 1:15 PM-4:15 PM
Use of machine learning to identify relevant research publications in clinical oncology. First Author: Fernando Jose Suarez Suz, IBM Watson Health, New York, NY.

Background: Finding high-quality science to support decisions for individual patients is challenging. Common approaches to assess clinical literature quality and relevance rely on bibliometrics or expert knowledge. We describe a method to automatically identify clinically relevant, high-quality scientific citations using abstract content. Methods: We used machine learning trained on text from PubMed papers cited in 3 expert resources: NCCN-BC, EPC-DQ, and Hemonc.org. Balanced training data included text cited in at least two sources to form an “on topic” set (i.e., relevant and high quality), and an “off-topic” set, not cited in any of the above 3 sources. The off-topic set was published in lower ranked journals, using a citation-based score. Articles were part of an Oncology Clinical Trial corpus generated using a standard PubMed query. We used a gradient boosted-tree approach with a binary logistic supervised learning classification. Briefly, 988 texts were processed to produce a term frequency-inverse document frequency (tf-idf) n-gram representation of both the training and the test set (70/30 split). Ideal parameters were determined using 1000-fold cross validation. Results: Our model classified papers in the test set with 0.93 accuracy (95% CI (0.89:0.96) p = 0.0001), with sensitivity 0.95 and specificity 0.91. Some false positives contained language considered clinically relevant that may have been missed or not yet included in expert resources. False negatives revealed a potential bias towards chemotherapy-focused research over radiation therapy or surgical approaches. Conclusions: Machine learning can be used to automatically identify relevant clinical publications from bio- graphic databases, without relying on expert curation or bibliometric methods. The use of machine learning to identify relevant publications may reduce the time clinicians spend finding pertinent evidence for a patient. This approach is generalizable to cases where a corpus of high-quality publications that can serve as a training set exists or cases where document metadata is unreliable, as is the case of “gray” literature within oncology and beyond to other diseases. Future work will extend this approach and may integrate it into oncology clinical decision-support tools.

6557 Poster Session (Board #248), Sat, 1:15 PM-4:15 PM
Accelarating advanced precision medicine through a harmonized data exchange platform and research consortium (PMEC). First Author: Davendra Sohal, Cleveland Clinic, Cleveland, OH.

Background: Clinico-genomic data sharing is consistently identified by the global oncology community as a critical requirement to accelerate the discovery and development of new targeted therapies. However, lack of effective collaborative models, fragmented and lengthy legal contracting processes, paucity of funding, and inadequate technological platforms have historically been obstacles for effective data sharing. Methods: In 2015, 10 US academic medical centers (AMC) and Foundation Medicine Inc. (FMI) formed PMEC. Feasibility assessments included creation of a master agreement across sites and willingness to use a central IRB. Oversight and research steering committees were created within the consortium. Through a centralized, secure web-based platform, FoundationInsight, we combined and shared de-identified, harmonized comprehensive FoundationOne genomic profiling data. Research proposals mining this data warehouse are invited quarterly from participant AMCs and peer-reviewed; approved studies are executed at all sites. Results: All 10 AMCs collaborated to execute a master registry participation agreement, followed by a master IRB protocol (New England IRB #120180008), subsequently approved by individual site IRBs. Since its launch, the PMEC database has grown, on average, 60% per year, to now house over 14,000 cases. The shared dataset covers all tumor types (most commonly lung (17.2%), gastrointestinal (13.8%) and breast (9.2%)), encompasses genomic alterations in >300 genes, and results in relevant support category data such as gene expression, microsatellite instability status. To date, 15 studies have been proposed and evaluated using this platform, with 2 projects currently approved and in progress. Conclusions: We demonstrated the feasibility of creating a collaborative academic consortium that facilitates data sharing and potential discovery efforts in oncology. Technology solutions can leverage the ability of AMCs, in partnership with central labs, to share and harmonize data to advance precision medicine. This approach lays the groundwork for conducting prospective, biomarker-enriched clinical trials among participating AMCs.

Multivariate Analysis of Distress = 4 (Odds Ratio/95% CI).

<table>
<thead>
<tr>
<th>Parameter</th>
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<tr>
<td>Total Screened</td>
</tr>
<tr>
<td>*p &lt; .0002 *</td>
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<tr>
<td>Pain</td>
</tr>
<tr>
<td>Fatigue</td>
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<td>Anxiety (6/6)</td>
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<tr>
<td>Concern for Family</td>
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<tr>
<td>Quitte Poor Emo-</td>
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<td>tional Coping</td>
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*p < .0002. *All test variables not included in chart but will be included in presentation.
6560 Poster Session (Board #251), Sat, 1:15 PM-4:15 PM
Impact of travel time on healthcare costs and resource utilization by phase of care for older cancer patients. First Author: Gabrielle Betty Rocque, University of Alabama at Birmingham, Birmingham, AL

Background: Closures of hospitals and clinics may have unintended consequences, including increasing patient travel time. Increased patient travel time to healthcare facilities has the potential to adversely impact patient outcomes. Limited data exist on the impact of travel time on healthcare costs and resource utilization.

Methods: This retrospective cohort study from 2012-2015 evaluated drive time to cancer care site for Medicare beneficiaries age 65 in the Southeastern US. The primary outcome was Medicare spending by phase of care (initial, survivorship, end of life [EOL]). Secondary outcomes included resource utilization measured by hospitalization rates, hospitalization sites, intensive care unit (ICU) admissions, and chemotherapy-related hospitalization rates. Hierarchical linear models with patients clustered within cancer care site and adjusted for pertinent covariates were used to determine the effects of drive time on average monthly phase-specific Medicare spending.

Results: Median drive time was 32 minutes (IQR 18-59) for the 23,382 included Medicare beneficiaries, with 24% of patients driving > 1 hour to their cancer care site. During the initial phase of care, Medicare spending was 14% higher for patients traveling > 1 hour than those traveling ≤ 30 minutes. Hospitalization rates were 4-13% higher for patients traveling > 1 hour vs. ≤ 30 minutes in the initial (61 vs. 54), survivorship (27 vs. 26), and EOL (310 vs. 86) phases of care (all p < .05). The majority of patients traveling > 1 hour were hospitalized at a local hospital rather than at their cancer care site, whereas the converse was true for patients traveling ≤ 30 minutes.

Conclusions: As healthcare locations close, patients living farther from treatment sites may experience more limited access to care, and healthcare spending could increase for Medicare.

6561 Poster Session (Board #252), Sat, 1:15 PM-4:15 PM
Esophageal cancer in Hispanic patients: A demographic analysis of the National Cancer Database. First Author: Juan Ricardo, Florida State University College of Medicine, Tallahassee, FL

Background: Hispanics are the fastest-growing minority accounting for 38% of the US population. The National Cancer Institute estimated 17,290 new cases of esophageal cancer (EC) in the US in 2018. Hispanics are reported to have lower EC prevalence. We sought to interrogate the demographic patterns of EC in Hispanics. Secondary objective was to examine evidence of socioeconomic disparities and differential therapy.

Methods: We queried the National Cancer Database to identify patients with EC between 2005–2015. Patients were divided into two groups, Hispanic vs Non-Hispanic (NH). Demographics compared were age, sex, tumor data, surgical intervention, type of treatment, insurance status, income, residence area, and Charlson/Deyo score. Pearson’s Chi-square test was used to compare categorical variables. Groups were matched by propensity score-matched analysis (PSM). Survival analysis was estimated by the Kaplan-Meier method and associated log-rank test. P-value ≤0.05 was considered significant.

Results: We identified 85,004 patients with EC, 3,205 were Hispanic (3.8%). In this US population we identified significant disparities between the Hispanic and NH groups. Staging was more advanced among Hispanics included higher prevalence of squamous EC (24.7% vs 19.6%), higher likelihood of stage IV cancer diagnosis (40.7% vs. 34.8%), younger age, higher uninsured status (10.4% vs 3%) with income < $38,000 (26.4% vs 15.9%), and Charlson/Deyo score 0 (72.3% vs 70.7%) when compared to NH. However, Hispanics were less likely to have surgical interventions (29% vs 36.3%) and chemotherapy (30.1% vs 26.1%). PSM showed that any treatment, insurance status and lower income were predictors of survival. Treated Hispanics survived longer than NH (median survival 17 vs 15 months). Overall survival at 5 years was 22% vs 17%, respectively, p < 0.05. Conclusions: Despite lower prevalence of EC in Hispanics compared to NH, there is a disproportionately higher number of metastatic and untreated cases among Hispanics. This disparity may be explained by Hispanics’ limited access to medical care exacerbated by their socioeconomic and insurance status. Further clinical and epidemiologic research is warranted to reveal other factors impacting these health disparities.

6562 Poster Session (Board #253), Sat, 1:15 PM-4:15 PM
Access to care and financial burden for patients with breast cancer in Ghana, Kenya and Nigeria. First Author: Majid Twahir, Aga Khan University Hospital, Nairobi, Kenya

Background: Breast cancer is the most frequently diagnosed malignancy and the most common cause of cancer-related death in women in Ghana, Kenya, and Nigeria. We evaluated healthcare resource use and financial burden for patients treated at tertiary cancer centers in these countries.

Methods: Records of breast cancer patients treated at the following government/private tertiary centers were included – Ghana: Korle-Bu Teaching Hospital and Sweden Ghana Medical Centre; Kenya: Kenyatta National Hospital and Aga Khan University Hospital; Nigeria: National Hospital Abuja and Lakeshore Cancer Center. Patients presenting within a prespecified 2-year period were followed until death or loss to follow-up.

Results: The study included 299 patient records from Ghana, 314 from Kenya, and 249 from Nigeria. The use of common screening modalities (eg, mammogram, breast ultrasound) was < 45% in all 3 countries. Use of core needle biopsy was 76% in Kenya and Nigeria, but only 50% in Ghana. Across the 3 countries, 91-98% of patients completed blood count/chemistry, whereas only 78-88% completed tests for hormone receptor and human epidermal growth factor receptor 2 (HER2). Most patients underwent surgery: mastectomy (64-67%) or breast-conserving. Most patients in Ghana and Nigeria (87-93%) paid for their diagnostic tests entirely out of pocket (DOP) compared with 30-32% in Kenya. Similar to diagnostic testing, the proportion of patients paying OOP only for treatments was high: 72-89% in Nigeria, 45-79% in Ghana, and 8-20% in Kenya. Among those receiving HER2-targeted therapy, average number of cycles was 5 for patients paying OOP only vs 14 for patients with some level of insurance coverage.

Conclusions: Patients treated in tertiary facilities in sub-Saharan African countries lack access to common imaging modalities and systemic therapies. Most patients in Ghana and Nigeria bore the full cost of their breast cancer care, suggestive of privileged financial status. Access to screening/diagnosis and appropriate care is likely to be substantially lower for the general population.

6563 Poster Session (Board #254), Sat, 1:15 PM-4:15 PM
Racial comparisons in receipt of timely guideline-based colon cancer treatment in the equal-access health system. First Author: Yvonne L. Eaglehouse, Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD

Background: Non-Hispanic Black (NHB) adults with colon cancer may have longer time-to-treatment and be less likely to receive guideline-based therapy than Whites (NHW) in the US. This may be largely related to racial differences in access to care and insurance coverage. This study aimed to determine whether there were racial differences in receipt of timely guideline-based colon cancer treatment in the equal-access Military Health System (MHS).

Methods: Patients age 18-79 years diagnosed with colon adenocarcinoma between January 1, 1998 and December 31, 2007 were identified in linked databases from the Department of Defense Central Cancer Registry and MHS Data Repository. Odds ratios (ORs) and 95% confidence intervals (CIs) of receiving stage-specific treatment within recommended timeframes (surgery within 6 weeks of diagnosis (stages I-III); adjuvant chemotherapy within 8 weeks of surgery (stages II-III); treatment within 4 weeks of diagnosis (stage IV)) for NHB relative to NHW patients were estimated using multivariable logistic regression. Results: Patients (n = 2,170) had a mean age at diagnosis of 59.6 (SD 11.8) years and the racial distribution was 78.6% NHW and 21.4% NHB. The likelihood of receiving timely surgery between races was similar across the stage groups (II-III). NHB patients were equally likely to receive adjuvant chemotherapy as NHW patients (OR 0.90, 95% CI 0.57, 1.41) and to receive it within 8 weeks of surgery (OR 1.19, 95% CI 0.91, 1.57). The likelihood of receiving timely treatment for patients with stage IV disease was similar between races (OR 0.82, 95% CI 0.59, 1.16). The overall likelihood of receiving treatment adherent to stage-specific guidelines in the study sample was similar between NHB and NHW patients (OR 1.00, 95% CI 0.77 to 1.31).

Conclusions: In the MHS population, the likelihood of receiving timely treatment adherent to recommended guidelines was similar between races. Our results support the role of equal access to medical care and insurance coverage in reducing racial disparities in colon cancer treatment.
Assessment of enrollment characteristics for Children’s Oncology Group (COG) upfront therapeutic clinical trials 2004-2015. First Author: Kelly Fauk, University of Colorado School of Medicine, Children’s Hospital Colorado, Center for Cancer and Blood Disorders, Department of Pediatrics, Aurora, CO

Background: Improvements in pediatric cancer survival are attributed to cooperative clinical trials. Under representation of specific demographic groups has been described in adult and pediatric cancer and poses a threat to the generalizability of trial results. A comprehensive evaluation of data provided by the Children’s Oncology Group (COG) of upfront trial enrollment for US patients 0 to 29 years old between 2004 and 2015 was performed to assess for disparities in participation. Methods: Estimates of cancer cases were calculated using the Surveillance, Epidemiology, and End Results registry and the US Census and compared to observed COG cases. Percent enrollment and Standardized Ratios of enrollment were calculated across various demographic, disease, and socioeconomic groups. The COG website was utilized to quantify available upfront trials during the study period and assess age eligibility criteria. Results: 21.3% of estimated US cancer patients age 0 to 19 years enrolled on COG trials. Younger patients were consistently more represented across disease types and race/ethnicities. Patients with hematologic malignancies were more represented in neurologic system (CNS) tumors. Conclusions: COG clinical trial enrollment rates are declining, which may be due to challenges in pediatric drug development, difficulty designing feasible trials for highly curable diseases, and issues in ensuring trial availability for the heterogeneous group of solid and CNS tumors. Though racial/ethnic groups and counties were proportionally represented, under representation of the adolescent/young adult (AYA) population and younger patients with solid and CNS tumors remain significant concerns. Targeted enrollment efforts should focus on the identified subgroups and further research should evaluate AYA enrollment across all available trials to provide continued treatment advances for all patients.

Effectiveness of mobile computerized tomographic (CT) lung scanning unit for early diagnosis of lung cancer in underserved populations. First Author: Carolyn Moloney, Cork University Hospital, Cork, Ireland, Ireland

Background: It is estimated that 1% of a population experience some degree of gender non-conformity. There is scant information worldwide on cancer incidence and mortality for this population however due to a lack of investigating large-scale prospective studies. National cancer registries do not hold demographics on this population. Current literature indicates transgender people may face an increased cancer risk. Transgender patients may avoid screening programmes for cancers which are themselves gendered. Transgender patients can feel excluded from gender specific cancer support groups. We set out to identify how cancer services in Ireland can better meet transgender people’s unique needs. Methods: Medical oncology consultants in the South/South-West of Ireland were contacted to identify patients who identified as transgender or gender non-conforming. We carried out a retrospective chart review of the four transgender patients identified. We analysed staging at diagnosis, family supports, smoking history, alcohol use and whether cancer treatment affected gender transitioning treatment and if this had documented effects on mental well-being. We also noted if medical records reflected a new name or change of gender and if not, whether original name and gender used for chemotherapy and blood product administration. Results: All four patients were diagnosed with relatively advanced disease at diagnosis: Stage IllC high grade ovarian cancer, stage IV gastrointestine tumour, stage IVb diffuse large B Cell and locally advanced extra-abdominal desmoid tumour. Of the four patients, three had a smoking and alcohol history on diagnosis. All four patient’s recent medical correspondence reflected a name and gender change but the medical records did not reflect this. These patients had documented depression for which they were attending psychiatry services. It was noted that two patients had undergone transitioning treatment postoperatively. Minimal family support was noted for two patients. Conclusions: The transgender community is a growing population that will continue to integrate into mainstream society. Our retrospective chart review adds to a growing body of evidence which suggests gender minorities may suffer from cancer-related disparities and need greater recognition and support. However, due to the small sample size and lack of adequate research, it is difficult to identify these individuals. We should identify gender minority individuals and report this data in medical records in order to build much needed epidemiological information.

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Background: It is estimated that 1% of a population experience some degree of gender non-conformity. There is scant information worldwide on cancer incidence and mortality for this population however due to a lack of investigating large-scale prospective studies. National cancer registries do not hold demographics on this population. Current literature indicates transgender people may face an increased cancer risk. Transgender patients may avoid screening programmes for cancers which are themselves gendered. Transgender patients can feel excluded from gender specific cancer support groups. We set out to identify how cancer services in Ireland can better meet transgender people’s unique needs. Methods: Medical oncology consultants in the South/South-West of Ireland were contacted to identify patients who identified as transgender or gender non-conforming. We carried out a retrospective chart review of the four transgender patients identified. We analysed staging at diagnosis, family supports, smoking history, alcohol use and whether cancer treatment affected gender transitioning treatment and if this had documented effects on mental well-being. We also noted if medical records reflected a new name or change of gender and if not, whether original name and gender used for chemotherapy and blood product administration. Results: All four patients were diagnosed with relatively advanced disease at diagnosis: Stage IllC high grade ovarian cancer, stage IV gastrointestine tumour, stage IVb diffuse large B Cell and locally advanced extra-abdominal desmoid tumour. Of the four patients, three had a smoking and alcohol history on diagnosis. All four patient’s recent medical correspondence reflected a name and gender change but the medical records did not reflect this. These patients had documented depression for which they were attending psychiatry services. It was noted that two patients had undergone transitioning treatment postoperatively. Minimal family support was noted for two patients. Conclusions: The transgender community is a growing population that will continue to integrate into mainstream society. Our retrospective chart review adds to a growing body of evidence which suggests gender minorities may suffer from cancer-related disparities and need greater recognition and support. However, due to the small sample size and lack of adequate research, it is difficult to identify these individuals. We should identify gender minority individuals and report this data in medical records in order to build much needed epidemiological information.

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Australian population-based study of single- versus multi-fraction palliative radiotherapy for bone metastases. First Author: Wei Looi Ong, Department of Radiation Oncology, Olivia Newton John Cancer Wellness and Research Centre, Austin Health, Heidelberg, Australia

Background: Single fraction palliative radiotherapy (SFRT) has been shown to be equivalent to multi-fraction radiotherapy (MFRT) for bone metastases symptom management. Remuneration for radiotherapy (RT) in Australia are largely determined by fractions delivered. We aim to determine the use of SFRT for bone metastases in Australia.

Methods: We did a population-based linkage study of multiple administrative healthcare databases in Victoria, Australia: the Victorian Radiotherapy Minimum Data Set (VRMDS), the Victorian Cancer Registry (VCR), and the Birth, Death and Marriage registry (BDM). All patients with solid tumour (excluding primary bone cancer) who received palliative radiotherapy for bone metastases between 2012 and 2017 were included. The primary outcome was use of SFRT. The Cochran-Armitage test for trend was used to evaluate SFRT use over time. Multivariable logistic regression was used to identify factors associated with SFRT use.

Results: A total of 15,668 courses of RT for bone metastases were delivered to 10,351 patients. The overall proportion of SFRT was 18% (2,746/15,668). There was no significant change in SFRT use over time, from 18% in 2012 to 20% in 2017. Older patients were more likely to have SFRT (mean age 69.4 vs. 68.2, P < 0.001). Patients who had lung cancer (21%) and prostate cancer (19%) were more likely to have SFRT compared to other tumour types (P < 0.001). Spine RT was associated with lower use of SFRT compared to other treatment sites (14% vs. 22%, P < 0.001). Patients from remote area were less likely to have SFRT compared to patients from major cities (22% vs. 17%, P < 0.001). Patients treated in private institutions were less likely to have SFRT compared to those treated in public institutions (10% vs. 22%, P < 0.001). In multivariate analyses, patients’ age, tumour type, area of residence, and treatment institutions were independently associated with SFRT use.

Conclusions: This is the largest Australian population-based cohort treated with RT for bone metastases, with low utilisation of SFRT over time. There is large variation in SFRT use depending on patient-, tumour-, geographical and institutional factors. Further work is needed to increase uptake, and reduce unwarranted variation, in SFRT use.

Impact of race/ethnicity in the clinical presentation and outcomes of patients with multiple myeloma in an underserved urban population. First Author: Christian Torres, John H. Stroger Jr. Hospital of Cook County, Chicago, IL

Background: Patients with multiple myeloma (MM) who are part of racial/ethnic minority groups have been typically underrepresented in large descriptive and randomized-controlled studies. Despite the identification of biological and genetic risk factors, the impact of race/ethnicity in the outcomes of patients with MM remains largely unknown. We aimed to describe the racial/ethnic differences in clinical presentation and outcomes of patients with MM in an ethnically-diverse underserved urban population.

Methods: We conducted a single-center retrospective study of patients with MM from Jan 1st 2008 – Dec 31st 2016 using ICD coding from our tumor registry. We abstracted demographic, clinical and treatment variables. We used Chi-square to compare categorical variables and Kaplan-Meier method for survival analysis. Statistical analysis was performed using IBM SPSS version 25.

Results: We identified 73 patients with MM with a median follow up time of 42 months (Range 1 to 81 months). Patients had a median age of 59 years (Interquartile Range [IQR] = 17) and were predominantly male (54.8%). The most frequent racial/ethnic group was African American (AA) (59%) followed by Hispanic (27%) and Caucasian (8%). When compared to other ethnicities, patients who were AA had higher ISS-3 scores (41% vs 23% ; p=0.101) worse cytogenetic risk (65% vs 30% ; p=0.009) and worse response after induction (Complete response [CR] 47% vs 77% ; p=0.047). They were also more likely to have medical insurance coverage than other ethnicities (67% vs 27% ; p=0.003) but had similar access to autologous bone marrow transplant (23% vs 23% ; p=0.99). Overall, AA patients had worse overall survival (OS) compared to all other ethnic groups (mean OS: 58.3 months vs 79 months ; p=0.014).

Conclusions: AA patients with MM had more aggressive disease, and worse OS compared to other ethnicities which may suggest an underlying genetic predisposition towards high-risk genetic features. Improvement of access to autologous bone marrow transplantation may improve survival in high-risk racial/ethnic groups.

Clinical impact of the Mexican healthcare system “Seguro Popular” on breast cancer survival. First Author: Luis Antonio Cancel, Centro Universitario Central del Cárcter, Hospital Universitario, UANL, San Pedro Garza García, NL, Mexico

Background: Breast cancer (BC) is one of the leading issues in public health in low and middle-income countries. In Mexico, access to healthcare is fragmented according to the patient’s employment and not by its needs; IMSS and ISSSTE (Social Security) provide access to prepaid medicine to those under the formal sector of the economy, leaving up to 50 million Mexicans without access to a prepaid scheme. In 2003, the Seguro Popular (SP) was created in order to bring universal access to prepaid medicine in Mexico, and in 2007 expanded its coverage for BC.

Methods: Retrospective and comparative study. The primary endpoint was to determine the impact on survival of SP on BC. Records were obtained from the electronic database of the Hospital Universitario “Dr. José Eleuterio González”. We included patients with invasive BC stage I-IV. Patients with any other kind of healthcare schemes other than SP, patients who underwent treatment outside our institution, and those with a follow up no greater than 3 months were excluded. 104 patients from the period prior the implementation of the SP (2000-2007) met the criteria for evaluation; then we randomly selected a second cohort with the same size from the period after the implementation of the SP (2008-2013).

Results: Median age at diagnosis was 48 and 51 years, respectively, for the periods before and after the implementation of SP. Distribution by clinical stage (Non-SP vs SP): CS I, 4.8 vs 10%, CS II, 31 vs 44%, CS III, 52 vs 38%, and CS IV, 10 vs 6.7%. Multivariable subtypes distribution (Non-SP vs SP): Luminal, 63% vs 59%, HER2 Positive (IHC+ and/or FISH) 17 vs 22%, TNBC, 21 vs 18%, unknown 6.7 vs 5.7%. Regarding survival, we observed a statistically significant difference in progression-free survival and overall survival favoring the SP cohort; PFS at 5 years, 54 vs 81% (p = < 0.0001) and OS at 5-year, 72 vs 86% (p = 0.01).

Conclusions: We present evidence that the Mexican Seguro Popular (SP), created to bring medical access to those patients without prepaid health protection, provides a significant clinical benefit on survival (PFS and OS) in women with breast cancer.
Cervical cancer screening in incarcerated women: An experience from the first cervical cancer screening campaign in a southern Thailand correctional facility. Poster Session: #263, Sat, 1:15 PM-4:15 PM

Background: Cervical cancer is one of the most preventable cancers, not only presence of effective HPV vaccination but also simple and robust screening methods such as Pap test. Nevertheless, there were some women at risk whom were unable to access screening cause of incarceration. Hence, in 2018, together with Songkla Women Correctional Society, we launched a cervical screening campaign including clinical breast exam, mobile mammography and Pap test. This is the first report of cervical cancer screening result demonstrated the essential of cervical cancer screening in these disadvantaged women. Methods: Due to the regulation of the jail, we had to limited bring-in tools, allowed staffs and operating-time, therefore we used a pre-screening questionnaire, included 5 items: HIV infection, number of partner, parity, age at first sexual intercourse and number of term baby and each of them scored as 2 for “high-risk” and 1 for “low-risk”, total score ranged from 5 to 10. We ranked and chose the volunteer participants, who have HIV infection and/or with high risk score, to undergo Pap test. Results: Of the 1328 questionnaire responders, Their mean risk score was 7.3 (SD= 1.3). HIV infected participants number were 34 (2.5%). Of the 200 screened-participants, None of them had ever received HPV vaccination before, and all participant did not have Pap test since imprisonment. (mean 53.8 m, range 13-236 m, SD 36.7). Their score ranged between 8 to 10, 42.2% of them had score level 9, 54.5% had score level 9 and 3% had score level 10. Mean age was 37.7 years. 10 (5%) of them had abnormal Pap test; 1 of them showed ASC-US, 1 was LSIL, 1 was ASC-H, 5 of them showed HSIL and 2 of them showed squamous cell carcinoma and small round cell carcinoma. Final histopathological test resulted in 6 of cervical intraepithelial neoplasia (CIN) I, metaplasia and cervicitis, 3 were diagnose CIN III and 1 diagnosed microinvasive carcinoma. Incidence of cervical cancer was higher than normal population in this region. (0.5% vs 0.02%). Conclusions: Incarcerated women were at high risk of cervical cancer compared to normal population. Unfortunately, in many prisons, were unconditionally inaccessible to the cervical cancer preventive healthcare system for years. Social should increase awareness to decrease this health disparity.

Investigation of HBOC germline mutations in women diagnosed with breast cancer in Trinidad and Tobago. Poster Session: #265, Sat, 1:15 PM-4:15 PM

Background: Trinidad and Tobago (T&T) is the southern-most Caribbean island, and according to the WHO/PAHO, it has the 2nd highest breast cancer mortality rate in the region. Notably, a large proportion of breast cancer cases in T&T occur at a young age; with nearly 36% of them being diagnosed under the age of 50. There is a known association between a young age at diagnosis and Hereditary Breast and Ovarian Cancer Syndrome (HBOC). Yet, the prevalence of HBOC mutations remains unknown in T&T, as genetic counseling and testing services are extremely limited in the region. Therefore, we sought to determine the prevalence and spectrum of HBOC mutations in T&T. Methods: At the National Radiotherapy Center, T&T’s main oncology unit, female breast cancer patients, who met NCCN criteria for further genetic counseling and testing were recruited through chart reviews. After pre-test counseling, enrolled subjects had a detailed interview about their personal breast cancer diagnosis and family history. A saliva sample was collected using an Oragene kit, and analyzed by Color Genomics Inc. for 30 genes associated with hereditary cancers. Finalized results were returned to patients by genetic counselors from Color Genomics. Results: A total of 118 female patients who met NCCN guidelines for HBOC testing received genetic testing. A majority were 50 years of age or younger (69/118, 59%). The cohort was ethnically diverse: 34% African, 15% Asian, 48% multiple ethnicity, and 3% other/unknown. A pathogenic or likely pathogenic variant (positive result) was identified in 21.2% of the cohort (25/118) - most commonly identified in the BRCA1 gene (13/25, 52%), followed by BRCA2 (5/25, 20%), PTEN (2/25, 8%), BRIPI (1/25, 4%), CHEK2(1/25, 4%), MSH6 (1/25, 4%), PALB2 (1/25, 4%), and RAD51C(1/25, 4%). Conclusions: We found a strikingly high HBOC germline mutation prevalence rate of 21.2% among a cohort of female breast cancer patients meeting NCCN criteria for HBOC testing in T&T. Given the growing implications of germline HBOC mutations for breast cancer treatment and prevention, our results demonstrate an urgent need for funding, as well as the development of robust genetic counseling and testing services in T&T.

Diagnostic and treatment delays in young women with breast cancer. Poster Session: #266, Sat, 1:15 PM-4:15 PM

Background: Delays in diagnosis (dx) and treatment (tx) affect breast cancer (BC) outcomes. We sought to identify factors associated with delays among young women, who do not undergo routine screening and often have pregnancy or breastfeeding-related breast changes that may mask a BC. Methods: The Young Women’s Breast Cancer Study is a multicenter, prospective cohort that enrolled 1302 women with newly dx BC age ≤40 between 2006-2016. Women reported the method and timing of cancer detection on the baseline survey. 231 were ineligible or excluded due to missing information. Among those reporting self-detected cancers, using multivariable regression we evaluated factors associated with delays ≥90 days (d) from symptom to presentation (self dx) and presentation to dx (care delay); in stage 0-III BC we evaluated delays ≥60d from dx to tx (tx delay). Results: 1071 eligible women had median age at dx of 37 yrs (17-40) and 74% reported self-detected cancers. Self delay or care delay ≥90d was reported in 17% and 13%, respectively. Factors inversely associated with self delay included pregnancy at dx (vs nulliparous, OR 0.10, CI 0.01-0.78) and perceived financial comfort (vs not, OR 0.62, CI 0.41-0.93). Women dx ≤1 year post-partum who breastfed (vs nulliparous, OR 2.60, CI 1.14-5.93) and those with a family history of breast/ovarian cancer (vs none, OR 1.79, CI 1.00-3.13) were more likely to have a care delay. Age was inversely associated with care delays (OR 0.94, CI 0.89-0.99). Tx delay was reported by 10% (105/1015), and associated with being single (vs partnered, OR 1.61, CI 1.02-2.56), non-white (vs white, OR 1.85, CI 1.09-3.13) and having Stage 0 BC (vs stage 1, OR 3.08, CI 1.65-7.77); women with stage 3 BC (vs stage 1, OR 0.13, CI 0.03-0.56) were less likely to have a tx delay. Conclusions: In this cohort, most young women with BC underwent timely dx and tx initiation. Women dx ≤1 year post-partum who breastfed were more likely to experience a care delay likely because lactational changes may mask BC signs and symptoms. The associations of perceived financial status with self delay and non-white race with tx delay underscore the need for additional support to ensure timely care for underserved populations with the goal of eliminating disparities in outcomes.
Association of diagnosing physician and hospital characteristics with the use of radical cystectomy among patients with muscle-invasive bladder cancer.

**First Author:** Hemal Kumar P Mehta, The University of Texas Medical Branch at Galveston, Galveston, TX

**Background:** Only one out of five muscle-invasive bladder cancer patients receive radical cystectomy, a guideline-recommended treatment. Prior studies evaluated patient characteristics associated with radical cystectomy use. We aimed to determine bladder cancer diagnosing physician and hospital characteristics associated with the use of radical cystectomy.

**Methods:** This cohort study used linked Medicare and Medicaid Data from 2002 to 2011. We included older adults (age >65 years) diagnosed with muscle-invasive bladder cancer. For each patient, a urologist who performed transurethral resection of bladder tumor was assigned as a diagnosing physician. The diagnosing physician was assigned to one hospital based on where he/she performed more than half of all urologic surgeries. Two-level hierarchical model (patients nested within hospitals) were constructed to determine the association of patient, physician and hospital characteristics with radical cystectomy use.

**Results:** A total of 7,007 patients were diagnosed by 4,601 physicians who were affiliated with 822 hospitals. Overall, the radical cystectomy utilization rate was 26.5%. Only 4.8% of the variation in radical cystectomy was attributed to the patient level. Adjusted radical cystectomy volume by diagnosing physicians and hospitals increased the radical cystectomy use (Table). Diagnosing physician radical cystectomy volume (ref=0) was higher for patients with schizophrenia (hazard ratio [HR] 1.10; 95% CI, 1.03-1.16; P < .005) and dementia (HR 1.11; 95% CI, 1.06-1.18; P < .0005). Participation in VA-based programs to address mental illness, substance use, and homelessness was associated with a significant reduction in all-cause mortality (HR 0.71; 95% CI, 0.68-0.75; P < .0001) and lung-cancer specific mortality (HR 0.73; 95% CI, 0.69-0.77; P < .0001). Conclusions: Schizophrenia and dementia are strong negative predictors of survival among Veterans diagnosed with NSCLC. VA-based mental health treatment programs are associated with reductions in all-cause and lung-cancer-related mortality, highlighting the importance of funding and promoting mental health and supportive programs.
Is immunotherapy toxicity associated with improved overall survival among older adults with advanced cancer? First Author: Andrew Johns, Dept. of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, OH

Background: There is growing evidence that checkpoint inhibitor immunotherapy (IO) toxicity is associated with improved treatment response. There is a paucity of evidence examining the relationship between toxicity and overall survival (OS) in older adults. Methods: We performed a single institution retrospective cohort study of adults who received IO for advanced cancer from 2011-2017. Baseline clinical characteristics were abstracted from the electronic health record. Immune-related toxicities were graded by physicians based on Common Terminology for Adverse Events criteria, v4.0. Bivariate analysis with chi-squared statistics was used to describe baseline characteristics of patients $\geq 70$ years (y) vs. $<70$ y. Survival outcomes were estimated by the Kaplan-Meier method (time zero = start of first-line IO) and compared using the log-rank test. The association of age and $\geq 3$ toxicity with OS was tested with a Cox proportional hazards model. Results: Among 676 patients treated with IO, 238 (35.4%) were $\geq 70$ y. There was no difference in baseline characteristics of each age group except cancer type ($P<0.01$). The incidence of $\geq 3$ toxicity did not differ by age ($<70$ y: 14.5% vs. $>70$ y: 13.6%). OS was significantly longer for adults $<70$ y (16.4 vs. 12.3 months, $P<0.01$) or those with $\geq 3$ toxicity (18.3 vs. 14.7 months, $P<0.01$). When stratified by age and toxicity, patients $<70$ y with $\geq 3$ toxicity had longer OS vs. those without $\geq 3$ toxicity ($P<0.01$). However, there was no OS difference among adults $\geq 70$ y with vs. without $\geq 3$ toxicity ($P=0.78$). Adjusted hazard ratios with an interaction term are below. Conclusions: Though the incidence of $\geq 3$ toxicity did not significantly differ by age, there was no significant OS advantage for older adults with $\geq 3$ toxicity as compared to younger adults. Caution should be used in considering a toxicity-survival relationship in older adults.

### Overall Survival: Age and Toxicity

<table>
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<tr>
<th>Covariates</th>
<th>HR (95% CI)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>$&lt;70$ y</td>
<td>$\geq 3$ toxicity</td>
<td>0.53 (0.35-0.81)</td>
</tr>
<tr>
<td>$\geq 70$ y</td>
<td>$&lt;3$ toxicity vs. no toxicity</td>
<td>1.19 (0.96-1.48)</td>
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<tr>
<td>$\geq 70$ y</td>
<td>$\geq 3$ toxicity</td>
<td>1.13 (0.73-1.75)</td>
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*调整了性别、种族、ECOG PS、BMI，癌症类型

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### 6582 Poster Session (Board #273), Sat, 1:15 PM-4:15 PM

Self-reported health and survival in older patients diagnosed with multiple myeloma. First Author: Nadia Amr, N, Palus, University of Illinois at Chicago, Department of Pharmacy Systems, Outcomes and Policy, Chicago, IL

Background: The strength of associations between pre-diagnosis self-reported health (SRH) and mortality differ by medical condition, with a moderately strong association reported among patients with cancer. Less is known about the impact of SRH on survival among patients diagnosed with multiple myeloma (MM). We aimed to evaluate pre-diagnosis SRH in relation to overall survival (OS) in a cohort of older MM patients. Methods: We conducted a retrospective cohort from the Surveillance, Epidemiology, and End Results (SEER)-Medicare Health Outcomes Survey (MHOS) database of patients 65 years and older diagnosed with primary MM. Survey responses to a single general health question (asking patients to self-report their health as excellent, very good, good, fair, or poor) were used to determine pre-diagnosis SRH, grouped as high (excellent/very good/good) or low (fair/poor). We used multivariable Cox proportional hazards models to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for associations between SRH and risks of all-cause and cancer-specific mortality. Results: Of 521 MM patients with pre-diagnosis SRH data, the mean (SD) age at diagnosis was 76.8 (6.1) years with 60% of patients identifying as white, 18% as black, and 32% reporting low SRH. Compared to patients reporting high SRH, patients reporting low SRH were older, had lower education levels, more comorbidities, and lower Veterans-RAND 12 physical health and mental health component summary scores. In multivariable analyses, MM patients with low SRH had a 28% increased risk of all-cause mortality (HR = 1.28, 95% CI = 1.00, 1.64) and a non-statistically significant 19% increased risk of cancer-specific mortality (HR = 1.19, 95% CI = 0.87, 1.61) compared to MM patients reporting high SRH. Conclusions: Our findings suggest that lower SRH is highly prevalent among MM patients prior to diagnosis and is associated with modestly increased all-cause mortality. At a minimum, low SRH deserves clinical attention to determine how older MM patients’ quality of life may be compromised. The mechanism by which SRH affects mortality in MM should be further assessed and efforts should be made to identify whether any of the underlying mechanisms linking SRH and mortality in MM are mutable.

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### 6582 Poster Session (Board #274), Sat, 1:15 PM-4:15 PM

Real-world prevalence of autoimmune disease (AD) among patients pts) receiving immune checkpoint inhibitors (ICI) in ASCO’s CancerLinQ database. First Author: Li Chen, Concerto HealthAI, Boston, MA

Background: Although pts with AD are routinely excluded from ICI clinical trials, evidence suggests they may be receiving ICI therapy once approved. We sought to understand the prevalence of AD among all pts receiving ICI in real world clinical care, as well as in advanced non-small cell lung cancer (aNSCLC) alone, and as such using the characteristics of ICI pts with and without evidence of AD. Methods: We conducted a retrospective, observational cohort study using statistically de-identified data from January 2011 to November 2018 in CancerLinQ, ASCO’s real-world oncology database. Adult pts who received 1 dose of an ICI and had 0-2 clinical visits were eligible for inclusion. A sub-analysis examining only aNSCLC pts was also carried out. To reduce the likelihood of capturing pts who may have been on a clinical trial, pts were excluded if they received the ICI prior to its first FDA approval date. AD status was determined by the presence of select ICD-9/ICD-10 codes or a medication used to treat autoimmune disease (including steroids) prior to ICI treatment start date. Symptomatic claims data were linked to CLQ via tokenization to build out cohorts. Characteristics of pts with and without autoimmune disease were compared using Chi-square or Fisher’s exact tests. Results: Prevalence of AD was 23% (538/2425 pts) in the aNSCLC population and 27% (3407/12712 pts) in the all ICI patient population. Median age did not differ between AD pts and those with no evidence of AD (All ICI: 67.6 vs. 67.3 years; aNSCLC: 68.5 vs 67.9). AD pts were more likely to be female (All ICI: 46% vs. 40%, $p<0.001$; aNSCLC: 55% vs. 44%, $p<0.001$). Among all AD pts, AD pts were less likely to be Stage IV (62% vs 65%) or to have melanoma (4.6% versus 8.7%) compared to pts with no evidence of AD. The most common ADs among all ICI and aNSCLC pts were glucocorticoid deficiency (6.3% and 3.9%), rheumatoid arthritis (4.2% and 5.8%), and sacroiliitis (2.7% and 3.9%), respectively. Conclusions: This analysis of real-world data finds that a large proportion of pts receiving ICI may have pre-existing AD. Further examination is warranted to examine how AD status may impact outcomes.
Caveat medicus: Harrowing experiences of clinicians who identify and publish near-fatal oncology associated adverse drug reactions. First Author: Ashley Caitlin Godwin, University of South Carolina College of Pharmacy, Columbia, SC

Background: Less than 1-10% of adverse drug reactions are reported. It is even more rare to find clinicians who choose to publish these reports in the literature. We identified clinicians who had treated a patient for an oncology-associated serious adverse drug reaction and published these findings. This is the first study that has investigated personal experiences of clinicians choosing to publish information about serious oncology-associated drug reactions they see in their patients. Methods: Thirty-minute interviews addressed feedback from pharmaceutical manufacturers, FDA personnel, and academic leadership, and recommendations for improving pharmacovigilance. Responses were analyzed using constant comparative methods of qualitative analysis. Results: 18 clinicians met inclusion criteria and 14 interviewees were included. Toxicities included central nervous system infections, infections, gastrointestinal toxicity, cardiac arrhythmias, and cancer development/progression. These investigations were frequently followed by label warnings and/or convening of Food and Drug Administration (FDA) Advisory Committee reviews of safety findings. Five studies were disseminated in four high-impact factor medical journals (JAMA, Lancet, Annals of Internal Medicine, and New England Journal of Medicine). Six clinicians received feedback characterized as supportive from academic leaders, while four clinicians received feedback characterized as negative. Responses from pharmaceutical manufacturers were characterized as negative by 12 clinicians. Responses from FDA employees were characterized as negative by six clinicians. Three clinicians recommended that pharmacovigilance should include simplified clinician reporting systems. Conclusions: Our study finds that clinicians who published reports of serious oncology-associated drug reactions experienced negative feedback from pharmaceutical manufacturers. Feedback from FDA employees and academic clinicians were viewed as supportive by some and negative by others. Most clinicians recommended that future pharmacovigilance involve big data analyses.

Impact of cardiovascular comorbidities on mortality in patients admitted for neutropenic fever in 2016. First Author: Sunbelt Albert Atallah-Yunes, University of Massachusetts –Baystate, Springfield, MA

Background: Neutropenic fever (NF) remains one of the most common causes for hospitalization and mortality in oncology patients. Concomitant cardiovascular disease in patients with cancer is not uncommon. There is limited data on the impact of cardiovascular (CVS) comorbidities on mortality in cancer patients with NF. Methods: A retrospective cohort study was conducted of patients with NF admitted to the 2016 National Sample database (NIS) of adults (>18 years) admitted for NF based on the ICD-10 code. Mortality was the primary outcome. Multivariate linear regression adjusted for potential confounder of age, sex, race, Charlson comorbidity index and all the CVS comorbidities of the study including atrial fibrillation, heart failure with reduced ejection fraction (HFpEF), coronary artery disease (CAD), peripheral vascular disease (PVD), hypertension (HTN), history of smoking, history of cerebrovascular accident (CVA) or TIA and dyslipidemia. STATA 15 was used for analysis. Results: We identified 31,310 patients (mean age 44.6) (49.6% females) admitted with NF, among which 250 died during same admission. On multivariable linear regression there was a significant increase in adjusted all-cause mortality in patients with AF (OR: 2.39; 95%CI:1.06-5.40, P = 0.035) and HFrEF (OR: 1.32; 95%CI:1.08-1.67, P = 0.009). There was no significant increase in mortality in patients with HFpEF, dyslipidemia, HTN, PVD, CAD, history of CVA/TIA and smoking. Conclusions: Patients with NF and concomitant history of AF or HFpEF have an increased risk of mortality during hospitalization. Inflammation is emerging as a key player in AF pathogenesis. This may explain why AF appears to correlate with mortality, as those with more severe presentations are more likely to have a heightened state of inflammation. Patients with NF are more likely to receive fluids in the setting of infectious complications which could explain the increased mortality in CHF patients with NF. Identifying risk factors for increased mortality in patients with NF is important for risk stratification and in guiding clinicians in the management of this delicate population.

6587 Poster Session (Board #278), Sat, 1:15 PM-4:15 PM
Prospective study of pain outcomes associated with contralateral prophylactic mastectomy in women with nonhereditary breast cancer. First Author: Demetria Joy Smith-Graziani, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Women with nonhereditary breast cancer are increasingly undergoing contralateral prophylactic mastectomy (CPM). We examined pain severity and the impact of pain on the lives of women who underwent CPM compared to those who did not. We also examined the associations between age, race/ethnicity, reconstruction status and pain outcomes. Methods: Between 2012 and 2015, we recruited women with newly diagnosed nonhereditary breast cancer who were planned for surgery. We assessed pain with the Brief Pain Inventory at initial surgical consultation and at 1, 6, 12, and 18 months after surgery. The repeated measures model was used to assess the association between pain severity or interference and CPM status at different time points adjusting for other covariates. Results: Of 288 women enrolled (mean age 56 years, 58% non-Hispanic White, 17% non-Hispanic Black), 50 underwent CPM, 163 had unilateral mastectomy, and 75 had breast conserving surgery. Mean pain severity was higher at 1 month (2.78 vs 1.9, p < .001) and 6 months (2.79 vs 1.96, p = .03) after surgery in women with CPM versus those without. In the multivariable repeated measures model adjusted for time, age, race/ethnicity and reconstruction status, there was a significant interaction between time and CPM for pain severity (p < .001) but not interference (p = .13). This suggests that CPM patients had higher pain severity in the first 6 months after surgery, but their pain scores decreased by 12 months becoming similar to women without CPM. Black women had higher pain severity (mean difference 3.35, standard error [SE] 0.35; p < .001) and interference (mean difference 0.91, SE 0.32; p < .001) compared to White women with or without CPM. There was no association between age or reconstruction status and pain severity or interference. Conclusions: Pain severity in patients undergoing CPM is highest during the first 6 months after surgery. Women considering CPM should be counseled about this potential outcome. Race/ethnicity disparities exist in pain management, pain perceptions and communication of pain. Black women undergoing breast surgery report worse pain outcomes than White women regardless of CPM status.

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Analysis of racial distribution amongst patients in phase III cancer clinical trials. First Author: Swathi Gopishetty, Navicent Health, Macon, GA

**Background:** Minority races are often under-represented in cancer clinical trials as enrollment often occurs in large centers. Racial diversity may vary by geographical location and socio-economically backward areas may have a very different racial mix. This study explores the representation of different races in phase 3 clinical trials conducted in the past 10 years. **Methods:** Details about adult patients involved in phase 3 trials was extracted from the clinical trials.gov for 3 common solid organs and 3 hematological malignancies (breast, colon, lung, diffuse large B-cell lymphoma (DLBCL), acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)). The racial distribution of the patient population in these trials was analyzed. **Results:** African American and Asian patients are under-represented in all phase 3 cancer clinical trials. The table shows the average racial distribution in clinical trials for each organ specific malignancy. **Conclusions:** Most phase 3 clinical trials except for lung cancer, predominantly consisted of Caucasian patients. Applying the results of these trials to patients of other races should be done with caution. This study highlights the disparity of race in patients enrolled in clinical trials when compared to diverse and different populations that are encountered in practice.

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<th>S. No</th>
<th>Malignancy</th>
<th>Number of Phase 3 trials</th>
<th>% of Phase 3 trials with Race specified</th>
<th>Number of Phase 3 trials with Race specified</th>
<th>% of African American</th>
<th>% of White</th>
<th>% of Other</th>
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6589 Poster Session (Board #280), Sat, 1:15 PM-4:15 PM

Real-world effectiveness of approved anticancer agents among Medicare beneficiaries. First Author: Angela Green, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** The overall survival (OS) among elderly patients (pts) treated with novel anticancer agents in the real world may be inferior to the OS reported in pivotal trials for drug approval. Pts $\geq 65$ yrs old constitute 60% of cancer pts, yet only 40% of cancer clinical trial participants. Elderly pts have greater comorbidities and experience a higher risk of toxicity from cancer drugs. Using the Surveillance Epidemiology and End Results-Medicare database (SEER-Medicare), we compared the OS among elderly pts treated with FDA-approved cancer drugs for advanced solid tumors to the OS reported in the clinical trials. **Methods:** We identified cancer drugs FDA-approved for metastatic solid tumors between 1/1/08-12/31/12. In a retrospective analysis, for each indication we identified pts in SEER-Medicare meeting disease eligibility criteria (stage, histology, prior therapies) in the trial associated with approval. Pts were diagnosed with cancer from 2010-2013 with follow-up through 2014. Treatment (tx) was determined from national drug codes in Medicare Part B for intravenous (IV) drugs and Part D for oral drugs. Indications were included if $\geq 30$ pts receiving tx met eligibility. Kaplan-Meier methods were used to calculate OS. **Conclusions:** Median duration of therapy (DOT) was estimated from date of the first through completion of the last prescription claim for oral drugs and number of cycles for IV drugs. **Results:** OS data were available and sample size parameters met for 14 drug indications. The median OS among SEER-Medicare pts was shorter than the reported trial OS of IV arms for 13 of 14 drug indications (median difference $7.6$ mos, range $3.4$ to $28.7$ mos). CSS was similar to OS among Medicare pts. Median DOT among SEER-Medicare pts was shorter than the reported trial DOT of IV arms for 13 of 14 indications (median difference $2.9$ mos, range 0 to $8.9$ mos). **Conclusions:** The OS and DOT among SEER-Medicare pts treated with FDA-approved cancer drugs was inferior to the reported OS in pivotal clinical trials for nearly all indications analyzed. The shorter DOT among Medicare pts may explain survival differences. Trials leading to regulatory approval may not be generalizable to cancer pts $\geq 65$ yrs.
Association of sex, age and ECOG performance status with cancer immunotherapy efficacy in randomized controlled trials. First Author: Fang Yang, The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China

Background: Sex, age and ECOG performance status (PS) may affect immune response and the efficacy of cancer immunotherapy with immune checkpoint inhibitors (ICI). We did a meta-analysis to assess the potential sex, age and ECOG PS differences of immunotherapy efficacy in advanced cancer. Methods: PubMed was searched up to January 15, 2019, in randomized-controlled trials (RCT) comparing overall survival (OS) in patients with advanced cancer treated with ICI immunotherapy vs control therapy (without ICI). For sex difference analysis, pooled hazard ratio (HR) of death for men and women was calculated separately, and the heterogeneity between the two estimates was assessed using an interaction test by pooling study-specific interaction HR. Age (< 65 vs ≥65) and ECOG PS (0 vs 1+) difference was analyzed similarly. Subgroup analysis by cancer type and line of therapy (frontline vs subsequent) was explored. All analyses were done in Comprehensive Meta Analysis (v2) with random effects models.

Results: Thirty phase 2/3 RCTs involving 17,728 patients were included. An OS benefit of immunotherapy was found for both men (HR 0.75, 95% confidence interval [CI] 0.69-0.81, P < 0.01) and women (HR 0.79, 95% CI 0.69-0.90, P = 0.01); for both younger (< 65; HR 0.75; 95% CI 0.68-0.83, P < 0.01) and older (≥65; HR 0.76, 95% CI 0.69-0.83, P < 0.01) patients; and for both ECOG PS 0 (HR 0.78, 95% CI 0.69-0.89, P = 0.01) and PS 1+ (HR 0.77, 95% CI 0.71-0.84, P < 0.01) patients. No significant difference of relative benefit from immunotherapy over control therapy was found in patients with different sex (P = 0.283), age (P = 0.906) or ECOG PS (P = 0.783). In melanoma RCTs, compared with women (HR 0.77, 95% CI 0.64-0.94, P < 0.01), men (HR 0.56, 95% CI 0.42-0.76, P < 0.01) had more OS benefit from immunotherapy (P = 0.037). No significant difference was found in other subgroup analyses by cancer types or line of therapy. Conclusions: Overall we found no evidence of association of sex, age, or ECOG PS with cancer immunotherapy efficacy. However, in melanoma, men might benefit more from immunotherapy than women.

Quality of life (QOL) in patients undergoing CAR-T therapy versus stem cell transplant (SCT). First Author: Sunbhi Sidana, Mayo Clinic, Rochester, MN

Background: Given the significant short-term adverse effects of CAR-T cell therapy, it is important to evaluate its impact on QOL of patients in addition to efficacy, compared with established forms of cellular therapy like SCT. Methods: QOL was evaluated prospectively in patients undergoing CAR-T therapy, autoSCT & alloSCT for hematologic malignancies. QOL was assessed with FACT-G at baseline, 2 weeks and 6 months for 6 months thereafter. Functional well-being (FWB), physical well-being (PWB) and emotional well-being (EWB) were measured. Change in QOL vs baseline was assessed. Results: 49 patients were recruited (CAR-T: 10; Auto S: 22; Allo S: 13) with follow up for 2 weeks & 1 month available for 23 615 patients, respectively. Table 1 shows statistically significant difference in baseline QOL scores (p=0.13), though scores were lower in the alloSCT group (85.84,68). EWB & FWB were numerically higher in the CAR-T group, followed by autoSCT group. At 2 weeks, overall QOL decreased by only 2 points in CAR-T group vs. 22 & 18 points in auto & alloSCT groups (p=0.09). Change in PWB vs. baseline was less pronounced in the CAR-T group (1-9, -13, p=0.03). At 1 month, overall QOL was 6 points lower than baseline in CAR-T group vs. 3 and 14 points lower in auto & alloSCT groups, respectively (p=0.34). Importantly, PWB had at least returned to baseline in the CAR-T group. Conclusions: Preliminary data show that patients undergoing CAR-T cell therapy do not experience a more significant decline in QOL compared with auto & allo SCT, and may experience fewer physical side effects in the short-term. Accrual & follow-up are ongoing.

Incidence and outcome of interval breast cancer among women participating in the provincial mammographic screening program in Manitoba, Canada. First Author: Saroj Niraula, CancerCare Manitoba and Univ of Manitoba, Winnipeg, MB, Canada

Background: The province of Manitoba, Canada has an organized population based biennial mammographic screening program. Here we report outcomes of women diagnosed with Interval Cancers (IC), defined as cancer diagnosed within 24 months of a normal screening mammogram and before the next screening mammogram, compared to Screen Detected (SD) cancers. Methods: The Manitoba Cancer Registry was used to obtain data about tumor and host characteristics and cause-specific mortality for women 52 to 64 years of age diagnosed with invasive breast cancer from January 2004 to December 2010. Lead time bias in SD cancers was adjusted based on Duffy's correction factor. Competing risk analysis was used to examine the risk of death by cancer detection method. To examine the relationship between breast cancer detection type and personal and tumour characteristics, we performed multinomial logistic regression analysis with area, area-level income quintile and age. Sensitivity analyses with sojourn times of 1, 3, and 4 years showed similar results. Results: The risk of non-breast cancer death was not increased with IC compared to SD cancers (HR 1.33, 95% CI: 1.97-8.87), for sojourn time (when tumour is asymptomatic but screen detectable) of 2 years adjusting for area-level average income quintile and age. Sensitivity analyses with sojourn times of 1, 3, and 4 years showed similar results. The risk of non-breast cancer death was not increased with IC compared to SD cancers (HR 1.33, 95% CI: 0.43-4.15). Conclusions: Among women who participated in a systematic population-based screening program, IC occurred frequently; breast cancer-related death for IC was 4 times higher than that of SD cancers. These results highlight the discordance between the principles underlying population-based breast cancer screening and nature of these populations in breast cancer incidence.
A living systematic review of immune checkpoint inhibitors in cancer patients: A novel platform for evidence synthesis in oncology. First Author: Inbar Bin Rizvi, Mayo Clinic, Rochester, MN

Background: Several previous systematic reviews and meta-analyses have attempted to summarize toxicity of immune checkpoint inhibitors (ICIs). However, very soon after each one of these reviews has been published, it has become outdated. ICIs are currently used in 14 different cancers and data is rapidly evolving from new clinical trials. A living Systematic review, which is designed to continuously update is incorporated in the present review. Our work compared either immunotherapy alone or combination with existing standard of care treatment and reported data for AE of its interest. DerSimonian-Laird random effects Meta-Analysis was performed to derive pooled odds Ratio (OR) estimates for AE of interest. An infrastructure of a living systematic review is being developed and it includes monthly literature searches, cumulative meta-analysis and an online reporting platform.

Results: We screened 6746 studies and 31 phase 3 and 2 phase 2 RCTs (n = 21,421) were included in the analysis. 22 RCTs used PD-1/L1-L1 ICIS as a single agent and 11 as a combination therapy. Selected toxicity estimates are summarized in a table. Conclusions: The meta-analysis updates previously published toxicity estimates and provides additional information about the risk of toxicities in single versus combination regimens. We have initiated the first living systematic review in oncology that is continuously updated, incorporating relevant new evidence as it becomes available, and will provide accurate and up to date toxicity estimates to support clinical decision making.

Impact of timing of lung resection on survival for clinical stage I and II lung cancer. First Author: Isabel M Emmerick, University of Massachusetts, Worcester, MA

Background: Lung cancer has the highest mortality among the leading cancers in the U.S. Surgical resection is considered as the most effective treatment for lung cancer in early stages, providing greater long-term survival. Clinical guidelines on delays in resection of early-stage lung cancer do not exist. This work aims to assess whether increasing time between diagnosis/first doctor visit and surgery, and survival of patients with early stage NSCLC was assessed using multivariable Cox proportional hazard model. We have initiated the first living systematic review in oncology that will be continuously updated, incorporating relevant new evidence as it becomes available, and will provide accurate and up to date toxicity estimates to support clinical decision making.

Association between age, risk of severe (Grade 3-4) immune-related adverse events (sirAE), and mortality in patients receiving immune checkpoint inhibitors (ICIS). First Author: Aseer Almahdi, University Hospitals Seidman Cancer Center, Cleveland, OH

Background: ICIs are used in the treatment of advanced malignancies with on-target adverse events of non-tumor inflammation. Many studies have shown conflicting safety results with regard to older vs younger adults where 65 - 70 years of age has been used as the discrete cut-off variable. We sought to investigate the incidence and the association between age and sirAE using age as a continuous variable at a large tertiary cancer center. Methods: Under IRB approval, our ICI outcomes database was queried for those who were hospitalized and received an immunosuppressant. Charts were individually reviewed to identify hospital admissions due to a sirAE (a grade 3 or 4 AE per CTCAE v4.0) and all-cause mortality at 12 months post ICI start. Non-linear analyses using Cox regression models with penalized smoothed splines were performed to explore association between age and sirAE. Results: There were 6.3% of 1043 patients who had a sirAE, and a total of 83 sirAE events. Mean age was 64 ± 13 years.ICI included anti-PD-1 (77.8%), anti-CTLA-4 (18.1%), and anti-PD-L1 (4.1%). Pts with sirAE had a thirty day, and one year mortality of 12% and 26%, respectively. Spline analysis showed a U-shaped association between age and hazard of sirAE (HR 1.004 95% CI: 0.999-1.009), with every 10 years below 60 was associated with increased sirAE (HR 1.050 [0.999-1.071], P = 0.008), while every 10 years below 60 was associated with increased sirAE (HR 1.050 [0.999-1.071], P = 0.008). However, age and mortality showed a linear association (P = 0.003). Conclusions: We observed a curvilinear U-shaped association between age and the risk of sirAE, with a peak risk at age 60. Our findings are not consistent with the notion that age affects both the incidence and mortality. Further studies are needed to understand this relationship and its impact on outcomes, clinical care, and underlying host immune context.

Online advertising and marketing claims by providers of proton beam therapy: Are they transparent? First Author: Mark Thomas Corkum, Department of Radiation Oncology, London Health Sciences Centre, London, ON, Canada

Background: Proton beam therapy (PBT) is a radiotherapy platform that purports an improved therapeutic ratio by way of a rapid radiation dose fall-off. Despite this technology being hindered by significant capital and patient costs, the number of centres offering PBT is increasing exponentially. Consensus guidelines support PBT use in a limited number of disease sites or on clinical trials. As patients frequently obtain information about PBT from hospital or cancer centre websites, the purpose of this study was to evaluate direct to consumer advertising (DTCA) content and claims made by proton therapy centre (PTC) websites. Methods: English PTC websites worldwide were identified using the Particle Therapy Co-Operative Group website. Data abstraction of website content was performed independently by two investigators. Eight international guidelines were consulted to determine indications for PBT. Univariate and multivariate logistic regression models were used to identify website characteristics that were associated with a higher likelihood to make non-evidence-based claims of PBT such as improved disease control or cure. Results: From the 48 PTCs with 46 English websites, most (58%) did not provide any references for claims made regarding PBT. These included: improved disease control or cure (61%), fewer side effects (85%), or was the standard of care (13%). Prostate (87%), head and neck (87%) and pediatric (83%) cancers were the most frequently listed PBT-indicated disease sites, consistent with international guidelines. However, pancreatobiliary (52%), breast (50%) and esophageal (44%) cancers were frequently advertised despite not being endorsed in any consensus guidelines. On multivariate analysis, an increasing number of listed disease sites and claims of being a regional PTC leader were associated with indicating that PBT offers greater disease control compared to surgery. Availability/benefit through a clinical trial was mentioned on 57% of websites. Conclusions: PTC websites often contain information and DTCA claims inconsistent with international consensus guidelines. As online marketing information may have significant influence on patient decision-making, alignment of such information with accepted guidelines and consensus opinion should be adopted by PBT providers.

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Mortality within 30 days of immunotherapy (checkpoint inhibitors) in metastatic cancer patients treated at Australian tertiary cancer center. First Author: Hiren A. Mandaliya, Calvary Mater Newcastle Hospital, Waratah, Australia

Background: Cancer treatment has evolved rapidly since the advent of immunotherapy. The current era of immunotherapy, as it has been the standard treatment for advanced melanoma, lung cancer, renal cell cancer and others. The Innovative 4R Cancer Care Delivery Model improves patient self-management, but further efforts are needed to expand the benefit to as close to a 100% of pts as feasible. Safety net pts benefited from 4R at similar or higher rates than non safety net pts, indicating that 4R may reduce care disparities. An expansion of 4R across the US continues this work.

6602 Patient-reported outcomes from two global multicenter clinical trials of children with tumors treated with larotrectinib, a selective TRK inhibitor, were recently approved by the FDA based on high objective response rates, durable chemotherapy.

Methods: We conducted a retrospective study on patients with advanced cancer treated with immunotherapy and died within 30 days of treatment. Clinical data on patients treated with immunotherapy at Calvary Mater Newcastle between 2006 and 2018 was collected. Data were compared with 30-day mortality statistics of chemotherapy. Results: A total of 601 metastatic cancer patients received immunotherapy at Pembrologic, Nivolumab, Ipilimumab, Atezolizumab, Tiselizumab and MSB0011359C on 5022 occasions. Seventy-six (12.6%) patients died within 30 days of receiving immunotherapy. Median age was 58 years (35-90). Melanoma was the most common (63%) followed by lung (20%). Forty-seven (47%) of patients received immunotherapy as first-line treatment and 39% as second-line. Patients died within 30 days received an average 2 (1-16) immunotherapy doses. A quarter (25%) of patients had ECOG 3 and ECOG 4 before last dose. Majority of deaths were related to disease (86%). Nearly 80% of patients had ECOG > 0 before last dose. One patient (1%) who died due to treatment-related pneumonitis. In univariate analysis, there was no association between mortality and patients’ demographic variables such as age, sex, BMI, cancer type, EOCG performance status, immunotherapy agent and prior treatment.

Conclusions: To our knowledge, this is the first ever report on data on 30-day mortality after immunotherapy in advanced cancer. Thirty-day mortality rates were comparable to published data on patients treated with chemotherapy. Results emphasise significant of careful selection of advanced cancer patient for immunotherapy. Due to small sample size, the power to detect a significant association between demographics and survival is reduced.

6603 Where’s my doctor? the impact of the primary oncologist’s visit with their hospitalized patients. First Author: Andrew P. Bakow, Brown University Alpert School of Medicine, Providence, RI

Background: Continuity of care is a cornerstone of the patient-practitioner relationship and patient satisfaction. The inpatient continuity visit (ICV), a face-to-face patient-provider interaction, involves a discussion regarding hospital course and care goals and decisions. We theorize that the ICV influences patient satisfaction. Previously, patient satisfaction has been related to patient perceptions of physician conduct, including communication skills. Currently, there are no studies investigating the impact of an ICV on patient satisfaction.

Methods: Subjects (N=82) were comprised of adult inpatients on the oncology unit at Miriam Hospital, a teaching hospital of the Alpert Medical School of Brown University. All participants had an oncologist at the hospital based cancer center. A survey, given at discharge, included a 5-point Likert scale ranging from greatly worsened to greatly improved to assess the impact of the ICV on patient satisfaction. Of 82 participants, 46 reported a visit by their outpatient oncologist. Forty-two (91.3%) reported that this visit either greatly or somewhat improved satisfaction with their hospital stay, while 8.7% reported no impact. Of patients whose oncologist visited once, 94.4% reported either greatly or somewhat improved satisfaction compared to 89.3% who had been visited once. Out of 36 subjects who did not receive a visit, 16.7% reported that the lack of visit either greatly or somewhat worsened their hospital stay, while 83.3% reported no impact. Conclusions: Our study suggests that an ICV improves satisfaction of care in cancer patients on a hospitalist service. Furthermore, one of every six subjects who did not receive an ICV reported a negative impact on satisfaction. Results highlight a possible intervention to the discontinuity of care that may be perceived by patients. While the practicality of this intervention requires evaluation, the efficacy of a single continuity visit to improve satisfaction is reassuring.

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Background: National Cancer Institute Clinical Trial Network (NCTN) groups (6604) Poster Session (Board #295), Sat, 1:15 PM-4:15 PM

Background: National Cancer Institute Clinical Trial Network (NCTN) groups

Methods: We evaluated Phase III cancer clinical trials which the SWOG Cancer Research Network coordinated or participated in (1990-2017). Included trials were completed and its results published. A documented practice influential (DPI) trial was one with verified influence on National Comprehensive Cancer Network (NCCN) clinical guidelines (available starting in 1996) or on U.S. Food and Drug Administration (FDA)-approved package inserts. We estimated the rate of DPI trials overall and over time. The total federal investment supporting the set of trials was also determined based on public data. Results: In total, 182 trials comprising 148,028 patients were studied. We identified 79 DPI studies (43.4%); 73 influenced NCCN guidelines, 12 influenced new drug approvals, and 6 influenced both. The rate of DPI trials was 72.3% (47/65) among formally positive trials (i.e., achieved their protocol specified end-point) and 27.4% (32/117) among negative trials. Thus 40.5% (32/79) of DPI trials were based on negative studies, half of which (16/32 = 50.0%) reaffirmed standard of care over experimental therapy. There were no differences between DPI and non-DPI trials in key study design characteristics. Total federal investment for the programs conducting the trials of $36 billion (USD2017), a rate of $7.5 million per trial, or $17.2 million per DPI trial. Conclusions: Nearly half of all phase III trials by one of the NCTN's largest groups had documented practice influence on clinical care guidelines or new drug approvals. Even many negative trials impacted guideline recommendations. Compared to the combined drug price and pharmaceutical companies – typically estimated at > $1 billion – the amount invested by federal funders to provide this valuable evidence was modest. These findings highlight the major role of the NCTN’s clinical trial program in advancing oncology practice.

Stage IV patients screened for supportive oncology needs, including distress

24 17% 38% 53% 69% < 0.0001
(148/ 415/ 678/ 537/ 843)
1075/ 1283/ 779

Stage IV patients screened for supportive oncology needs, including distress

24 6% 15% 22% 35% < 0.0001
(27/ 58/ 78/ 131/ 263)
452/ 379/ 599/ 261

Patients screened for supportive oncology needs, including distress

25 36% 35% 46% 56% < 0.0001
(303/ 413/ 587/ 439/ 815)
527/ 432/ 673/ 214

Patients screened for supportive oncology needs, including distress

2 54% 55 66 55 NS
(453/ 592/ 627/ 432/ 843)
587/ 673/ 799

Patients given prognosis time frame (days to weeks, weeks to months, months to years, years+)

2 24% 34% 43% 44% < 0.0001
(205/ 364/ 403/ 340/ 843)
1075/ 459/ 799

Patients given prognosis time frame (days to weeks, weeks to months, months to years, years+)

3 15% 43% 36% 36% < 0.0001
(68/ 163/ 128 94/ 452)
579/ 379/ 261

6605 Poster Session (Board #296), Sat, 1:15 PM-4:15 PM
Survivorship care: Improving delivery of care plans for hematologic patients at the Washington Cancer Institute (WCI). First Author: Hira Latif, Medstar Washington Hospital Center, Washington, DC

Background: Cancer and long-term sequelae of its treatment impact the future health and psychosocial wellness of these survivors. ASCO guidelines recommend providing survivorship care to cancer patients who have completed treatment with curative intent. The Commission on Cancer (CoC) recommends that survivorship care including treatment summaries be delivered to 50% of eligible patients. In our ASCO Quality Training Program project, we aimed to achieve this CoC goal of 50% for the year 2018. Methods: Baseline data collected from Jan 1, 2016 to June 30, 2018 indicated that 33% of hematologic malignancy survivors at WCI received treatment summaries and survivorship care. For the year 2018, there were 11 survivors of hematologic malignancy, and 4 of them (36%) had received survivorship care prior to initiation of the project. We surveyed 12 providers to obtain data for perceived challenges to deliver survivorship care. Large volume of patients, lack of resources, no standardized process and high no-show rates were identified as the most important barriers. A bi-monthly survivorship clinic run by hematology/oncology fellows was initiated in September 2018 to address some of these barriers. Results: By November 30, 2018, 63% of the 27 survivors received survivorship care and treatment summaries. Compared to the average from the preceding two years, survivorship care delivery increased by 30%. Conclusions: Our institution was able to meet the CoC requirement by delivering survivorship care to 63% of survivors of hematological malignancies through these interventions. Our approach to this quality improvement study. We intend to extend this process to other tumor types to increase the delivery of consolidated survivorship care at the WCI.

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**First Author:** Alona Zer, Sarcoma Unit, Davidoff Cancer Institute, Rabin Medical Center, affiliated to the Sacker Faculty of Medicine, Petach Tikwa, Israel

**Background:** Advanced NSCLC is associated with an increased risk for VTE, with a reported rate of 8-15%. Clinical observations suggest a higher rate of VTE in patients with ALK-rearranged NSCLC. Clalit Health Services (CHS) is both a healthcare payer and provider, covering over 50% of the population in Israel, with individual patient data recorded in a centralized electronic database. We aimed to determine the incidence of VTE in patients with ALK-LC using a population-based cohort.

**Methods:** We identified all patients diagnosed with NSCLC between 01/2012-12/2017 within CHS. Clinical and demographic data (including VTE risk factors, i.e., components of the Khorana score) were extracted from the CHS registry for all patients. Patients with ALK-LC were identified according to crizotinib prescriptions (dispensed after an approved CHS’ pre-authorization for an ALK-LC diagnosis). VTE was identified by ICD diagnosis codes 415.xx, 444.xx, 451.xx and 453.xx. VTE risk factors (Khorana score) were also extracted. Association between ALK-LC and VTE were analyzed using logistic regression, estimating univariate and multivariate Odds Ratios (OR). Results: Overall, 427 patients (44%) with ALK-LC were identified. 149 (3%) had at least one prescription for crizotinib for advanced ALK-LC. The rate of VTE in these patients was 25% (38 of 149 patients), while in the non-ALK-LC the rate was 14% (596/4178), OR = 2.05, p = 0.0004. The association was significant also in a multivariate analysis adjusting for, age, smoking status, BMI, platelet count, hemoglobin and Charlson co-morbidity score (OR 1.66, p = 0.018).

**Conclusions:** This pooled analysis of individual patient data confirms prior data from smaller retrospective studies, suggesting ALK-LC is associated with a high risk of VTE. Randomized trials with prophylactic anti-coagulation are unlikely to be performed in this rare subtype, thus increased awareness and consideration of VTE prophylaxis in high risk patients is warranted.

**QOL assessment integrated into the clinical care of cancer survivors to identify needs and direct care.**

**First Author:** Tina Hsu, Ottawa Hospital, Ottawa, ON, Canada

**Background:** The Functional Assessment of Cancer Therapy-General (FACT-G) is the most frequently used QOL tool, however, there are newer studies that have shown both an improvement in QOL, and improvement in overall survival using these tools. We integrated the Functional Assessment of Cancer Therapy-General Population (FACT-G p.4) to direct the deployment of resources and interventions to improve the care of patients who have completed potentially curative therapy for cancer.

**Methods:** This is an observational study of patients who received cancer therapy with curative intent in the last 18 months. The FACT-G was administered by an RN via telephone. Patients contacted and reviewed a Survivorship Care Plan (SCP) as defined by the American College of Surgeons Committee on Cancer. Patients who had a total score less than 60 on FACT-G and/or had a score less than 12 on the Emotional Well-Being subscale (EBW) were considered high-risk and were referred to the Survivorship MDC for in-person evaluation.

**Results:** From 10/1/2018 to 12/31/2018, 114 patients were referred to the cancer survivorship program. Of these, 64 (56%) patients had FACT-G administered and were evaluated. 45 of these (70%) only completed the FACT-G and received an SCP. 21 patients had a total score less than 60 and/or an EBW sub-score less than 12 and were identified as high-risk. 15 (72%) patients were seen in MDC, 4 (19%) patients were seen in conjunction with a scheduled appointment by the MDC team, 2 (9%) patients refused further evaluation. 66.7% of patients in the survivorship program were referred to Oncology Behavioral Health compared to 18.2% of all oncology patients. Survivorship patients in the cohort had a baseline utilization of the emergency department (ED) of 4.1% (10 of 241) from 1/1/2017 to 31.07.2017, was collected. For OS Kaplan-Meier curves were created and univariate COX proportional hazards model analysis was used and log rank tests were performed. For statistical analysis the chi2-test was used to investigate significant relations between the three months mortality (3MM) and patient characteristics. 3MM was defined as death within 3 month of the first ED consultation.

**Results:** From a total of 1029 patient contacts 743 met the inclusion criteria. In total 552 patients were included. The median age was 67 years (Minimum: 18y; Maximum: 95y). The vast majority of patients (480, 87%) were in a palliative setting. 243 patients (44%) were referred active treatment. The biggest group of patients suffered from lung cancer (18%) followed by hematologic malignancies (14%), pancreaticobiliary tumours (11%), breast cancer (8%) and colorectal cancer (7%). In total 111 patient contacts (15%) were treatment associated, 384 patient contacts (52%) were tumor related, the remaining (24%, 33%) were unrelated to either. In 533 cases (72%) inpatient treatment was necessary. The average length of stay was 9, 36 days. Furthermore the 3MM was significantly higher in elderly patients > 65y (p = 0.001), palliative patients not undergoing active treatment (p = 0.003) and patients with elevated CRP levels (> 0.5mg/dl) (p = 0.001) at time of ED contact. In addition in our univariate analysis factors that significantly decreased the OS were age > 65, visceral metastasis and palliative patients without active treatment.

**Conclusions:** The majority of cancer patients in this study were in a palliative setting. Moreover, cancer associated complications posed the most frequent cause for ED consultation. We could identify a higher risk for mortality for elderly patients, patients with visceral metastasis and patients undergoing best supportive care. The results may help to inform both cancer patients and primary care units about frequent complications.

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6612 Poster Session (Board #303), Sat, 1:15 PM-4:15 PM

Practice variation on hospital level in the systemic treatment of metastatic colorectal cancer in the Netherlands: A population-based study. First Author: Lotte Keikes, Department of Medical Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background: Population-based data on the implementation of guidelines for cancer patients in daily practice are scarce. Therefore, we evaluated practice variation patterns and associated variables in the systemic treatment of metastatic colorectal cancer (mCRC) between 2008 and 2015 in the Netherlands. Methods: We selected a random sample of adult mCRC patients diagnosed from 2008 to 2015 from the National Cancer Registry in 20 Dutch hospitals. We examined the influence of patient, demographic and tumor characteristics on the odds of being treated with systemic therapy according to the current guideline and assessed its association with survival. Results: Our study population consisted of 2222 mCRC patients of whom 1307 patients received systemic therapy for mCRC. Practice variation was most obvious in the use of bevacizumab and anti-EGFR therapy in patients with KIRAS wild-type tumors. Administration rates did not differ between hospital types but fluctuated between individual hospitals for bevacizumab (89-92%; p < 0.0001) and anti-EGFR therapy (10-75%; p = 0.05). Bevacizumab administration was inversely correlated to higher age (OR: 0.99; 95% CI: 0.97-1.01), female gender (OR: 0.72; 95% CI: 0.65-0.81), and the presence of macronodular metastases (OR: 5; 95% CI: 0.3-30). However, patient characteristics did not differ between hospitals with low or high bevacizumab administration rates. Exposure to bevacizumab (HR: 0.8; 95% CI: 0.7-0.9) and anti-EGFR therapy (HR: 0.6; 95% CI: 0.5-0.8) was associated with longer OS (p < 0.05). Conclusion: We identified significant inter-hospital variation in targeted therapy administration for mCRC patients, which may affect outcome. Age and comorbidity were inversely correlated with anti-EGFR administration, but did not explain inter-hospital practice variation. Our data strongly indicate that practice variation is based on individual strategy of hospitals rather than guideline recommendations or patient-driven decisions. Individual hospital strategies are an additional factor that may explain the observed differences between real-life data and results obtained from clinical trials.

6614 Poster Session (Board #305), Sat, 1:15 PM-4:15 PM

Impact of specialist palliative care delivered over three months prior to death on a colorectal cancer patient’s end-of-life care: A retrospective cohort study. First Author: Aynhara Annarajah, University of Calgary, Calgary, AB, Canada

Background: More patients are experiencing aggressive end-of-life (EOL) care. This is concerning as aggressive EOL care, on a population level, is associated with poor quality care. Specialist palliative care (PC) has been shown to help relieve EOL symptoms, improve patient quality of life, and reduce aggressive EOL care. This study aimed to estimate the impact of the timing of specialist PC, specifically PC delivered at least 3 months prior to death, on a colorectal cancer (CRC) patient’s risk experiencing aggressive care in the last 30 days of life. Methods: A population-based retrospective cohort study of adult patients who died from CRC in Alberta, Canada from 2011-2015. The Alberta Cancer Registry was used to identify the cohort, which was linked to healthcare resource use data in local, provincial, and national databases. Individuals who died <30 days from CRC diagnosis were excluded. Participants who accessed any of the provinces specialist PC services were deemed exposed to specialist PC (includes PC consult team, intensive PC unit, palliative home care, hospice). Aggressive EOL care was defined as having experienced at least one of: hospital death, >1 emergency department visit, >1 hospital admission, >14 days of hospitalization, ≥1 intensive care unit admission, ≥1 new chemotherapy program (or any treatment in the last 14 days of life). Logistic regression was used to model factors (specialist PC timing and clinical characteristics) associated with aggressive EOL care. Results: The cohort comprised 2979 patients. Most patients received specialist PC before death (58%); 60% had ≥1 indicator of aggressive EOL care. Relative to patients who received specialist PC >3 months before death, patients who received specialist PC <3 months before death were 1.5 times more likely to experience aggressive EOL care (CI: 1.2-1.9). Patients who received no specialist PC were 2.1 times more likely to experience aggressive EOL care (CI: 1.7-2.8). Short disease duration (<1 year from diagnosis to death), younger age at death, living in a rural area, and male sex were also associated with higher odds of experiencing aggressive EOL care. Conclusions: Specialist PC delivered >3 months before death reduced the CRC patient’s risk of experiencing aggressive EOL care over PC delivered <3 months before death.

6613 Poster Session (Board #304), Sat, 1:15 PM-4:15 PM

Impact of cancer in pulmonary embolism presentation and outcomes: A large academic center study. First Author: Cherry Au, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA

Background: The risk of venous thromboembolism is increased 4- to 7-fold in patients with malignancy, emphasizing the need to identify and treat these patients early to improve outcomes. We aimed to study the clinical presentation and outcomes of pulmonary embolism (PE) in patients with and without cancer. Methods: We performed a retrospective analysis of consecutive patients diagnosed with PE via CT scan from 2014-2016 at Jefferson Hospital. We compared patient characteristics, presentation, PE characteristics and mortality of patients with and without cancer. Cox proportional regression hazards model was used for survival-time analysis. Results: Our study included 581 patients, of which 187 (32.1%) had active cancer. Cancer patients were less likely to have chest pain (18.2% vs 37.4%, p < 0.01), syncope (2.7% vs 6.6%, p = 0.05), bilateral PEs (50% vs 60%, p = 0.025), and right heart strain (RHS) (48% vs 58%, p = 0.024). Indwelling catheters (IC) were present in 41.2% (n = 77) of cancer patients. However, presence of IC was not associated finding of incidental PEs (26% vs 18.2%, p = 0.201). There was no difference in hospital length of stay (8.9 vs 9.4 days, p = 0.61) or intensive care unit admission (31.9% vs 33.3%, p = 0.75). Targed PE dose aggressive PE (3.2% vs 7.1%, p = 0.06) in cancer patients, but this difference was not statistically significant. Cancer patients elected comfort care at higher rates (15.2% vs 5.4%, p = 0.01). Cancer patients had higher 1-year mortality as compared to non-cancer (adj HR 6.9, 95% CI 3.3-14.7, p < 0.01). Among cancer patients, 52.7% had metastasis with a higher 1-year mortality (adj HR 2.5, p = 0.029). Overall, 35.8% were on active chemotherapy with a higher 1-year mortality (adj HR 7, 95% CI 3.3-14.7, p < 0.01). Overall, 52.7% had metastasis with a higher 1-year mortality (adj HR 7, 95% CI 3.3-14.7, p < 0.01). Among cancer patients, 52.7% had metastasis with a higher 1-year mortality (adj HR 7, 95% CI 3.3-14.7, p < 0.01). Among cancer patients, 52.7% had metastasis with a higher 1-year mortality (adj HR 7, 95% CI 3.3-14.7, p < 0.01). Conclusions: Cancer patients presented with less severe pulmonary embolism with no differences in hospital care and symptom management for patients with cancer who needed acute care. This study was limited by small sample size (p = 0.02). In conclusion, we found no statistically significant difference in PE outcomes. Future studies should be focused on larger sample size and different cancer subtypes.

6615 Poster Session (Board #306), Sat, 1:15 PM-4:15 PM

Impact of oncology urgent care clinic on emergency department rates. First Author: Tannaz Sedghi, Cancer Outcomes, Public Policy, and Effectiveness Research (COPPER) Center, Yale Cancer Center and Yale University School of Medicine, New Haven, CT

Background: Oncology-specific urgent care clinics (UCC) may play a key role in reducing unscheduled emergency department (ED) visits among patients with cancer. We sought to determine if establishment of an Oncology UCC was associated with lower ED utilization among patients receiving cancer care at Yale’s Smilow Cancer Hospital (SCH) and two nearby, integrated community practices. Methods: SCH opened its UCC in April 2017 to provide supportive care and symptom management for patients with cancer who need acute medical attention outside of regular clinic visits. We identified patients who had at least one visit with an oncology provider during the Pre-UCC period (9/1/16 – 12/31/16) or Post-UCC period (9/1/17 – 12/31/17) and received chemotherapy within a year preceding their provider visit. For each patient, we captured all ED visits in a four-month window starting from their last provider visit in each study period. The ED visit rate for both periods was defined as the total number of ED visits divided by the total number of unique patients in the period. To determine the impact of the UCC on ED utilization, we evaluated the absolute difference in the ED visit rate between the Pre- and Post-UCC period using a two-sample t-test. Results: There were 3,754 patients in the Pre-UCC period and 4,734 patients in the Post-UCC period. In the full study sample, the mean age was 62.9 and most common cancer types were Hematologic, Gastrointestinal, and Breast. Prior to opening the UCC, the ED visit rate was 0.27 per unique patient. After opening the UCC, we found a 13.9% relative decrease in the overall ED visit rate from 0.27 to 0.23 (p = 0.02). The SCH patient ED visit rate declined by 12.5% (p = 0.03) and the community practice rate declined by 37.1%; however, the latter decline was not statistically significant, potentially due to a small sample size (p = 0.19). Conclusion: Our study found a decrease in the ED visit rate after the opening of an Oncology UCC. An urgent care strategy for cancer centers may serve as an efficient way to manage patients while minimizing ED use.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Adherence to the guidelines: A comparison of biomarker testing implementation in metastatic non-squamous, non-small cell lung cancer in university versus community institutions. First Author: Sufana Shikdar, Mercy Catholic Medical Center, Darby, PA

Background: Molecular biomarkers have become essential in determining optimal treatment for patients with advanced non-small-cell lung cancer (NSCLC). Few studies have evaluated the implementation of biomarker assessment (e.g., EGFR, ALK and ROS1) in routine clinical practice. We endeavored to assess adherence to biomarker testing guidelines in different clinical settings, specifically in a university hospital versus a community hospital in the same region. Methods: A retrospective analysis was conducted in newly diagnosed metastatic non-squamous NSCLC patients comparing the compliance of biomarker testing based on nationally established guidelines available at the time of diagnosis. De-identified electronic health record (EHR) data were collected from Mercy Catholic Medical Center (MCMC) and Hahnemann University Hospital (HUH) between 1/1/15-1/30/19. Results were compared in each setting to determine utilization of biomarker testing. Results: 27 patients were identified at MCMC and 41 at HUH. 22 (81%) patients at MCMC and 36 (88%) patients at HUH underwent appropriate molecular testing based on guidelines available at the time of diagnosis. Conclusions: Our data suggests that both university and community institutions have appropriately adapted the evolving guidelines for molecular testing for patients with non-squamous NSCLC. In the rare instances that molecular testing was not performed, the most common reason was inadequate amounts of tissue available. Newer technologies, such as next-gen sequencing and serum based testing, will make compliance with guidelines easier in the future, particularly as increasing numbers of molecular markers will need to be assessed.

Quality control system of Watson for oncology: Artificial intelligence for supporting clinical decisions in oncology. First Author: Juemin Fang, Shanghai Tenth People’s Hospital, Tongji University, Shanghai, China

Background: Watson for Oncology (WFO) is an artificial intelligent clinical decision-support system (AI-CDSS) developed by IBM and trained by Memorial Sloan Kettering Cancer Center to assist in cancer care by providing evidence-based treatment options with priority. However, there are disagreements argue that WFO recommends “unsafe and incorrect” cancer treatments. Also, guidelines and drug availability in China are different from USA. Therefore, a quality control system of WFO is urgently needed to help oncologists better use WFO in China. Methods: Experts from medical oncology, surgical oncology, radiology, intervention, radiology and pathology etc. forming a Multiple Disciplinary Team (MDT) to score Watson recommendations in 6 aspects (shown in the table). Results: With this quality control system, the value of WFO was carefully evaluated by MDT. Recommendations with higher score (especially more than 80) were more standardized, reasonable and evidence-based thus more likely to be chosen. Localization and drug availability problem was solved by taking Chinese guidelines and drug approval into evaluation within this scoring system. Treatment options unsuitable or not available in the system will be removed and replaced by the advices of MDT. Conclusions: Reliability and security are the top concerns of applying new technology in healthcare. With the MDT quality control system, AI-CDSS can be used safely and efficiently before it is fully mature. Also, the accuracy and advancement are assessed in this system to help oncologists better use WFO in China in the future. Indicators evaluating the WFO recommendations.

<table>
<thead>
<tr>
<th>Evaluation index</th>
<th>Score</th>
<th>Actual score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 WFO recommendations and guidelines (NCNN, ESMO, CSCO)</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>2 WFO recommendations and MDT suggestions compliance rate</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>3 Evidence-based level of WFO recommendations</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>4 Evidence-based level of references supporting options by WFO</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>5 Patient-specific level</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>6 Drug availability</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Note: : NCNN, the National Comprehensive Cancer Network ; ESMO, European Society for Medical Oncology; CSCO, Chinese Society of Clinical Oncology.

Qualifying sites for oncology clinical trials. First Author: Dax Kurbegov, Sarah Cannon Research Institute, Nashville, TN

Background: Current methods to assess trial sites for clinical trial participation are onerous, with unnecessary redundancies and “no-value” steps that impact clinical trial participation. This project assessed the impact of current sponsor and contract research organizations (CRO) methods to evaluate sites for trials. Methods: A survey was conducted with community- and academic-based trial sites. Samples of feasibility questionnaires (FQs) used by sponsors and CROs to confirm site feasibility for clinical trials posed tremendous burden on site resources. Results: 113 oncology practices (63 community, 50 academic) reported completing 11 FQs and 4 pre-study visit sites (PSV) on average per month. On average, each FQ took 4 hours (528 hours/site and 59,664 hours for all respondents, annually) and each PSV took 10 hours (480 hours/site and 54,240 hours for all respondents, annually) to complete. Thus, the total staff hours required to complete site feasibility assessments was 113,904 annually. Respondents reported that content in both FQs (82%) and PSVs (91%) was redundant and unnecessary and 36% (42 sample FQs) reported insufficient study documentation to accurately complete FQs. It took 7 months on average from first contact to first patient enrolled. The current methods of assessing site feasibility for clinical trials poses tremendous burden on site resources and is not sustainable. New methods are needed that standardize, harmonize, and streamline criteria and site assessments. Such changes will reduce burden and costs for all stakeholders, and will expedite and increase patient enrollment onto clinical trials.

Combination of statin/vitamin D and metastatic castration-resistant prostate cancer (mCRPC): A post-hoc analysis of two randomized clinical trials. First Author: Guillermo de Veijer, Department of Medical Oncology, University Hospital 12 de Octubre, i+12, Madrid, Spain, Madrid, Spain

Background: Retrospective database studies have suggested that statins and vitamin D have a positive impact on prostate cancer survival and specifically in mCRPC patients (pt). Methods: We conducted a post-hoc analysis of individual pt data of mCRPC pts treated with abiraterone (AA) and/or Prednisone (P) on two randomized phase III clinical trials COU- AA-301 and COU-AA-302 to analyze the impact of statins and vitamin D in overall survival (OS). Statistical analyses were performed using the Kaplan Meier method and Independent predictors were investigated using Cox regression analysis. This study, carried out under YODA Project #2016-1136, used data obtained from the Yale University Open Data Access Project. Results: These two studies included 2280 patients (1340 treated with AAP and 640 with P). Use of Statin + vitamin D was associated with a 38% reduction in mortality in the postdocetaxel setting and 52% in the predocetaxel setting in patients treated with abiraterone (Table 1 and 2). No significant reduction in the rate of skeletal-related events was seen in patients treated with vitamin D or statins. Conclusions: To our knowledge this is the first report suggesting the impact of vitamin D-statin in mCRPC treated with abiraterone. The potential benefits of vitamin D do not seem to be secondary to concomitant statin use in this population. Further studies are needed to confirm these results.

Impact of vitamin D and statin in overall survival.

<table>
<thead>
<tr>
<th>Medication use</th>
<th>n</th>
<th>Median OS</th>
<th>HR for OS (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COU302 Predictions (control, no statin, no vit D)</td>
<td>228</td>
<td>29.2 (26.0, 31.6)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Abiraterone (no statin, no vit D)</td>
<td>215</td>
<td>25.7 (23.8, 27.7)</td>
<td>0.76 (0.61, 0.96)</td>
<td>0.0191</td>
</tr>
<tr>
<td>Abiraterone+statin+vitD</td>
<td>95</td>
<td>35.0 (30.6, 42.8)</td>
<td>0.68 (0.51, 0.92)</td>
<td>0.0108</td>
</tr>
<tr>
<td>COU301 Predictions (control, no statin, no vit D)</td>
<td>254</td>
<td>10.8 (9.6, 13.3)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Abiraterone (no statin, no vit D)</td>
<td>47</td>
<td>14.7 (13.9, 15.6)</td>
<td>0.91 (0.77, 1.07)</td>
<td>0.2958</td>
</tr>
<tr>
<td>Abiraterone+statin+vitD</td>
<td>45</td>
<td>21.7 (20.0, 25.5)</td>
<td>0.62 (0.44, 0.77)</td>
<td>0.0075</td>
</tr>
</tbody>
</table>

Multivariate analysis of overall survival.

<table>
<thead>
<tr>
<th>HR for OS (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>0.68 (0.43, 0.93)</td>
</tr>
<tr>
<td>Abiraterone (no statin, no vit D)</td>
<td>0.89 (0.75, 1.00)</td>
</tr>
<tr>
<td>Abiraterone+statin+vitD</td>
<td>0.68 (0.50, 0.91)</td>
</tr>
<tr>
<td>Abiraterone+statin+vitD</td>
<td>0.54 (0.38, 0.76)</td>
</tr>
</tbody>
</table>

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**6620**  
**Poster Session (Board #311)**, Sat, 1:15 PM-4:15 PM  
**Impact of Oncology Care Model (OCM) reporting requirements on quality of care.**  
*First Author: Emily Castellanos, Flatiron Health, New York, NY*  
**Background:** The OCM is a voluntary Center for Medicare and Medicaid Innovation alternative payment model pilot program. As of Oct 2017, OCM practices are required to report the biomarker status for NSCLC pts. Our objective was to assess the effect of OCM reporting on quality of care in aNSCLC.  
**Methods:** We developed a decision-analytic model to compare the likelihood of receiving biomarker testing and corresponding appropriate therapy. We populated the model using real-world data from pts (n=7,075) at OCM sites (n=45) and non-OCM sites (n=105) in the Flatiron Health database from 2015-2016.  
**End Points:** Biomarker testing rate, positive result, and negative result.  
**Results:** Among OCM and non-OCM practices prior to the reporting requirement. In the post-period, OCM was associated with higher odds of biomarker testing and appropriate therapy.  
**Conclusions:** To our knowledge, this is the first study of the association of OCM reporting requirements with downstream quality of care. Our results suggest that OCM documentation and reporting requirements are associated with modestly higher quality of care for pts with aNSCLC.  

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Non-OCM (%)</th>
<th>OCM (%)</th>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarker testing rate</td>
<td>81.3</td>
<td>85.2</td>
<td>1.32</td>
<td>0.036</td>
</tr>
<tr>
<td>Positive result</td>
<td>18.1</td>
<td>20.6</td>
<td>1</td>
<td>0.74</td>
</tr>
<tr>
<td>Negative result</td>
<td>78.5</td>
<td>76.8</td>
<td>1</td>
<td>0.74</td>
</tr>
<tr>
<td>Overall Total: testing and appropriate therapy delivered</td>
<td>72.1</td>
<td>76.4</td>
<td>1.25</td>
<td>0.042</td>
</tr>
<tr>
<td>Appropriate first-line therapy (TKI) among biomarker positive</td>
<td>63.6</td>
<td>68.5</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>Appropriate first-line therapy (non-TKI) among biomarker negative</td>
<td>98.3</td>
<td>98.3</td>
<td>1</td>
<td>0.42</td>
</tr>
</tbody>
</table>

**6621**  
**Poster Session (Board #312)**, Sat, 1:15 PM-4:15 PM  
**Decreasing postoperative opioid prescriptions in ambulatory extended recovery patients.**  
*First Author: Nkechi Fearon, Memorial Sloan Kettering Cancer Center, New York, NY*  
**Background:** Over-prescription of opioids after surgery contributes to the opioid abuse epidemic. Optimum post-operative opioid dosing is not defined. We evaluated prescribing patterns among different surgical services and created a standardized practice to reduce dispensation of unnecessary opioids.  
**Methods:** Opioid-naive patients over 18 who underwent urologic, gynecologic, or breast surgery between March 2018 and January 2019 were eligible. A 4-month pre-intervention evaluation of number of opioid pills prescribed, number of pills taken, additional refills, and pain-control was obtained by contacting patients 7-10 days post-operatively. Findings were used to standardize prescriptions. Following implementation, patients undergoing surgery for the following 4-months were contacted to assess the impact of standardized opioid prescriptions. Data was compared with the institution’s electronic prescription system.  
**Results:** Pre-intervention, 368 eligible urology and gynecology patients (75.6%) responded and were prescribed between 6 and 40 opioid pills. Urology patients received median 28 (20, 30) tablets and 33% reported taking none. Gynecology patients received median 20 (19, 28) tablets and 41% took none. Of 238 mastectomy patients, 176 (74%) reported taking median 3 and 4.9 of 20 prescribed opioid pills and 39% or 61% took no opioid pills (without vs with reconstruction). Prescriptions were standardized to 8, 7, and 10 tablets for urology, gynecology, and breast services. Post-intervention surveys revealed opioid tablets taken to be unchanged with minimal increase in refill requests.  
**Conclusions:** Prior to standardization, a large variation in opioids prescribed was observed. Standardizing opioid prescriptions resulted in fewer opioids dispensed without impacting pain control or refill requests.

**6622**  
**Poster Session (Board #313)**, Sat, 1:15 PM-4:15 PM  
**Virtual visits for children, adolescents, and young adults with cancer.**  
*First Author: Peter Meade Anderson, Cleveland Clinic, Cleveland, OH*  
**Background:** Children, adolescents, and young adults have rare cancers and standard-of-care treatment is commonly very aggressive. Virtual visits provide include many of the nuances of face-to-face communication. These are much friendlier than phone calls or email and can be scheduled and structured to provide a large amount of information efficiently.  
**Methods:** Cleveland Clinic uses HIPPA-compliant software from American Well (Boston, MA) that allows the health care provider and patient to use a phone, tablet, or desktop computer for video visits. Our intake process involves obtaining a Medical Record Number (MRN), sending a brief summary, uploading or sending a CD with images in DICOM, and having an administrative assistant schedule the virtual visit. Telemedicine sessions typically last ~60 minutes. During the visit a summary is updated, images are reviewed, and this and other information shared via email after the visit.  
**Results:** In 2017+ 2018 we conducted 223 virtual visits; 85% were <30 years old (table). The summary has been a key to efficient and effective organization and includes not only contact information and past medical history, but also an “Opportunities to Improve Health” section (problem list /action plan). Topics discussed in solid tumor patients include: 1) local control, 2) medical therapy (chemotherapy), 3) imaging and tumor markers, 4) control of side effects and nutrition, 5) social issues and goals of care (which can include palliative care and hospice), and 6) follow-up. A power point with key images and the updated summary and articles are emailed at the end of the visit to the patient & caregivers and often referring physician, NP, or PA. Visit diagnoses have included osteosarcoma, rhabdomyosarcoma, DSRCT, paraganglioma, and adrenal cortical carcinoma. Survivorship and cGVHD have also been discussed.  
**Conclusions:** Telephonic nurse care management is now possible for all regions of North America. A management program. Patients were identified based on having been prescribed or initiating treatment with a high toxicity chemotherapy agent within the previous 60 days, following which notification was received from an oncology pathways intermediary. Nurse care managers engaged patients one or more times per month based on patient need, educating on side effects, pain management, where to seek care, and general well-being. IP and ER were measured during the 14 days following chemotherapy administration (Risk-Period) and compared to a baseline of all remaining patient claims history, excluding 28 days following chemotherapy administration (14 day Risk Period and 14 day washout period).  
**Results:** IP rates per 1,000 Risk Period Days for managed patients decreased during the 14 days following chemotherapy by 4.4% as compared to their baseline (3.02 v 3.59, p<0.001), while non-managed patients increased by 29% (2.33 v 1.81, p=0.003). ER rates per 1,000 Risk Period Days were not significantly different for managed patients (2.72 v 2.35, p=0.188) and significantly increased by 117% for non-managed patients (2.34 v 0.8, p<0.001). Baseline utilization for managed patients was more than twice the rate of non-managed patients, suggesting that a greater need for support may influence voluntary participation in care management.  
**Conclusions:** Telephonic nurse care management meaningfully reduced IP and ER admissions and their associated costs.

<table>
<thead>
<tr>
<th>Managed Patients</th>
<th>Non-Managed Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>802</td>
</tr>
<tr>
<td>Average Days at Risk per Member</td>
<td>71.4</td>
</tr>
<tr>
<td>Number of IP Admits (B; RP)</td>
<td>363; 173</td>
</tr>
<tr>
<td>Number of ER Admits (B; RP)</td>
<td>158; 156</td>
</tr>
<tr>
<td>Average Cost per IP Admit (B; RP)</td>
<td>$44,006; $38,606</td>
</tr>
<tr>
<td>Average Cost per ER Admit (B; RP)</td>
<td>$1,292; $1,173</td>
</tr>
<tr>
<td>IP Rate Change</td>
<td>(44%), p&lt;0.001</td>
</tr>
<tr>
<td>ER Rate Change</td>
<td>16%; p=0.188</td>
</tr>
</tbody>
</table>

*B=Baseline; RP=Risk Period*
6624 Poster Session (Board #315), Sat, 1:15 PM-4:15 PM
Evaluating the American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) value frameworks for Food and Drug Administration (FDA) approved checkpoint inhibitors (CIs). First Author: Sophie Feng, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Although the development of CIs has led to a dramatic change in the oncology landscape, these agents are associated with significant costs and toxicity. ASCO and ESMO have developed separate frameworks to define the value of emerging cancer treatments in order to encourage cost-effective therapies. We apply these frameworks to trials supporting FDA approvals of CIs and explore the correlation between these two scoring systems.

Methods: We searched the FDA database for CIs and indications approved between January 1, 2011 and January 1, 2019. Only randomized phase II/III trials for solid tumors were included. Data on survival, toxicity and quality of life were extracted from the most recent publications by two reviewers independently. A trial showing a substantial benefit was defined as an ASCO score of ≥ 45, or ESMO Grade 4-5 (palliative setting) or Grade A/B (curative setting). Concordance for substantial benefit was assessed using Cohen kappa while Spearman coefficients were used to determine the degree of correlation in individual scores. Results: We identified 40 FDA indications for 7 CIs; of these, 18 indications based on Phase III single-arm trials were excluded. The remaining 22 indications were based on 21 randomized phase II/III trials (3 adjuvant, 18 metastatic). In the palliative setting, 73% and 86% trials showed substantial benefit based on ASCO and ESMO frameworks respectively (median ASCO score: 54.8, interquartile range (IQR) 46.2-64.0; median ESMO score 5; IQR: 4-5: 27% trials were scored ≥75% with low benefit by ASCO, while 9% were ineligible for ESMO scoring. Weighted kappa was 0.719 between the two frameworks. Spearman rho was 0.84. All 3 adjuvant trials were assigned ESMO grade A but low benefit with ASCO (median 37.7, IQR 20.5-40.9). Conclusions: The ESMO-SOE framework is more inclusive of the potential benefit of CIs in the palliative setting. The ASCO framework may be more stringent for CIs in the adjuvant setting.

6625 Poster Session (Board #316), Sat, 1:15 PM-4:15 PM
Is neratinib following trastuzumab in early-stage HER2-positive breast cancer cost-effective? First Author: Naomi RM Schwartz, University of Washington, Seattle, WA

Background: Neratinib after adjuvant trastuzumab significantly improves disease-free survival (DFS) in human epidermal growth factor receptor 2-positive (HER2+) breast cancer, but the median absolute DFS gain is only 1.3 months. There has been much controversy in the clinical and lay media as to whether the substantial cost of neratinib is justified by its effects, including a prominent ASCO Post article from Dr. Vogl about a year ago. We performed a cost-utility analysis to re-evaluate the value of adding neratinib based on Phase III ExeNet trial results. Methods: We developed a Markov state-transition model to assess the value of neratinib in Stage I-II HER2+ breast cancer. Five-year recurrence rates were derived from ExeNet. Mortality and recurrence rates after 5 years were derived from the HER2+ present Adjuvant (HERA) trial. Costs were derived from wholesale acquisition costs and peer-reviewed literature. Health state utilities were derived from ExeNet and prior publications. Outcomes included life years (LY), quality-adjusted life years (QALYs), direct medical expenditures, and cost per QALY gained. The analysis took a payer perspective over a lifetime horizon and results were discounted at 3% per year. One-way and probabilistic analyses were conducted to evaluate uncertainty. As neratinib conferred more clinical benefit in hormone receptor-positive (HR+) disease, we also assessed value in that specific subgroup.

Results: Base case results are presented in Table. At typical U.S. willingness to pay thresholds of $100,000 and $150,000 per QALY gained, neratinib had 16.6% and 27.2%, probability of cost-effectiveness respectively. In the HER2+ subgroup, neratinib had a cost of $275,311 per QALY gained (19.9% & 31.2% probability of cost-effectiveness at $100,000 & $150,000 per QALY). Conclusions: In the first independent assessment of the value of neratinib after adjuvant trastuzumab, neratinib is not projected to be cost-effective, even among patients who derived the most clinical benefit. Future analyses should reassess the cost-effectiveness of neratinib treatment as trial data mature. Base case results.

6626 Poster Session (Board #317), Sat, 1:15 PM-4:15 PM
Relationship of emergency department use pre- and post-cancer diagnosis in safety-net adults. First Author: Arthur Hong, University of Texas Southwestern Medical Center, Dallas, TX

Background: Safety-net adults generate a high rate of emergency department (ED) visits within the 180 days after a new cancer diagnosis, many of which could be alternatively triaged to an urgent care clinic. It is unclear how much of this ED use is attributable to the cancer and treatment vs. ED-seeking behavior. To identify patients at risk of frequent ED use, we explored whether a patient’s prior ED use and demographic factors were associated with the pan-Canadian oncology drug review (pCODR) funding decisions and European Society for Medical Oncology Magnitude of Clinical Safety (ESMO) score. Using a structured and explicit approach, a criterion-based Drug Assessment Framework (DAF) was developed with a framework and scoring system in order to evaluate new cancer treatments.

Methods: We recruited a diverse multi-stakeholder group who identified and weighted key criteria to establish the DAF framework. The final validated DAF included ten criteria: efficacy, cost-effectiveness, unmet need, equity, feasibility, disease severity and caregiver well-being. The final five clinical benefit criteria represent 64% of the total weight. DAF scores range from 0 to 300, reflecting both the expected impact of the drug and the stakeholders’ face and content validity of the DAF were established in an iterative process. Construct validity assessed the degree to which DAF scores were associated with the pan-Canadian oncology drug review (pCODR) funding decisions and European Society for Medical Oncology Magnitude of Clinical Safety score (ESMO-MCBS, version 1.1). Sensitivity analyses were performed on the final results. Results: The final validated DAF includes ten criteria: overall survival, progression-free survival, response rate, quality-of-life, toxicity, unmet need, equity, feasibility, disease severity and caregiver well-being. The first five clinical benefit criteria represent 46% of the total weight. DAF scores range from 0 to 300, reflecting both the expected impact of the drug and the quality of the supporting evidence. When the DAF was retrospectively applied to the last 60 drugs (in blinded fashion) reviewed by pCODR (2015-2018), the mean total DAF score was 94 (range, 18-179). Drugs with positive pCODR funding recommendation had higher DAF scores than drugs not recommended for reimbursement (103 vs. 63, t-test p = 0.0007). Funded drugs had fewer SOE points deducted than those that were not funded (median 0 vs. 24 points deducted, Wilcoxon p = 0.03). The correlation coefficient for DAF and ESMO-MCBS was 0.37 (95% CI, 0.10 to 0.59). Sensitivity analyses that varied the subjective criteria either positively or negatively did not change the results.

Conclusions: Using a structured and explicit approach, a criterion-based valuation framework was designed and validated. The DAF can provide a transparent and consistent method to value and prioritize cancer drugs, in order to facilitate the delivery of affordable cancer care.

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6628 Poster Session (Board #319), Sat, 1:15 PM-4:15 PM
Followup mammography after breast conservation therapy: Is 3D Tomosynthesis(3DT) worth it? First Author: Shaakir Hasan, Department of Radiation Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA.

Background: Screening three-dimensional tomosynthesis mammography (3DT) is more cost-effective than two-dimensional mammography (2DM) for detecting breast cancer, however cost-effectiveness as a follow-up for treated breast cancer is unknown. We retrospectively analyzed the downstream workflow and costs associated with 3DT compared to 2DM when employed as initial follow-up imaging in breast conservation therapy (BCT).

Methods: Between the years 2015-2017, 741 patients ages 32–89 with a follow-up 3DT (n = 162) or 2DM (n = 288) were reviewed in this IRB-approved study. The primary endpoint was further workup after follow-up mammogram and associated healthcare costs at 1 year. Downstream workup was secondarily tested for correlation with clinical and treatment-related variables. A single 3DT cost an estimated $149 compared to $111 for a 2DM, based on Centers for Medicare claims data Oncology Care Model.

Results: Patient clinical characteristics were: 6% DCIS, 10% T1a, 29% T1b, 35% T1c, 19% T2, 88% N0, 9% N1, 3% N2, 76% ER/PR+ /Her2Neu2+, 12% TNBC, and 14% Her2Neu+. Whole breast radiation was given in 89% (95% confidence interval 99% and 80%), 10% received axillary dissection (81% with a boost), and 10% received accelerated partial breast irradiation. First post-treatment mammogram was performed within 3 months (20%), 3-6 months (32%), and after 6 months (48%) following RT. There were no differences in breast density, patient age, TN stage, receptor status, type of RT, or mammogram timing between those in the 3DM and 2DM groups. The following downstream workup ensued for 3DT compared to 2DM imaging: 18% vs 29% short-interval (6-month) mammogram (OR = 1.83, P = 0.01), 6% vs 11% breast MRI (OR = 1.90, P = 0.08), 4% ultrasound for each, and 3% biopsy for each (1 positive in the 2D group). Including downstream workup, the estimated cost of each patient in the 3DT group was $253.64 in the 2DM group.

Conclusions: Excess workup was reduced with 3DM compared to 2DM in the post-treatment setting. A single 3DM cost approximately 34% more than 2DM, however in this study the associated reduction in downstream workup with 3DT actually made it more cost-effective.

6630 Poster Session (Board #321), Sat, 1:15 PM-4:15 PM

Background: Sentinel lymph node biopsy (SLNB) is recommended as a staging procedure for patients with cutaneous melanoma (CM), but SLNB is associated with additional surgical risks and costs. The SLN positivity rate is approximately 12-16% overall and varies by age. Older patients have lower SLN positivity rates despite a higher metastatic rate. A 31-gene expression profile test (31-GEP) was developed to improve the rate of false-negative results in the SLNB of patients with cutaneous melanoma. The 31-GEP test has been shown to reduce the rate of negative SLNBs from 20% to <5% by eliminating unnecessary SLNBs in low-risk patients [1]. Methods: We conducted a cost-utility analysis for stage IV NSCLC. Variables of interest were extracted from registry data linked by the Institute for Clinical Evaluative Sciences (ICES). The mean total cost of care including systemic therapy and supportive care, was calculated in 2015 CAD dollars by fiscal year of diagnosis. Results: Of all NSCLC cases diagnosed in Ontario (n = 37,786), 17,203 (45.5%) were de novo stage IV, of which 29.7% of patients received any chemotherapy for their disease (n = 5,113), and 281 patients are presumed alive. In this population, median age was 65 to 69 years, 51.9% were male, 43.5% were adeno carcinomas, and 25.1% received second line chemotherapy. After adjusting for comorbidities, income, gender, year of diagnosis, and rural versus urban living, the average lifetime costs per patient remains significantly inversely related to age (p < 0.001). Belonging to the highest income quintile (p = 0.006) and being diagnosed in more recent years (p < 0.001) contributes significantly to increasing overall healthcare costs. Elderly patients (80+) cost less (71%) and have shorter survival time (HR of death 1.28, 95% C.I. 1.10 to 1.49 compared to you in your 60s). Accounting for longer survivorship in younger patients, the youngest group still incur a higher cost per day alive than other age groups ($471/day in ≤ 45 group, $301/day in > 85 group). Hospitalization accounts for ~30% of total cost in both age groups. Chemotherapy accounts for 1% of total health care costs, particularly amongst the elderly (81% of group 1 and 79% of group 45).

Conclusions: Our study shows that, despite everyone receiving systemic therapy in this patient population, younger patients incur significantly higher costs than elderly patients with advanced NSCLC, both before and after adjusting for survival. While hospitalization accounts for the biggest component of total costs, patients with high income and more recent years of diagnosis drive the higher costs of care, and chemotherapy remains a driver of higher costs amongst younger patients.

6631 Poster Session (Board #322), Sat, 1:15 PM-4:15 PM

Background: Rising pharmaceutical costs threaten affordability and access to cancer care. Methods: We conducted a retrospective cohort study of patients diagnosed with non-small cell lung cancer (NSCLC) in Ontario, Canada. First Author: Ying Wang, Department of Medical Oncology, Sunnybrook Cancer Hospital, Toronto, ON, Canada.

Results from this study demonstrated a reduction in costs. In addition to T1-T2 melanoma, in patients ages 65 years with T1-T2 CM who are Medicare-eligible, in 2013 $7,521.64 to $11,734.68, and seven drugs more than doubled in per patient cost. Cost per patient increased by 4.5 times for imbruvica (ibrutinib), 3.5 times for targetin (bexantene), 3.2 times for solotam (tamofoxen citrate), 3.1 times for nilandron (nilutamide), 2.6 times for gilotrif (afatinib dimaleate), 2.5 times for cyclophosphamide, and 2.5 times for ivermectin (onabotulinum hydrochloide). Conclusions: Rising pharmaceutical costs threaten affordability and access to cancer care.

6632 Poster Session (Board #330), Sat, 1:15 PM-4:15 PM
Cost disparities with age in the treatment of advanced non-small cell lung cancer (NSCLC) in Ontario, Canada. First Author: Ying Wang, Department of Medical Oncology, Sunnybrook Cancer Hospital, Toronto, ON, Canada.

Background: Previous studies noted an association between age and cost of care in NSCLC. The drivers of these cost disparities have not yet been fully examined. We conducted a cost analysis study examining the differences in, and drivers of, costs of NSCLC care across age groups in Ontario, Canada.

Methods: We conducted a retrospective cohort study of patients diagnosed in Ontario from Apr 1, 2007 to Mar 30, 2014, who received palliative chemotherapy for stage IV NSCLC. Variables of interest were extracted from registry data linked by the Institute for Clinical Evaluative Sciences (ICES). The mean total cost of care including systemic therapy and supportive care, was calculated in 2015 CAD dollars by fiscal year of diagnosis. Results: Of all NSCLC cases diagnosed in Ontario (n = 37,786), 17,203 (45.5%) were de novo stage IV, of which 29.7% of patients received any chemotherapy for their disease (n = 5,113), and 281 patients are presumed alive. In this population, median age was 65 to 69 years, 51.9% were male, 43.5% were adeno carcinomas, and 25.1% received second line chemotherapy. After adjusting for comorbidities, income, gender, year of diagnosis, and rural versus urban living, the average lifetime costs per patient remains significantly inversely related to age (p < 0.001). Belonging to the highest income quintile (p = 0.006) and being diagnosed in more recent years (p < 0.001) contributes significantly to increasing overall healthcare costs. Elderly patients (80+) cost less (71%) and have shorter survival time (HR of death 1.28, 95% C.I. 1.10 to 1.49 compared to you in your 60s). Accounting for longer survivorship in younger patients, the youngest group still incur a higher cost per day alive than other age groups ($471/day in ≤ 45 group, $301/day in > 85 group). Hospitalization accounts for ~30% of total cost in both age groups. Chemotherapy accounts for 1% of total health care costs, particularly amongst the elderly (81% of group 1 and 79% of group 45).

Conclusions: Our study shows that, despite everyone receiving systemic therapy in this patient population, younger patients incur significantly higher costs than elderly patients with advanced NSCLC, both before and after adjusting for survival. While hospitalization accounts for the biggest component of total costs, patients with high income and more recent years of diagnosis drive the higher costs of care, and chemotherapy remains a driver of higher costs amongst younger patients.

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Sustaining the gains in cancer care from the oncology care model. First Author: Valene P Cusk, Sidney Kimmel Cancer Center, Philadelphia, PA

Background: The Oncology Care Model (OCM) is a 5-year demonstration project led by the Centers for Medicare and Medicaid Services (CMS) to create a framework for the future of oncology care in the United States. OCM is designed to standardize care pathways and reduce unnecessary variations in care. The project was introduced to the field in 2012 and has since served as a valuable tool for cancer centers to improve patient outcomes and reduce costs. However, it is important to note that the success of the OCM is contingent upon the alignment of financial incentives with clinical outcomes, and the implementation of evidence-based guidelines. Without proper alignment, there is a risk of escalating costs and compromising patient care.

Methods: This study aimed to evaluate the impact of the OCM on patient outcomes and costs. The research team employed a retrospective cohort design to compare the outcomes of patients treated before and after the implementation of the OCM. Patient data was collected from electronic medical records at 70 participating cancer centers across the United States. The primary outcome measure was the reduction in hospital readmissions within 30 days of discharge.

Results: The study found that the implementation of the OCM was associated with a significant reduction in hospital readmissions within 30 days of discharge. Specifically, the readmission rate decreased by 20% in the OCM group compared to the pre-OCM group. Additionally, the mean cost per patient was lower in the OCM group, with a savings of $2,500 per patient. These findings suggest that the OCM is an effective tool for reducing costs and improving patient outcomes.

Conclusions: The results of this study highlight the potential benefits of the OCM in improving patient care and reducing costs. Further research is needed to explore the sustainability of these findings and to identify strategies for widespread implementation of the OCM across the oncology community.
6636
Poster Session (Board #327), Sat, 1:15 PM-4:15 PM
Clinical and economic outcomes of pegfilgrastim in metastatic colorectal cancer. First Author: Lelan S. Wilfong, Texas Oncology, Dallas, TX
Background: Febrile neutropenia (FN) resulting from myelosuppressive chemotherapeutic treatment in patients with metastatic solid tumors is often associated with increased hospitalizations and mortality. Reduction in FN-related hospitalization rates, a validated surrogate of clinical benefit, is associated with pegfilgrastim (Peg) use. The present study evaluated the economic impact of Peg use on hospitalization rates in patients with metastatic colorectal cancer (MCC) treated with fluoropyrimidines (FU) and oxaliplatin (Ox) in the United States (US) and ESMO-MCBS (MBCS) scores.
Methods: Outcomes of 37,070 metastatic colorectal cancer patients from the US and 4,684 patients from the EU (January 1, 2013 - December 31, 2014) were analyzed. The primary endpoint was median hospitalization rates during the study period. Propensity score analysis was used to adjust for differences between US and European patients. Infection-related hospitalization rates were compared between Peg-treated and Peg-unintertreated patients using a linear regression model and non-parametric Kruskal-Wallis test. As infection-related hospitalization rates were different in Peg-treated vs. Peg-not-treated cohorts, a more conservative analysis approach was also evaluated by defining a composite score of 6-month CMS (Palliative Setting) and scores 4-5 (Palliative Setting) on the ESMO-MCBS scale. Differences in the infection-related hospitalization rates were tested using a 2-sample t-test.
Results: Of 37,070 patients treated in the US, 8,238 received Peg. U.S. hospitalization rates were 52% (IQR: 37–67%) in Peg-treated patients vs. 64% (IQR: 51-72%) in Peg-not-treated patients, P < 0.001 (Table). Infection-related hospitalization rates were similar in both groups (9.4% vs. 8.8%, P = 0.23). In the European cohort, infection-related hospitalization rates were 23% (IQR: 18–28%) in Peg-treated patients vs. 22% (IQR: 19–26%) in Peg-not-treated patients, P = 0.12. Conclusion: Pegfilgrastim use is associated with lower hospitalization rates in patients with metastatic colorectal cancer treated with FU and Ox in the US and EU. This difference was not statistically significant in the European cohort.

6637
Poster Session (Board #328), Sat, 1:15 PM-4:15 PM
Burden of cytokine release syndrome (CRS) and neurologic events (NE) in patients (Pts) with relapsed/refractory non-Hodgkin lymphoma (NHL) receiving lisocabtagene maraleucel (Liso-cel; JCAR017) in TRANSCEND NHL 001. First Author: Jeremy S. Abramson, Massachusetts General Hospital Cancer Center, Boston, MA
Background: We assessed incidence, healthcare resource utilization (HCRU), and costs of CRS and NE in pts in TRANSCEND receiving liso-cel, an investigational, anti-CD19 CAR T cell agent. Routine adverse events (AE) were not defined within the Treatment Administration Module (TAM) of the study. Methods: HCRU within the dates of onset of resolution of CRS and NE was identified from case report forms and trial management guidelines. Costs associated with grade (G) of CRS or NE were applied using published databases and literature on national average costs from a provider perspective. Results: Of 102 pts, 21 (21%) had CRs only (G0), 16 (16%) had NE only (G4), 6 (6%) had concurrent CRS and NE, and 11 (11%) had concurrent CRS and NE. Most pts had G2 events (31/44, 70%). Of pts with both CRS and NE, 16/17 (94%) had concurrent CRS only (G2), and 1/17 (6%) had concurrent NE only (G2). Median costs vs G were $20,490 vs $37,811 ± 19,593 respectively, P (< .001). OS was 19.5 months (peg-bx) vs. 19.7 months (no peg), P = 0.882. Conclusions: While peg use in curative treatment settings for high-risk patients is standard of care, in our Medicare population use in metastatic CRC did not result in a lower all-cause or infection-related hospitalization rate or impact in OS. There was a higher 6-month total cost of care associated with those patients who received peg during chemotherapy.

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Cost-minimization analysis of using tumor cell-free DNA as monitoring tool in cancer immunotherapy.

**Background:** Albeit showing great benefit in individual cancer patients, only the minority of patients benefit from checkpoint inhibitor immunotherapies (IMTs). Mutation load and PD-L1 staining are used for response prediction, but are imperfect predictors. A universal method to quantify tumor cell-free DNA (TcfdNA) enables the early and effective evaluation of individual IMT efficacy,[1] by comparing TcfdNA to pre-therapeutic values. Here we present a health economic evaluation of test usage. **Methods:** This cost-minimization study determines the economic efficiency of TcfdNA-test from the perspective of the statutory health insurance in Germany. The assumption is that the effectiveness of the intervention (TcfdNA monitoring) and of the comparator (no test), is comparable with regards to the patient-relevant-endpoints (morbidity, mortality, quality of life). The model simulates the course of treatment for each patient with and without TcfdNA testing, calculating the respective cost.

**Results:** Both testing strategies correctly classified 68% of progressive disease patients. TcfdNA enables the early and effective evaluation of individual IMT efficacy,[1] by comparing TcfdNA to pre-therapeutic values. Here we present a health economic evaluation of test usage. **Methods:** This cost-minimization study determines the economic efficiency of TcfdNA-test from the perspective of the statutory health insurance in Germany. The assumption is that the effectiveness of the intervention (TcfdNA monitoring) and of the comparator (no test), is comparable with regards to the patient-relevant-endpoints (morbidity, mortality, quality of life). The model simulates the course of treatment for each patient with and without TcfdNA testing, calculating the respective cost. Treatment details, outcome (RECIST) and TcfdNA results are derived from an earlier clinical trial.[1] Costs are obtained from publicly accessible data bases. Two testing strategies are explored. Strategy 1: Testing all patients only before the second cycle. Strategy 2: Same as strategy 1 plus a confirmation test before the third cycle, in patients with initial result in a defined grey zone. **Results:** Both testing strategies correctly classified 68% of progressive disease patients. TcfdNA enables the early and effective evaluation of individual IMT efficacy,[1] by comparing TcfdNA to pre-therapeutic values. Here we present a health economic evaluation of test usage. **Methods:** This cost-minimization study determines the economic efficiency of TcfdNA-test from the perspective of the statutory health insurance in Germany. The assumption is that the effectiveness of the intervention (TcfdNA monitoring) and of the comparator (no test), is comparable with regards to the patient-relevant-endpoints (morbidity, mortality, quality of life). The model simulates the course of treatment for each patient with and without TcfdNA testing, calculating the respective cost. 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**Conclusion:** TcfdNA monitoring is a cost-saving strategy. However, a confirmatory strategy is necessary to avoid early discontinuation of successful IMT. [1] Weiss GJ et al.: Clin Cancer Res: 2017;5074-81.
Cost-effectiveness of CHOP in treating DLBCL in Malawi. First Author: Matthew Painsins, Lineberger Comprehensive Cancer Center; University of North Carolina, Chapel Hill, NC

Background: DLBCL is common in Africa, and often curable, but treatment costs and cost-effectiveness are key considerations. Who defines extremely cost-effective interventions as having an incremental cost-effectiveness ratio (ICER) < $50,000 per QALY? Methods: We used a decision tree model to conduct a cost-effectiveness and budget impact analysis from a health systems perspective in Malawi (2017 GDP per capita $340). Comparisons were made between CHOP vs. palliative care with diagnosis (PC-D), and palliative care without diagnosis (PC-D). Microcosting and clinical outcomes were derived from published prospective data. Costs reflect treatment and 2 years of follow-up. Outcomes reflect a lifetime time horizon. Life expectancies were derived from UNdata, and disability-adjusted life year (DALY) weights from the Global Burden of Disease Study. Costs were analyzed in 2017 US $, and costs and outcomes were discounted at 3% annually. Annual estimates for new DLBCL cases (n=161) were used as input incidence. Probabilistic sensitivity analysis was conducted using Crystal Ball software over 1000 simulations. Results: For the base case, the ICER of CHOP versus PC-D is $150,000/DALY averted, and versus PC-D is $200,000/DALY averted (Table). The ICER was stable across a wide range of sensitivity analyses. The ICER varied most across the range of progression-free survival estimates ($117-209), and range of costs for CHOP plus follow-up ($71-308). CHOP was extremely cost-effective by the WHO definition in 99% of simulations versus PC-D, 94% of simulations versus PC-D. In the base case, total annual cost of DLBCL treatment with CHOP in Malawi was $306,221. Conclusions: CHOP is one of the first rigorous cost-effectiveness and budget impact analyses for cancer treatment in a low-income country. CHOP is extremely cost-effective compared to palliative care, with $300,000 needed annually to treat all DLBCL cases in Malawi. These findings merit external validation, and support continued regional investments in cancer care.

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Scope of practice of advanced practice providers (APP) in US community oncology. First Author: Andrew Klink, Cardinal Health, Dublin, OH

Background: Oncology practices are increasingly employing nurse practitioners (NPs) and physician assistants (PAs) known collectively as advanced practice providers (APPs) to improve practice workflow, increase efficiency, and enable physicians to focus on complex patient care. Understanding variations in scope of practice for APPs may help establish a benchmark against which future changes are measured. Methods: US community physicians responded to a web-based survey from Sep to Nov 2018. Physicians were asked how frequently their APPs performed certain tasks on a 5-point scale (i.e., never, occasionally, sometimes, frequently, and always). Responses have been summarized using descriptive statistics. Results: In this study, 163 physicians were surveyed, most (81.0%, n = 132) used NPs and 49.2% (n = 65) used PAs. Most physicians stated that APPs were frequently/always involved in providing patient education (84.1%), ordering imaging and laboratory studies (68.9%), and/or making supportive care decisions (62.1%). Over 85% (57.6%–98.8% occasionally/sometimes; 28.0%–28.8% frequently/always) of physicians agreed that APPs discussed imaging reports and end of life (EOL) care (57.6% occasionally/sometimes, 28.8% frequently/always) with patients. Regarding procedures: 51.9% (28.0% occasionally/sometimes; 24.1% frequently/always) responded that APPs performed bone marrow biopsies and intrathecal chemotherapy. Regarding systemic therapy: 68.2% (38.3% occasionally/sometimes; 9.8% frequently) allowed APPs to modify existing regimens e.g., dose/schedule change; 39.4% responded that APPs made decisions about new therapy selection. Conclusions: While substantial variation in the role of APPs in community oncology practices was observed, similar themes emerged. APPs appear to be integral in patient education, ordering laboratory and imaging studies, and discussing EOL care. Fewer are involved in managing and selecting supportive care and systemic therapy. Longitudinal and longer follow up are warranted to ascertain whether the scope of these practices change over time.

Cost-minimization analysis for biosimilar pegfilgrastim in the prophylaxis of chemotherapy induced (febrile) neutropenia and expanded access based on budget neutral basis. First Author: Wei Jia Wang, Sandoz Inc., Princeton, NJ

Background: Pegfilgrastim (pegfil) injection is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Assuming biosimilarity of biosim-pegfil and pegfil in the prevention of febrile neutropenia, we estimated cost minimization of conversion from pegfil to biosim-pegfil and subsequent potential expanded access due to cost savings. Methods: A cost minimization model was conducted based on a hypothetical panel of 20,000 patients using average selling price (ASP) for one chemotherapy cycle. ASP was obtained from IQVIA payment allowance limits. The simulation included two steps: 1) cost minimization was calculated per cycle (biosim-pegfil and pegfil is administered 1 dose per cycle) when patients were converted to biosim-pegfil from pegfil on ratio of 10% to 100% at 10% intervals and at a discount from 15% to 5% at 5% intervals, and 2) expanded access to biosim-pegfil was calculated based on budget neutrality. Since pegfil has two forms of availability (Neulasta and Neulasta-Onpro) with the same price, results are reported against Neulasta-Onpro. Per-cycle cost minimization from converting pegfil to biosim-pegfil ranged from $702.27 (15% discount) to $1,638.63 (35% discount). For 20,000 patients, this yields savings of over $4 million (15% discount) to $32 million (35% discount) at 100% conversion rate. When half the patients were converted to biosim-pegfil, savings could range from $7 million (15% discount) to $16 million (35% discount). With 100% conversion rate and 15% discount, 3,529 additional patients could be treated with the savings generated. At 50% conversion rate, cost savings could be applied to another 1,765 patients with 15% discount, 3,333 patients with 25% discount, and 5,385 patients with 35% discount, respectively. Conclusions: Conversion from pegfil to biosim-pegfil can lead to potential cost savings and these savings can be applied to offer increased access to supportive care with biosim-pegfil for patients receiving chemotherapy on a budget-neutral basis. For payers with larger populations, savings can be substantial. More studies are warranted to evaluate such potential cost savings due to use of biosim-pegfil over reference pegfil.
Background: Adjuvant chemotherapy (AC) for stage II colon cancer remains a controversial topic. We used Surveillance Epidemiology End Results (SEER) linkage with Medicare claims to explore the benefits of AC and cost of care in pts with CC-II diagnosed between 2004-2010. Methods: Colon cancer was identified using ICD-O-3 codes. TNM staging was used to classify pts as stage II. Cohort was restricted to pts who had surgery within 4months (mos) of the diagnosis and excluded pts who died within 4mos after the surgery as well as those who were enrolled on a health maintenance organization. We searched claims in the 4mos after surgery to identify pts who received AC using ICD-9 diagnosis and procedure codes, HCPCS, and revenue center codes. Kaplan-Meier method was used for survival analysis. Cost of care from payer’s perspective (Medicare) starting from surgery service to death or 3 years after surgery was captured from claims data. Results: A total of 16948 pts with CC-II diagnosed 2004-2010 were included in this analysis. Among those 14% received AC and 33% of them oxaliplatin. After adjusting for pts and tumor characteristics, probability of survival at 3years was 72.9% for pts who received AC and 74.2% for those who did not. HR = 1.06 (95% CI 1.0, 1.0-1.17), with P-value: 0.229. The cost of care for the AC was significantly higher than the no-AC group (median $254,116 vs. $91,086). The biggest difference in between two groups was cost of outpatient and physician services. Costs for AC group was higher in years 1, 2, and 3 as seen in table. Conclusions: AC for CC-II has a low value in elderly pts and should be avoided.

TPS6650 Poster Session (Board #442b), Sat, 1:15 PM-4:15 PM

TPS6651 Poster Session (Board #441a), Sat, 1:15 PM-4:15 PM

TPS6649 Poster Session (Board #442a), Sat, 1:15 PM-4:15 PM

Digitally captured step counts for evaluating performance status in advanced cancer patients: A single cohort, prospective trial (Digi-STEPS). First Author: Gillian Gresham, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Advanced cancer patients undergo dynamic changes in their functionality and physical activity over the course of their treatment. Monitoring patient function is important because it can inform treatment decisions and allow for timely and appropriate intervention. Current scales that assess patient function, such as the ECOG Performance Status (PS), are limited in their ability to capture the range of cancer-related physical activity that patients can experience on a daily basis outside of the clinic setting. Given recent technological advances in wearable activity monitors, we can collect real-time, objective information about a patient’s daily activity including steps, stairs, heart rate, sleep, and activity intensity. Thus, the primary objective of this study is to determine whether longitudinal changes in objectively-assessed activity are associated with change in physician-rated ECOG PS. Methods: This is a prospective, single cohort trial being conducted at Cedars-Sinai Medical Center. Stage 3/4 cancer patients who are English or Spanish-speaking, ambulatory (assistive walking devices are allowed) and expected to be seen for treatment or follow-up with their oncologist at least every 8 weeks are eligible for study. Consenting patients will be asked to wear a Fitbit Charge HR continuously for 8 weeks during the study period and for one week prior to the 6 month and 1 year follow-up visits. Primary outcomes are change in average daily step counts and ECOG PS at 8 weeks from baseline. Secondary outcomes include: 1) Change in patient-reported outcomes (physical function, pain, sleep, emotional distress, and fatigue), 2) Change in frailty status at 8 weeks, 3) Occurrence of adverse events, and 4) 6-month and 1-year survival outcomes. Baseline assessments include a physical exam, medical history, and frailty assessment. The attending oncologist will rate the patient’s ECOG PS at baseline and at the end-of-study visit. Weekly NIH PROMIS questionnaires will be administered online over the 8-week study and again at 6 months and 1 year follow-up. The occurrence of serious cancer-related adverse events, chemotherapy-associated toxicities, and hospitalizations will be documented up to 12 weeks from baseline. Survival will be assessed at 6 months and 1 year. Recruitment is ongoing with 20 patients currently enrolled. Target sample size of 60 patients. Clinical trial information: NCT03757182.
Design and accrual of S1417CD: Development of a prospective financial impact assessment tool in patients with metastatic colorectal cancer (mCRC). First Author: Veena Shankaran, Fred Hutchinson Cancer Research Center, Seattle, WA

Background: Few studies have assessed the financial impact of cancer diagnosis (dx) in diverse patients (pts) and caregivers (cgs) using objective and standard financial measures. S1417CD, led by the SWOG Cancer Research Network, is the first prospective cohort study assessing financial outcomes to be conducted in the NCI Community Oncology Research Program (NCORP). We present our experience with design and accrual.

Methods: Pts age $\geq 18$ within 120 days of mCRC dx were considered eligible and asked to identify a caregiver (cg) who could participate concurrently. The primary endpoint is incidence of treatment-related financial hardship, defined as $\geq 1$ of the following: debt accrual, selling/refinancing home, $\geq 20\%$ income decline, or borrowing money. Measures include 1) pt and cg surveys (baseline (BL), 3, 6, 9 and 12 months (mo)) assessing out-of-pocket spending, financial impacts, cg burden, and quality of life and 2) pt credit reports (BL, 6, and 12 mo). Linkage to records from TransUnion, a national credit agency, required pt social security number (SSN) and processes for batched credit report transfer via secure web portal. The accrual goal was n = 374 pts in 3 years. The study activated on Apr 1, 2016 and closed on Feb 1, 2019 after reaching its accrual goal. A total of 380 pts (median age 59.7 years) and 155 cgs enrolled (41% cg participation). Enrollment steadily increased during the study period; 56% enrolled in the last 12 mo. Credit data were not obtainable for 76 (20%) pts due to early death, lack of credit, or inability to match records. S1417CD, the first cooperative group led study assessing financial outcomes in the community setting, completed enrollment faster than anticipated. Required SSN collection was not a barrier to enrollment, which improved as sites became familiar with data security measures. Robust accrual to S1417CD demonstrates pts’ and cgs’ desire to improve understanding of financial toxicity and its solutions. Follow-up will conclude in 12 mo with results to follow. SWOG plans to launch a randomized study (S1912) assessing the impact of financial navigation on household finances, using credit data for primary endpoint assessment. Clinical Trials Registry Identifier NCI-2015-01885. Clinical trial information: NCT02728804.
Effect of gilteritinib on survival in patients with FLT3-mutated (FLT3\textsuperscript{mut+}) relapsed/refractory (R/R) AML who have common AML co-mutations or a high FLT3-ITD allele burden.

**Background:** The FLT3 inhibitor, gilteritinib, showed superior response and overall survival (OS) compared with salvage chemotherapy (SC) in patients (pts) with FLT3\textsuperscript{mut+} R/R AML in the phase 3 ADMIRAL study. We analyzed the impact of baseline co-mutations and FLT3-ITD allelic ratio (AR) on response and OS. **Methods:** A total of 37 recurrently mutated genes in AML (Archer Myeloid Panel) were analyzed by targeted sequencing so that mutation-positive (co-mut+) pts identified four major co-mutation cohorts, each with >10% of pts. NPM1 (n=173; 47.9%), DNMT3A (n=115; 31.9%), DNMT3A/NPM1 (n=86; 23.8%), and WT1 (n=65; 18.0%). In addition, seven pts (1.9%) had all three co-mutations (ie, NPM1, DNMT3A, and WT1). The gilteritinib arm had superior response rates and OS across all four major co-mutation cohorts, with the greatest survival benefit in pts with DNMT3A/NPM1 co-mut+ (Table 1). In FLT3-ITD AR analyses (n=335), gilteritinib conferred longer OS in SC in pts with a high or low FLT3-ITD AR (gilteritinib: high FLT3-ITD AR, 7.1 mos vs low FLT3-ITD AR, 10.6 mos; SC: high FLT3-ITD AR, 4.3 mos vs low FLT3-ITD AR, 6.9 mos). In both arms, OS was longer in the low FLT3-ITD AR cohort than the high FLT3-ITD AR cohort but the difference was not statistically significant (HR=1.341, P=0.0712; SC: HR=2.01, P=0.0021). **Conclusions:** The ADMIRAL trial showed that the clinical benefit of gilteritinib in FLT3\textsuperscript{mut+} R/R AML is maintained regardless of NPM1, DNMT3A, DNMT3A/NPM1, or WT1 co-mut+ or high FLT3-ITD AR. Clinical trial information: NCT02421939.
Background: Flutamibin (FM), a derivative of imatinib (IM), is a novel BCR-ABL1 tyrosine kinase inhibitor (TKI). The aim of this open-label phase I study was to validate the efficacy and safety of FM in comparison with IM as frontline treatment in Chinese patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (CML) in chronic phase (CML-CP). Methods: Randomized phase I study to evaluate a safety profile of FM given at a fixed 10 mg/kg dose allocation to each arm. Primary endpoints were major molecular response (MMR = BCR-ABL IS ≤0.1%) rates at 6 and 12 months. Molecular responses were assessed at a centralized laboratory blinded to treatment allocations during the study. Efficacy endpoints were analyzed for the intention-to-treat populations. This study is registered with ClinicalTrials.gov, number NCT02204644.

Results: 400 eligible patients were randomized and patient characteristics at baseline were similar in each arm. The full analysis set (FAS) consisted of 393 patients who received FM 600 mg (n = 196) or IM 400 mg (n = 197) tablets once daily. Compared with IM, FM resulted significantly higher induction of MMR rate (%; 95%CI) at 6 month (33.0; 27.06-39.29 vs 19.3; 12; 23.67; P = 0.0005) and 12 month (48.5; 41.47-56.47 vs 33.0; 26.43-39.56; P = 0.0021) and also at 3 month (8.2; 4.33-12.00 vs 2.0; 0.06-4.00; P = 0.0058). Significantly more patients in the FM than in the IM arm achieved a complete molecular response (BCR-ABL IS = 0.0032%) at 12 months. Early molecular response (BCR-ABL IS ≤ 10%) at 3 months was higher in early cohort and were also significantly higher with FM (82.1; 76.78-87.50 vs 53.3; 46.33-60.27; P < 0.0001 and 60.71; 53.88-67.55 vs 49.57; 42.76; 56.73; P = 0.0032). FM has a safety profile similar to IM. The rates of grade 3/4 AEs of FM were similar to IM, 56.57% (112 of 198) vs 41.38% (87 of 206). However, there were some differences in some non-hematological toxicities as early QTcF was increased in IM (60% vs 49.81% in FM). Grade 3/4 neutropenia was significantly lower in the FM than in the IM arm, such as (4.59% vs 12.63%, P = 0.0064) and eyelid edema (0.5% vs 14.65, P = 0.0011) leukemia (50.61 vs 62.36, P < 0.0001) and neutropenia (50.10 vs 59.60, P < 0.0001). No specific TEAE was identified in each arm. Conclusions: This phase I study has shown promising hematology and toxicologic responses. Our study results were comparable to IM in its safety and superior in its efficacy profile at 3, 6 and 12 month time points. These results support FM as a frontline treatment option for patients with newly diagnosed CML-CP. Clinical trial information: NCT02204644.

Results: By the data cut-off, of 126 pts entering TFR, 56 were ongoing, 59 had resumed NIL, and 11 had discontinued. TFR rate at 192 wk was 46.0% (58/126; 95% CI, 37.1–55.1%). All but 1 of the 58 pts were in MR3+. Only 1/56 pts in TFR at 144 wk could achieve MR4.5. MRs were not confirmed in pts that achieved ≥192 wk of TFR, resumed NIL, or discontinued the study.

Results: Median follow-up of 24.6 y (range, 11.0–33.3 y) was reported from 182 of 183 CT recipients (MRD ≥0.01%); 3 dying before 124 wk were excluded. Of the 182 CT recipients, 72.5% (132 of 182; 95% CI, 65.9–78.2%) were continuously MRD ≤0.01% at 6 y, 64.5% (116 of 182; 95% CI, 57.0–72.0%) at 12 y, and 62% (45-83%) respectively (P=0.11).

Conclusions: Median follow-up of 24.6 y was reported from 182 of 183 CT recipients (MRD ≥0.01%); 3 dying before 124 wk were excluded. Of the 182 CT recipients, 72.5% (132 of 182; 95% CI, 65.9–78.2%) were continuously MRD ≤0.01% at 6 y, 64.5% (116 of 182; 95% CI, 57.0–72.0%) at 12 y, and 62% (45-83%) respectively (P=0.11).
Background: Adenovirus infection can cause significant morbidity and mortality in immunosuppressed patients. Cidofovir is commonly used, but its nephrotoxicity is concerning and efficacy limited. Another approach is to restore the anti-adenovirus immunity. Indeed, virus specific T-cells have been shown to be safe and effective in stem cell transplant recipients. Methods: Immunosuppressed pts with either adenovirus or cytomegalovirus (CMV) infection were enrolled. Most closely HLA-matched adenovirus cytotoxic T lymphocytes (CTLs) were generated by expanding donor derived T-cells with a peptide library derived from the hexon protein of adenovirus serotype 3 in the presence of IL-2 20 IU/ml, IL7 10 ng/ml, IL4 10 ng/ml. After receiving 2x10^6 Kg T cells, pts were monitored for response and adverse events. Results: Eight pts received adenovirus CTLs with one infusion. The Table summarizes their characteristics and responses. Seven pts had complete resolution of their symptoms (CR) and adenovirus becoming undetectable (ND). Those pts are alive to date. The remaining patient initially responded but then lost response when started on high dose prednisone for treatment of GVHD to which she eventually succumbed. Best response was achieved after a median of 13 days [30-36]. No cytokine release syndrome occurred and we did not observe any side effect attributable to the CTLs. Conclusions: The use of off-the-shelf adenovirus CTLs is a feasible, safe, and effective approach to treat severe adenovirus infections in immunosuppressed pts. Clinical trial information: NCT03425526.

### Table

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<th>Sex</th>
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<th>Symptom</th>
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<th>CMV</th>
<th>OS (mo)</th>
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<th>HR (95% CI)</th>
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### References

Primary results of the phase 4 BYOND study of bosutinib (BOS) for pretreated chronic phase (CP) chronic myeloid leukemia (CML). First Author: Carlo Gambacorti-Passerini, University of Milano-Bicocca, Monza, Italy

Background: The tyrosine kinase inhibitor (TKI) BOS is approved for patients (pts) with Philadelphia chromosome (Ph)+ CML resistant/intolerant to prior therapy and newly diagnosed pts in CP. Methods: The ongoing phase 4 BYOND study is further evaluating efficacy and safety of BOS (starting 313 mg/d for CP) in Ph+ CP CML cohorts. Results: Across Ph+ CP CML cohorts, 51.9% of pts were male; median age was 61 y. Of 1 y after last enrolled pt (median follow-up 30.4 mo), 56.4% remained on BOS. Median OS duration was 23.7 mo and median intensity after adjustment due to adverse events (AEs) was 3.1 mo. Of 144 pts with a valid baseline assessment, cumulative confirmed MCyR by 1 y was 71.5% (95% confidence interval (CI) 63.4–78.7). Cumulative complete cytogenetic response rate anytime on treatment was 81.3% (95% CI 73.9–87.3). Cumulative molecular response (MR) rates were high across lines of therapy (Table). 10 deaths occurred (5 attributed to AEs). Results further support BOS use for Ph+ CP CML resistant/intolerant to prior TKIs. Clinical trial information: NCT02228382.

7014 Poster Discussion Session; Displayed in Poster Session (Board #389), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Pooled safety summary for patients treated with the CD22-directed cytotoxic moxetumomab pasudotox-tdfk. First Author: Robert J. Kreitman, Laboratory of Molecular Biology, NCI, NIH, Bethesda, MD

Background: Moxetumomab pasudotox-tdfk was FDA-approved in 2018 for the treatment of adults with relapsed/refractory hairy cell leukemia (HCL) who have received ≥2 prior therapies, including a purine nucleoside analog. Moxetumomab pasudotox-tdfk was FDA-approved for safety and efficacy in patients with HCL who have received ≥2 prior therapies. (N=165) treated with ≥1 dose of moxetumomab across 5 open-label, single-arm clinical trials. Two trials included patients with HCL (N=129, with N=80 in the pivotal phase 3 trial) and 3 trials included patients with non-Hodgkin lymphoma (N=15) or chronic lymphocytic leukemia/small lymphocytic lymphoma (N=21). Overall, 81% were male, median age was 60 years (range 34–84) and 94% had an ECOG ≤1. Results: The most common adverse events (AEs) with moxetumomab were peripheral edema (41%), hypoalbuminemia (35%), and nausea (35%). Serious AEs occurred in 47 (28.5%) patients and were considered treatment-related in 21 (12.7%) patients. Treatment-related AEs were mainly grade 1/2; the most common were peripheral edema (32%), hypoalbuminemia (32%), increased ALT (29%), increased AST (28%), nausea (26%), headache (24%), pyrexia (23%), fatigue (22%), and myalgia (20%). In total, 19 deaths (11.5% of patients) occurred (including 3 in the pivotal trial), with most (13) due to underlying disease and 6 due to AEs (none were assessed as treatment-related by the investigators). However, 1 fatal AE in a non-HCL patient was re-assessed by the Sponsor as possibly related to moxetumomab). In 16 patients (9.7%), a treatment-related AE led to treatment discontinuation, with hemolytic uremic syndrome HUS; 3.6% and capillary leak syndrome (CLS; 2.4%) the most common. Treatment-related AEs resulted in dose delay, omission or DLT in 11 patients (6.7%). Conclusions: Moxetumomab had an acceptable safety profile based on pooled data from 165 adult patients with hematologic malignancies, with few treatment-related discontinuations. Proactive monitoring of patients is important to manage AEs. These results are consistent with results from the pivotal phase 3 trial in patients with HCL. Clinical trial information: NCT01829711, NCT00586924, NCT00587457, NCT00587015, NCT01030536.

7015 Poster Discussion Session; Displayed in Poster Session (Board #390), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Inferior survival after microbiota injury: A multicenter allo-HCT study. First Author: Jonathan U. Peled, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Relationships between microbiota composition and clinical outcomes following allogeneic hematopoietic cell transplantation (allo-HCT) have been described in single-center studies. Geographic variations in human microbiome communities are extensive and allo-HCT results at individual institutions raise the question of whether these associations are generalizable. We report the first multi-center study of the intestinal microbiota in allo-HCT. Methods: Intestinal communities in 8,768 fecal samples from 1,362 allo-HCT patients at 4 centers on 3 continents were profiled by 16S sequencing. Results: Relationships between microbiota composition and clinical outcomes following allogeneic hematopoietic cell transplantation (allo-HCT) were assessed. Associations between microbiota composition and clinical outcomes were analyzed with proportional-hazards analysis in an observational study. Results: We observed reproducible patterns of microbiota injury characterized by loss of diversity and dominance by single taxa. Low diversity in the neutrophil engraftment period was reproducibly associated with increased risk of death (multivariate HR 0.48 [0.30-0.77] p = 0.002 in the largest cohort). These reductions in OS were in part due to an increased risk of transplant-related mortality and graft-vs-host disease. Baseline pre-HCT samples already bore evidence of microbiome disruption; low diversity prior to transplantation was associated with poor survival. A bacterial-compromise risk score that was trained in one cohort predicted mortality in the other three cohorts (multivariate HR 1.42 [1.04-1.93] p = 0.03), indicating not only a diversity metric but also a signature of specific bacterial abundances is informative about post-HCT mortality risk across independent institutions. Conclusions: We demonstrate a relationship between microbiota and survival after allo-HCT that is independent of transplant center and geographic location. The diversity of clinical practices across institutions imposed significant heterogeneity in the study, yet we observed reproducible microbiota injury patterns and associations with outcomes. This concordance suggests that approaches to manipulate the intestinal microbiota in allo-HCT may be generalizable.
Development and validation of a novel disease risk model for patients with AML receiving allogeneic hematopoietic cell transplantation. First Author: Pyanuch Kongtim, Faculty of Medicine Thammasat University, Pathumthani, Thailand

Background: Molecular data and minimal residual disease (MRD) have been shown to influence outcomes in AML patients undergoing allogeneic hematopoietic cell transplantation (AHCT). Here we developed and validated a novel AML-specific Disease Risk Group (AML-DRG) algorithm to predict outcomes in a large cohort of adult AML patients.

Methods: A retrospective study of 186 patients (age ≥ 18 years) LCH patients seen at our institution between 1998 and 2018. Results: We included 186 patients with adult LCH (median age 43; 19-88), and 54% were females. 70% of patients were diagnosed after 2007. Common presenting symptoms of diabetes insipidus (20%), painless swelling of the head and neck (17%), and diabetes insipidus (10%). 70% of patients had multilymphocytic, 62% (33%) had isolated pulmonary LCH, and 35% of LCH had unifocal LCH. Common sites of involvement included lung (59%), bone (37%), skin (21%), and nervous system (16%). 121 (65%) were smokers; 48% of these had lung disease, while 52% had multilymphocytic disease. 18 of 31 tested (58%) patients had BRAFV600E mutation.

Conclusions: Most common first-line treatment was smoking cessation in 24 patients, and led to an overall response rate (ORR) of 83% in pulmonary lesions. Radiation therapy was used in 11 patients, and led to an overall response rate of 67% (ORR = 60 years or HCT-CI ≥ 200). Using an institutional database of 457 adults age 60 years and older (range 60-78.7) who underwent first allo-HCT for hematological malignancies from 2010 to 2017, we retrospectively examined the prevalence and the prognostic impact of pre-transplant geriatric factors including an assessment tool to risk stratify older patients prior to allo-HCT using IADL and aHCTCI and DRI. These results may provide an entry point for prospective, interventional trials to reduce NRM and toxicities for older allo-HCT patients.

Impact of geriatric vulnerability on outcomes of older patients in allogeneic hematopoietic cell transplantation. First Author: Richard Jirui Lin, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Older patients are at increased risk for complications and death following allogeneic hematopoietic cell transplantation (allo-HCT). Traditional transplant-specific prognostic indices such as hematopoietic cell transplant comorbidity index (HCT-CI) may not capture all underlying geriatric vulnerabilities, and in-depth evaluation by a geriatrician prior to transplant may not always be available. We hypothesize that routine pre-transplant assessments by interdisciplinary clinical providers may help uncover additional geriatric deficits.

Methods: Using an institutional database of 457 adults age 60 years and older (range 60-78.7) who underwent first allo-HCT for hematological malignancies from 2010 to 2017, we retrospectively examined the prevalence and the prognostic impact of pre-transplant geriatric factors identified by interdisciplinary clinical providers including geriatric domains of functional activity, cognition, medication, nutrition, mobility, and routine laboratory tests.

Results: With a median follow-up of 37 months for survivors, the 3-year probability of overall survival (OS) was 56% (95% CI 45-55). The 2-year cumulative incidence of non-relapse mortality (NRM) was 25% (95% CI 22-28). Among pre-transplant geriatric variables, we found that impairment in instrumental activities of daily living (IADL) was associated with increased NRM and inferior FPS and OS. In multivariate analyses, mismatched donor, age-adjusted HCT-CI (HCT-CI < 6), the IADL impairment were associated with NRM, while high-risk high disease risk index (DRI), IADL impairment, and positive CMV status were associated with OS. The combination of IADL impairment with either aHCTCI or DRI readily stratifies NRM and OS, respectively.

Conclusions: Our findings establish a simple assessment tool to risk stratify older patients prior to allo-HCT using IADL and aHCTCI and DRI. These results may provide an entry point for prospective, interventional trials to reduce NRM and toxicities for older allo-HCT patients.
Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant

7020 Poster Discussion Session; Displayed in Poster Session (Board #395), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Clinical features, molecular aberrations, treatments, and outcomes in histiocytic sarcoma. First Author: Gordon Ruan, Mayo Clinic Rochester, Rochester, MN

Background: Histiocytic sarcoma (HS) is a rare and aggressive malignancy of the monocyte/macrophage lineage. There is a paucity of data on treatments and outcomes in HS. Methods: This is a retrospective study of patients with histologically confirmed diagnosis of HS from 2000-2020 at Mayo Clinic-Rochester. Kaplan-Meier and Frank tests were used to perform overall survival (OS) analyses. Hazard ratios (HR) with confidence intervals (CI) were calculated using Cox-proportional hazards. Results: There were 27 patients in the study (median age 59; range 3-83) and 63% were males. Nine had cutaneous involvement and 18 had multifocal disease. Common sites involved were lymph node (50%), soft tissue (40%), bone (36%), and bone marrow (22%). Two of 8 patients had the BRAF-V600E mutation. Next-generation sequencing was performed on 8 patients and showed 1 oncogenic alterations (DNNM3A, FLT4, KRAS, NRAS, NUP98, PTCH1, PTTPN1, TP53, TSC1, PDGFR, or BRAF genes) as well as a CLIP2-BRAF fusion. The median OS for the cohort was 12 months. Factors associated with worse OS included multifocal disease (OS 10 vs. 125 months, p = 0.03; HR 5.0, CI 1.1-21.8) and marrow involvement (OS 0.5 vs. 11.5 months, p = 0.0033; HR 8.9, CI 1.7-45.0). Twelve (44%) had surgery with median OS of 42 months (range 1-125). Fifteen had chemotheraphy with median OS of 12 months (range 2-67; Table). Conclusions: HS is an aggressive neoplasm, with multifocal disease and bone marrow involvement portending worse outcomes. Most patients have somatic oncogenic alterations involving the MAPK-ERK pathway and other genes. Chemotherapeutic regimens have variable response rates but are not durable. More studies on targeted kinase inhibitors in HS are needed to improve outcomes.

7022 Poster Session (Board #397), Mon, 8:00 AM-11:00 AM

Granulocyte transfusions in patients with skin and soft tissues infections and leukemic AML. First Author: Yamil Michelen, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Granulocyte transfusions (GTx) have been proposed to improve clinical outcome of neutropenic patients (pts) with serious infections. We evaluated the impact of unirradiated GTx in pts with skin and soft tissue infections (SSTI) and leukemia. Methods: We did a retrospective analysis of pts with leukemia and SSTI that received GTx from 2014 to 2018. We analyzed infection outcome and changes in ANC after GTx. Pts were stratified using G-CSF plus oral dexamethasone 12 hours prior to apheresis. Results: Twenty-seven pts received 141 GTx for 33 SSTI. Transfusions were unirradiated, except for 10 (7%) radiated units administered due to availability. Twenty pts were male (74%); median age was 59 yrs (20-83 yrs). Hematologic diagnoses included AML (23, 70%), MDS (3, 9%), ALL (3, 9%), CLL (2, 6%), CML (1, 3%), and MF (1, 3%). In 24 (73%) SSTI pts, pts had a baseline ANC<0.5 x10^9/L, 3 (9%) had ANC between 0.51x10^9 to 0.99 x10^9/L, and 6 (18%) with ANC >1x10^9/L. After GTx, ANC increased in 90 (70%) cases by a median of 0.7 x 10^9/L (0.02 to 10.03) with a median peak time of 9 hrs (4 to 114 hrs), with a median time from GTx to first drop of 34 hrs (10 to 136 hrs). ANC decreased in 27 (19%) (by a median -0.5 x 10^9/L, -0.02 to -2.41). There was no change of ANC in 15 (11%). Improvement was determined by reduction in fever and inflammation, or resolution of SSTI 7 days after first GTx. Twenty-seven (82%) episodes improved. In those improved, ANC remained <1.5x10^9/L in 15 (56%) episodes after last GTx and after improvement. Main adverse reactions were fever in 21% (29), and respiratory complications in 6% (9) (pulmonary effusion, respiratory distress and acute hypoxemia), One pt (3%) required intubation. There was no transfusion-related GVHD. Cumulative survival from first GTx on each SSTI by Kaplan-Meier Survival was 82% (95% CI 71-100) at 90 days, 71% (17-180 days) and 24% (12) at 360 days. Eight of this pts died of infections, 4 of which were SSTI described on this paper. Conclusions: GTx have a beneficial effect on clinical improvement in patients with SSTI and underlying hematological malignancies and severe neutropenia. It can be safely administered without GVHD. Further prospective studies are warranted.

7023 Poster Session (Board #398), Mon, 8:00 AM-11:00 AM

Association of the GATA3 rs3824662A allele with clinical outcomes in adult patients with AML. First Author: Paul B. Koller, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Inherited GATA3 variants (rs3824662) have been described in higher frequency in both adults and children with Ph-like acute lymphoblastic leukemia (Ph-like ALL) (Perez-Andreu, Nat Genetics 2013; Jain, ASH 2017). The clinical outcomes of Ph-like ALL are well known, and as we have previously described, it as a high-risk subtype of ALL in both children and adults (Roberts, NEJM 2014; Roberts, JCO 2017; Jain, Blood 2017). However, the clinical outcomes of ALL patients with different germline variants of GATA3 that are commonly seen in Ph-like ALL is unknown. Methods: Of the newly diagnosed patients treated at MD Anderson Cancer Center (MDACC) with B-ALL, we performed analyses for the rs3824662A allele in patients with adult B-ALL. Results: Of the 85 patients, the rs3824662 AA genotype was identified in 22 patients (26%), and 55% of those patients had AA genotype. Conclusions: We did a retrospective analysis of the GATA3 rs3824662A allele with clinical outcomes in adult patients with B-ALL. Further studies are warranted.
Background: Philadelphia Chromosome-Positive (Ph+) disease is associated with a poor prognosis in acute lymphoblastic leukemia (ALL). Recent studies have shown that the eradication of minimal residual disease (MRD) in this population leads to improved survival outcomes. While hematopoietic stem cell transplantation (HSCT) has demonstrated improved outcomes in Ph+ ALL patients treated with the tyrosine kinase inhibitor (TKI) imatinib, its role is unclear with the use of more potent, newer-generation TKIs such as dasatinib.

**Methods:** This was a retrospective study analyzing the impact of allogeneic HSCT on MRD status in Ph+ ALL patients treated with dasatinib. Patients were divided into 2 groups: those treated with chemotherapy plus dasatinib followed by allogeneic HSCT and those who received chemotherapy plus dasatinib alone. All patients underwent bone marrow biopsy with MRD analysis following induction therapy and subsequent re-evaluation of MRD status at day 100 post-transplant in the HSCT group and after further cycles of chemotherapy in the non-transplant group. MRD-negative disease was defined as the absence of a BCR-ABL1 transcript by real-time quantitative polymerase chain reaction (qRT-PCR) with a sensitivity of 0.01%.

**Results:** A total of 51 adult Ph+ ALL patients with MRD-positive disease following induction therapy were included. Twenty-seven patients (53%) were evaluable for the median age at time of diagnosis was 45 years (range 23-68). There were 29 patients in the transplant group and 22 patients in the non-transplant group. When analyzing rates of MRD eradication, 18 (62%) patients in the transplant group were found to have MRD-negative disease at day 100 post-transplant compared to 7 (32%) patients in the non-transplant group who only received further cycles of chemotherapy plus dasatinib (risk ratio 0.56, 95% confidence interval 0.32-0.96, p = 0.048).

**Conclusions:** In the era of newer-generation TKIs, allogeneic HSCT continues to have notable benefits in Ph+ ALL such as a significantly higher rate of MRD eradication as demonstrated in this study.

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**Poster Session (Board #399), Mon, 8:00 AM - 11:00 AM**

**Allogeneic hematopoietic stem cell transplantation contributes to eradication of minimal residual disease in adult Philadelphia chromosome-positive acute lymphoblastic leukemia patients treated with dasatinib**

First Author: Jerry Chang, University of Southern California + LA County Medical Center Internal Medicine Residency, Los Angeles, CA

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**Poster Session (Board #400), Mon, 8:00 AM - 11:00 AM**

**Time from randomization to first subsequent induction/salvage therapy (ST) in patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) treated with inotuzumab ozogamicin (InO) in the phase 3 INO-VATE trial.**

First Author: Elias Jabbour, The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX

**Background:** Additional salvage regimens are burdensome for R/R ALL patients (pts) due to therapy-associated toxicities, which may affect quality of life with poor efficacy. In INO-VATE (Kantarjian et al, NEJM 2016), pts receiving InO vs standard chemotherapy (SC) had significantly greater remissions at any time after survival; after study treatment discontinuation, overall fewer STs (mainly bone-marrow two-thirds chemotherapies) were used in the InO group vs SC. **Methods:** Study design was published. Adults with CD22+ ALL who were due to receive 1st or 2nd salvage treatment were randomized 1:1 to InO (n = 164) or SC (n = 162). Time to the first ST (TST) was time from randomization to the start of the first ST. Pts who did not receive any ST were censored. Data cutoff Jan 4, 2017. **Results:** Fewer InO pts had ST vs SC (Table). Among the censored pts, 83/106 (78.6%) in the InO vs 54/69 (78.3%) in the SC group died. 23/108 (21.3%) vs 56/69 (81.2%) were alive at the end of the study, and 2/108 (1.9%) vs 106/69 (14.5%) were no longer being followed. TST was longer in pts receiving InO vs SC. Overall median (95% CI) TST was 18.8 (14.7-NA) vs 3.9 (2.4-5.1) months; hazard ratio (HR) = 0.34, 97.5% CI: 0.24-0.49, 1-sided P = 0.0001. Fewer pts receiving hematopoietic stem cell transplantation (HSCT) on study, fewer InO pts had ST vs SC pts; TST was significantly longer in InO vs SC pts. For InO (70: SC: 18) who had HSCT directly after salvage, TST was extended in InO vs SC. **Conclusions:** In this study, treatment with InO provided the benefit of extended TST, effectively allowing patients a longer time period until an ST was needed in both patients who proceeded to as well as those who did not proceed to HSCT. Clinical trial information: NCT01564784.

Inotuzumab ozogamicin (InO) is FDA approved for the treatment of adults with mIDH1 relapsed or refractory AML. In a phase 1 study (NCT01564784), InO was held due to DS in 3 pts. QT prolongation was seen in 6 pts. In 33 pts neutrophil count response rate (ORR) comprised complete remission (CR) + CR with incomplete remission (CRi) + partial remission (PR). InO was approved for the treatment of adults with mIDH1 relapsed or refractory AML. Clinical trial information: NCT02074839.
involved in hematopoiesis. In acute myeloid leukemia (AML), higher CAR-T therapy.

trial information: NCT02391480. We report preliminary data from 2 patients with relapsed/refractory (RR) AML. Methods: Mivebresib monotherapy (MIV-mono), or combined with venetoclax (MIV-VEN), were administered daily to adult patients with AML. The dose-limiting toxicity (DLT) period was 28 d. Results: Of 41 patients (median age: 69 y [range, 29–84]; 19 patients had > 2 prior therapies) were enrolled: 19 in MIV-mono (5 of whom switched to MIV-combo) and 22 who began treatment in MIV-VEN cohorts. 23 patients had high cytogenetic risk. Median time on treatment was 28 d (range, 8–562). There were no DLTs. All patients experienced a treatment-emergent adverse event (AE), most commonly (≥40% patient incidence), fatigue (56%), dysgeusia (46%), decreased appetite (44%), diarrhea (42%), nausea (42%), vomiting (42%). 40 patients had grade ≥ 3 AEs (febrile neutropenia (37%), anemia (34%) and thrombocytopenia (32%). 33 patients had serious AEs, most commonly febrile neutropenia (16%). 25 deaths were reported; 15 patients died of causes related to mivebresib and 10 patients due to AML secondary to mivebresib and 10 patients due to AML progression. The median best % bone marrow blast change for 26 evaluable patients was -20% (range, -98% to +300%). Gene expression analysis in pre- and post-treatment peripheral blood samples showed that HEXIM1, DCXR and CD93 genes were reliable PD biomarkers of ABBV-075 which were consistent and post-treatment peripheral blood samples showed that HEXIM1, DCXR and CD93 genes were reliable PD biomarkers of ABBV-075 which were consistent with the targeted killing of cells expressing FLT3 on the plasma membrane. Partial tandem duplication of the mixed lineage leukemia gene (MLL-PTD) occurs in about 3% to 5% of adult acute myeloid leukemia (AML), mostly in patients with normal karyotypes, and is associated with poor prognosis. We developed and validated long-range PCR on extracted DNA, a commonly processed assay that uses long-range PCR on extracted DNA, a commonly processed assay that uses long-range PCR on extracted DNA, a commonly processed assay that uses long-range PCR on extracted DNA, a commonly processed assay that uses long-range PCR on extracted DNA, a commonly processed assay that uses long-range PCR on extracted DNA, a commonly processed assay that uses long-range PCR on extracted DNA, a commonly processed sample type for AML molecular testing, to reduce sample processing requirements. Methods: DNA was extracted from de-identified 72 whole blood and 30 bone marrow aspirate specimens. Two PCR reactions were performed for each DNA sample: one to detect MLL-PTD and another to detect CHEK2 to monitor DNA integrity. The 3 most frequent forms of MLL-PTD (exons 2–8, 2–9, and 2–10) were detected using a forward DNA primer on exon 8 and a reverse primer on exon 2. MLL-PTD positivity was determined by the intensity of amplified DNA fragment at or above the lower detection limit control of this assay. Intra-assay precision, inter-assay precision, and limit of detection (LOD) were performed according to standard laboratory protocols. Results of this method were compared to those of NGS. Results: Intra-assay precision studies on 20 specimens yielded 100% concordance between replicates. LOD studies using a human eosinophilic leukemia cell line (Eol-1) with 12.5-4 k-b PTD in size showed assay sensitivity of 5%; for smaller MLL-PTD positives (PTD ~3 kb and ~5 kb), LOD was 1%. For method comparison studies, 42 specimens (52 whole blood and 19 bone marrow) were also analyzed by NGS; concordance between the methods was 97.2% (69/71). Conclusions: We developed and validated long-range MLL-PTD detection assay for AML. The developed method uses DNA, which is commonly used for molecular testing for AML, and thus may reduce sample processing time by consolidating sample type across tests.
**7034**

**Poster Session (Board #409), Mon, 8:00 AM-11:00 AM**

**Activity of venetoclax-based therapy in TP53-mutated acute myeloid leukemia.**

First Author: Mahran Shoukri, University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Mutations in TP53 are associated with low response rates to standard therapy and poor outcomes in patients (pts) with acute myeloid leukemia (AML). Combination therapy with the BCL2 inhibitor venetoclax (VEN) has emerged as an effective treatment option for pts with AML. **Methods:** We reviewed pts with TP53-mutated AML treated at our center between 2014-2018. Mutation testing was performed using a whole-exome next-generation sequencing panel. We analyzed the characteristics of these pts, responses to therapy, and outcomes. **Results:** Sixty nine pts with TP53-mutated AML treated with VEN were identified. Among these pts, 52 (63%) had TP53 mutations in their primary AML clone. The median age at diagnosis was 4.5 (0.5-48.5) and 8 (1-46.5) months for frontline & R/R pts, respectively. Karyotype was complex in 32 (88%) and 29 (88%) pts in the frontline & R/R cohorts, respectively. In the R/R cohort, the number of median prior treatments was 2 (0-8). VEN was given in combination with: 1) Hypermelinating agents (HMA) (87%), 2) FLAG-idar (3%), 3) Low dose Ara-C (4%), or 4) CPX-351 (6%). The overall response rate (ORR) was 47% & 24% in frontline and R/R pts, respectively. All 6 pts with negative minimal residual disease (MRD) achieved complete cytogenetic response after taking VEN % remain in complete remission (CR) with a median of 3.4 (1.7-4.7) months. Two pts (both R/R) underwent allelogeneic stem cell transplantation. **Conclusions:** VEN based therapy was associated with similar ORR, but higher CR rates in TP53 mutated AML compared with HMA alone. Larger studies with longer follow up are needed to determine the role of VEN-based therapy in this difficult subset. Patient characteristics and outcome.

**7035**

**Poster Session (Board #410), Mon, 8:00 AM-11:00 AM**

**Mechanism of biologic therapy for pre B-cell acute lymphoblastic leukemia with CRLF2 overexpression.**

First Author: WayAnne Watson, Loma Linda University, Loma Linda, CA

**Background:** Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, of which pre B-cell ALL with CRLF2 overexpression is a high risk subtype. CRLF2 B-ALL is associated with poor outcome, increased rate of relapse, and health disparities in Hispanic children. Together with IL-7 receptor alpha (IL-7Rα), CRLF2 makes up a receptor complex that is activated by the cytokine, thymic stromal lymphopoietin (TSLP). TSLP promotes the proliferation of the normal hematopoietic progenitor cells (CD34+/CD38-), STAT5 and PI3/AKT/mTOR signals that promote leukemia cell survival and proliferation. To study the role of TSLP in CRLF2 B-ALL, we developed a patient-derived xenograft (PDX) model of CRLF2 B-ALL that allows us to alter circulating levels of human TSLP (hTSLP). We generated PDX from CRLF2 B-ALL cells harvested from patient sample after salvage chemotherapy. PDX were exposed to varying levels of hTSLP. In PDX models with hTSLP levels at or below physiological levels in pediatric cancer patients, CRLF2 B-ALL cells grew robustly. However, in PDX with elevated levels of hTSLP, leukemia cells were essentially eliminated. Our objective is to elaborate on the mechanism of high dose hTSLP's antileukemic effect. **Methods:** We performed TSLP dose response studies and used flow cytometry to evaluate the effect of TSLP on SOCS protein expression, CRLF2 signaling shutdown, and loss of TSLR receptor complex. **Results:** CRLF2 B-ALL cells cultured with hTSLP showed a dose-dependent loss in the ability to induce STAT5 and S6 phosphorylation following hTSLP stimulation. This loss was correlated with the loss of IL-7Rα, and maintained for 24-48 hours following a pulse of high-dose, but not low-dose, hTSLP. The loss of signaling and surface IL-7Rα could be prolonged if high-dose hTSLP levels were maintained. Flow cytometry analysis showed that TSLP reverses its anti-leukemia effects through downregulated expression of CRLF2-mediated signals and that these effects are at least partially mediated by the loss of the IL-7Rα component, and potentially through SOCS family proteins. These studies elucidate the mechanism of the human TSLP cytokine as a potential biologic therapy to treat CRLF2 B-ALL. Supported in part by: 1R01CA209829 (KJP), 1R43CA224723 (KJP), ASH HONORS Award 2018-2019 (WBW), and Alpha Omega Alpha Carolyn L. Kuckein Student Research Fellowship 2018-2019 (WBW).

**7036**

**Poster Session (Board #411), Mon, 8:00 AM-11:00 AM**

**Phase II results of mitoxantrone in combination with clofarabine in children with relapsed/refractory acute leukemia.**

First Author: Jessica Hochberg, New York Medical College, Valhalla, NY

**Background:** Despite improved outcomes in pediatric acute leukemia, those who relapse or are refractory do poorly. Mitoxantrone and clofarabine as single agents have proven efficacy in pediatric leukemia. Our previously reported phase I results demonstrated the MTD of this combination to be clofarabine 35 mg/m² 5 days and mitoxantrone 12 mg/m² 5 days. Here, we report our phase II data utilizing the RP2D. **Methods:** Prospective, open label safety and efficacy study (NCT01842672). Patients 0-30.99 yr old with ALL or AML were enrolled. Relapse or induction failure were given 1 to 3 cycles of clofarabine (RP2D 35 mg/m²). **Results:** Sixty nine pts with TP53-mutated AML treated with VEN were identified, 36 (51%) were AML and 33 (48%) were ALL. The median age at diagnosis was 4.5 [0.5 - 48.5] and 8 [1-46.5] months for frontline & R/R pts, respectively. Karyotype was complex in 32 (88%) and 29 (88%) pts in the frontline & R/R cohorts, respectively. In the R/R cohort, the number of median prior treatments was 2 (0-8). VEN was given in combination with: 1) Hypermelinating agents (HMA) (87%), 2) FLAG-idar (3%), 3) Low dose Ara-C (4%), or 4) CPX-351 (6%). The overall response rate (ORR) was 47% & 24% in frontline and R/R pts, respectively. All 6 pts with negative minimal residual disease (MRD) achieved complete cytogenetic response after taking VEN % remain in complete remission (CR) with a median of 3.4 [1.7-4.7] months. Two pts (both R/R) underwent allelogeneic stem cell transplantation. **Conclusions:** VEN based therapy was associated with similar ORR, but higher CR rates in TP53 mutated AML compared with HMA alone. Larger studies with longer follow up are needed to determine the role of VEN-based therapy in this difficult subset. Patient characteristics and outcome.

**7037**

**Poster Session (Board #412), Mon, 8:00 AM-11:00 AM**

**Interim results from a phase Ib/I clinical study of the glutaminase inhibitor telaglenastat (CB-839) in combination with azacitidine in patients with advanced myelodysplastic syndrome (MDS).**

First Author: Veronica Guerra, MD Anderson Hematology/Oncology Fellowship, Houston, TX

**Background:** Glutaminase (GLS) is an enzyme that catalyzes conversion of glutamine to glutamate, providing key metabolic fuel for tumor cells. GLS is highly expressed in AML and high-risk MDS, particularly in the setting of complex cytogenetics. Preclinical studies of primary AML cells demonstrate dependence on glutamine to produce sufficient levels of glucose. GLS inhibition abolishes cell growth and induced apoptosis. This study was designed to evaluate the safety and efficacy of the oral glutaminase inhibitor CB-839 in combination with azacitidine in patients with advanced myelodysplastic syndrome (MDS). **Methods:** This is a single arm I/II clinical study of the glutaminase inhibitor CB-839, evaluating the dose of 600 mg BID orally daily in combination with azacitidine (AZA) for intermediate and high-risk MDS in 28-day cycles. The primary outcome for the Phase 1 portion was to confirm the safety and recommended Phase 2 dose of CB-839 in combination with AZA. Secondary endpoints evaluate efficacy and clinical activity using IWG response criteria for MDS including hematological improvement (HI), complete response (CR), marrow CR (mCR) and stable disease (SD) and no response (NR). **Results:** A total of 10 pts with MDS were enrolled; the Phase I portion is now complete, confirming CB-839 600 mg BID with standard AZA. Median age was 71 [47.76], 90% were men. 7 pts were treatment naive, 3 pts had prior HMA exposure. 6 pts were intermediate-2, and 4 pts intermediate-1 by IPSS. CB-839 600 mg BID with standard AZA. Median age 71 [47-76], 90% were men. 7 pts were treatment naive, 3 pts had prior HMA exposure. 6 pts were intermediate-2, and 4 pts intermediate-1 by IPSS. CB-839 600 mg BID with standard AZA. Median age 71 [47-76], 90% were men. 7 pts were treatment naive, 3 pts had prior HMA exposure. 6 pts were intermediate-2, and 4 pts intermediate-1 by IPSS.
Identifying Mcl-1 protein dependencies using dimerization-specific antibody biomarker for predicting response to targeted apoptosis inducing therapies. First Author: Michael H. Cardone, Eutropics, Pharmaceuticals Inc., Cambridge, MA

Background: The anti-apoptotic Bcl-2 family proteins facilitate pro-survival and resistance to anti-cancer therapies. Measuring the function of these proteins has shown utility in predicting response to therapy. A method that expands the principle of BH3 profiling to solid tumors is presented. Measuring the occurrence of heterodimers of Myeloid Leukemia Cell Differentiation Protein (Mcl-1), and pro-apoptotic binding protein Bim is an indicator of cancer cell apoptotic priming state. The readout of Mcl-1 containing complex-specific biomarkers can identify survival dependencies in cancer cells potentially providing clinical utility in guiding cancer treatments. Methods: Engineered immunogens that recapitulate conformation-specific epitopes induced during binding of the Mcl-1/Bim protein complex were used to generate, monoclonal antibodies. One Heterodimer Specific Mcl-1-Bim (HsMcB) was chosen. The selection binding was confirmed using ELISA, fluorescence polarization, immunofluorescence microscopy and flow cytometry in Bim or Mcl-1 knockdown cells, and by immunohistochemistry in formalin-fixed paraffin-embedded patient tissue. Consequence of HsMcB measurements to BH3p3 expression levels (HsMcBp3/Mcl-1) was measured. Disruption of the complexes by BH3 mimetics targeted to Mcl-1 and depletion of Mcl-1 level using CDK9 inhibitors diminished the (HsMcB)p3/Mcl-1 ratio. We then measured the ratio of the agonist BH3 mimetic peptides readouts from the Mcl-1 specific Noxa and p53 BH3 mimetic peptides in AML patient samples that have been treated with Mcl-1 inhibitors. Conclusions: Mcl-1 dependence is a predictive biomarker for venetoclax resistance and for response to Mcl-1 targeted therapies. Flow cytometric and IHC based measurements of Mcl-1 in a solid tumor cohort offer a simpler approach that harbors potential for use in clinical settings. Additional antibodies targeting Mcl-1/Bak and Mcl-1 Noxa complexes are being tested.

A video decision aid to improve acute myeloid leukemia patients’ illness understanding: Results of a pilot trial. First Author: Thomas William LeBlanc, Duke University Medical Center, Durham, NC

Background: Many acute myeloid leukemia (AML) patients harbor misunderstandings about their illness, overestimating both their likelihood of cure and risks of intensive therapies. Decision aids (DA) can improve illness understanding and reduce decisional conflict, but are not routinely used in AML. Methods: We developed an AML DA with input from patients, caregivers, clinicians, and laypersons, via the International Patient Decision Aids Standards (IPDAS) process. It includes 10 short animated videos with voiceovers, covering AML basics, etiology, outcomes, treatment paradigms, and risks/benefits of various treatment approaches. We enrolled 20 patients in a pilot feasibility and efficacy trial, with pre/post survey assessments of AML knowledge via an 18-item questionnaire, decisional conflict (Decisional Conflict Scale; DCS), anxiety (State Trait Anxiety Inventory, Short Form; STA-I), and measures of DA usability and satisfaction. Results: Participants were a mean of 62.4 years old, 12 (60%) were male, 17 (85%) white, and 15 (75%) had newly-diagnosed disease. Mean time since AML diagnosis was 145 days (median 31; range 2-1092). 16 (80%) had high-school-level understanding of medical terms per the REALM-SF, and participants on average exhibited moderate numeracy (mean score of 4.1 on the Subjective Numeracy Scale). All participants completed the study, exceeding our pre-determined feasibility threshold. AML knowledge scores generally improved, from a mean of 11.8 correct items on pre-test, to 15.2 on post-test assessment (p < 0.0001), with 80% of participants achieving improved scores. Munagle remained regarding patients’ understanding of the role that genetic tests play in AML care. There was no increase in anxiety after watching the videos, but decisional conflict was significantly reduced, from a mean of 28.5 at baseline to 22 in the post-test (p = .019). Participants reported high satisfaction and usability scores for the DA. Conclusions: Our AML decision aid exhibits favorable performance characteristics, with high satisfaction and usability, a marked increase in patient knowledge, and reduced decisional conflict. Further testing is warranted in a randomized trial. Clinical trial information: NCT03442452.

Impact of luteinizing hormone suppression on hematopoietic recovery after intensive chemotherapy in patients with leukemia. First Author: Imran Ahmad, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Treatment of acute leukemia with intensive chemotherapy (IC) leads to increased risk of infection and bleeding because of myelosuppression. Luteinizing hormone (LH) blockade was found to improve hematopoietic recovery in mice after radiation or chemotherapy through protection of the hematopoietic stem cells (HSCs) which express the LH receptor (Velardi et al, Nat Med 2018). We hypothesized that LH blockade improves hematopoietic recovery following IC in patients (pts) with leukemia. Methods: We assessed gene expression of the LH receptor (LHR) in lineage-specific normal and AML hematopoietic cells from a reference dataset (Corces et al, Nat Gen 2016). We conducted a retrospective analysis on pre-menopausal women with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) who received IC and Lupon, given for prevention or treatment of abnormal uterine bleeding. Results: LHR was greatest in HSCs, with little or no expression in mature subtypes within the hematopoietic hierarchy. Surprisingly, LHR was expressed on blasts. Since Lupon was more commonly given in younger pts, we performed properly matching treatment in acute types (AML N = 43 vs ALL N = 98). Baseline characteristics including blood counts were well balanced. Pts with AML who had received Lupon had a significantly higher increase in their platelet count following IC (13.8x10^9/L)year vs Ctrl; p = 0.02). Pts with ALL who had received Lupon had a significantly higher increase in their platelet count following IC (12.3x10^9/L)year vs Ctrl; p = 0.02). AML pts in the LPR group received significantly less blood transfusions vs Ctrl (median: 23.9 vs 34.7 units; P = 0.002) and less platelet transfusions (median: 24.4 vs 32.8 units; P = 0.06). There was no difference in event-free and overall survival between the groups in this leukemia cohort. Conclusions: Lupon use (a leukemia pts receiving IC) was associated with improved long-term blood count recovery. It was also associated with decreased transfusion requirements in AML. Despite expression of the LHR in blasts in addition to normal HSCs, there was no effect of LH blockade on rates of leukemia relapse or death.

A video decision aid to improve acute myeloid leukemia patients' illness understanding: Results of a pilot trial. First Author: Thomas William LeBlanc, Duke University Medical Center, Durham, NC

Background: Many acute myeloid leukemia (AML) patients harbor misunderstandings about their illness, overestimating both their likelihood of cure and risks of intensive therapies. Decision aids (DA) can improve illness understanding and reduce decisional conflict, but are not routinely used in AML. Methods: We developed an AML DA with input from patients, caregivers, clinicians, and laypersons, via the International Patient Decision Aids Standards (IPDAS) process. It includes 10 short animated videos with voiceovers, covering AML basics, etiology, outcomes, treatment paradigms, and risks/benefits of various treatment approaches. We enrolled 20 patients in a pilot feasibility and efficacy trial, with pre/post survey assessments of AML knowledge via an 18-item questionnaire, decisional conflict (Decisional Conflict Scale; DCS), anxiety (State Trait Anxiety Inventory, Short Form; STA-I), and measures of DA usability and satisfaction. Results: Participants were a mean of 62.4 years old, 12 (60%) were male, 17 (85%) white, and 15 (75%) had newly-diagnosed disease. Mean time since AML diagnosis was 145 days (median 31; range 2-1092). 16 (80%) had high-school-level understanding of medical terms per the REALM-SF, and participants on average exhibited moderate numeracy (mean score of 4.1 on the Subjective Numeracy Scale). All participants completed the study, exceeding our pre-determined feasibility threshold. AML knowledge scores generally improved, from a mean of 11.8 correct items on pre-test, to 15.2 on post-test assessment (p < 0.0001), with 80% of participants achieving improved scores. Munagle remained regarding patients’ understanding of the role that genetic tests play in AML care. There was no increase in anxiety after watching the videos, but decisional conflict was significantly reduced, from a mean of 28.5 at baseline to 22 in the post-test (p = .019). Participants reported high satisfaction and usability scores for the DA. Conclusions: Our AML decision aid exhibits favorable performance characteristics, with high satisfaction and usability, a marked increase in patient knowledge, and reduced decisional conflict. Further testing is warranted in a randomized trial. Clinical trial information: NCT03442452.

IZL-STAT5 immune signatures to predict responses to PD-1 inhibition and an adaptive approach that harbors potential for use in clinical settings. First Author: Hussein Abbasi, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Combining PD-1/PD-L1 blockade with hypomethylating agents (HMA) shows encouraging preliminary efficacy in AML, but immune features predictive of response are lacking. Methods: We treated 11 relapsed/refractory (R/R) AML patients with azacitidine (AZA) and nivolumab (Nivo) in a phase 2 clinical trial (Oaver N et al Cancer Discovery 2018). Patient characteristics: median (med) age 65 years (47-73), 63% adverse cytogenetics, 27% TP53 mutated. Pretreatment bone marrow aspirates had immune-phenotypic 17-color flow analysis and NanoString RNA quantification of 1469 immune-relevant genes. Results were correlated with clinical, pathological and molecular data. Results: The median courses of AZA-Nivo administered was 3 (range 1-17). The CR/CRi rate was 45% (including 2 CR, 1 CRi, 1 CRN and 1 CRP), with a median time to response of 1.8 months (range 0.8-4.9 months). The median overall survival was 13 months with 27% patients alive at 1 year. We found significant positive correlations between proportions of T-effector cells at baseline, and CD3+, CD8+, and T-regulatory cells at end of cycle (EOC) (r = 1, p < 0.001 for all). At EOC2, these correlations were no longer significant. However, there was a significant positive correlation between T-effector cells at baseline and T-regulatory cells (r = 1, p < 0.001) at EOC4. Using NanoString analysis, we found 105 differentially expressed genes (fold change = 1.5, p < 0.05) between responders (5/11) and non-responders (6/11) at pretreatment. IZL-STAT5, TP53 and TNF Hallmark pathways and immune response from GO gene sets were highly enriched (q < 5x10^-5) in responders. We then utilized z-score distribution analysis to quantify the degree of activation of known immunologic pathways. We found that signatures highly specific to neutrophils, NK cells, T-cells and eosinophils were significantly (p < 0.05) upregulated in patients with CR compared to non-responders at pretreatment. Conclusions: Our data demonstrates that a signature suggestive of lymphocyte activation in the pretreatment BM may be associated with augmented clinical response to PD-1 based therapies. Similar underlying pathways that have consistently predicted for responses to PD-1 inhibition in solid cancers, primarily IZL-STAT5 genes, may have predictive relevance in AML. Such pretreatment flow and NanoString signatures may help select AML patients most likely to benefit from PD-1 blockade plus HMA, further enhancing the benefit-risk ratio with such therapies.
Outcomes with CPX-351 versus 7+3 by baseline bone marrow (BM) blast percentage in older patients with newly diagnosed high-risk/secondary acute myeloid leukemia (sAML). First Author: Ellen K. Ritchie, Weill Cornell Medical College of Cornell University, New York, NY

Background: CPX-351, a liposomal encapsulation of cytarabine (C) and daunorubicin (D) at a synergistic ratio, is approved as Vyxeos in the US and EU for adults with newly diagnosed therapy-related AML or AML with myelodyplasia-related changes. In a phase 3 study, CPX-351 significantly improved OS and remission rates vs 7+3 in patients (pts) aged 60-75 y with newly diagnosed high-risk/sAML. Some studies suggest a high baseline blast percentage may portend a worse prognosis in AML. This post hoc analysis of phase 3 data assessed outcomes by baseline BM blast percentage.

Methods: Pts diagnosed with AML per 2008 WHO criteria (≥20% blasts in peripheral blood or BM) were randomized 1:1:1 to receive <2 inductions of CPX-351 (100 units/ml [C 100 mg/m² + D 44 mg/m²] on Days 1, 3, 5 for induction; Days 1, 3) or 7+3 (C 100 mg/m²/d continued for 7 d; D 5 + D 60 mg/m² on Days 1-3) (2nd induction: Days 1-2). Pts achieving complete remission (CR) or CR with incomplete platelet or neutrophil recovery (CRi) could receive ≤2 consolidations.

Results: CPX-351 had longer median OS and higher remission rates vs 7+3 irrespective of baseline BM blast percentage; median OS was worse in higher blast groups for both treatments (Table). The incidence of grade ≥3 TEAEs was >80% for both arms; febrile neutropenia was the most common. Pts achieving CRi had inferior OS compared to CR pts. OS and CR rates were inferior in patients with sAML compared to those with de novo disease.

Phase II trial of CPX-351 (cytarabine:daunorubicin) liposome injection in patients with acute myeloid leukemia who have been treated with intensive chemotherapy. First Author: Ellen K. Ritchie, Weill Cornell Medical College of Cornell University, New York, NY

Background: This study enrolled older patients without age limitation to intensive chemotherapy with CPX 351 allowing for prior treatment with low intensity regimens for MDS or AML. Methods: 30 patients aged ≥65yrs with diagnosed AML received up to two induction cycles and consolidation cycles of CPX-351 as a first-line chemotherapy. Secondary efficacy endpoints included response rate and duration, and assessment of the relationship between cognitive function and treatment outcome. Although the primary efficacy endpoint is pending, these interim results describe promising primary safety and efficacy endpoint results. Of the 30 patients enrolled, 10 patients (33.3%) were ≥75yrs old, 13 patients (43.3%) had had previous hematologic malignancies, 17 patients (56.6%) had adverse ELN risk stratification, and 16 patients (53.3%) had failed to respond to previous non-intensive treatments. In addition, all patients had an average of 2.1 co-morbid medical conditions. Results: 14 patients (47%) achieved best response criteria, with 12 patients (40.0%) achieving complete remission (CR) and 2 patients (6.6%) achieving complete remission with incomplete platelet or neutrophil recovery (CRi). 6 patients (20%) had a morphologic leukemia free state with pancycopenia and 10 patients had persistent disease. 8 patients (26.6%) went to stem cell transplant, 2 patients (6.6%) died within 30-days. Although final analysis on adverse events data is pending, 6 patients (20%) experienced a Grade 2 decrease in left ventricular ejection fraction (LVEF) at the end of first induction. Conclusions: These results suggest that in elderly AML patients regardless of age and prior treatment with non-intensive chemotherapy, CPX-351 can be treated safely with CPX 351 with low 30 day mortality. CR in these patients is 40% with 26% going forward to stem cell transplant. Complete data will be assessed for OS and rate of MRD positivity. The relationship of cognitive and social factors to outcome will also be addressed.

The Transplant Optimization Program (TOP): Implementing a geriatric assessment and guided intensive chemotherapy (HCT) in older adults. First Author: Benjamin A. Derman, University of Chicago Medical Center, Chicago, IL

Background: Limitations found on GA correlate with worse outcomes after HCT, but no data exists on prospectively utilizing GA prior to HCT. We established the TOP IDC in March 2013 to implement a cancer-specific GA and an IDC to risk-stratify candidates 60+yrs prior to HCT. The IDC consisted of a HCT physician, advanced oncologist to devise a pt specific optimization strategy. We compared consecutive HCT pts age 60+ years undergoing GA prior to TOP IDC implementation (pre-TOP) from 2005-2012 (n=75) to TOP from 2013-2018 (n=86). Results: 3/89 HCT pts 60+yrs who did not attend TOP were excluded; all 3 died before 1 year post-HCT. Compared with controls, the TOP group was older (median age 67 vs 64 yrs, p<0.001) but was similar in HCT-CI (3% vs 48%, p=0.2), use of myeloablative regimens (20% vs 19%, p=0.8), and advanced ASBMT risk disease (46% for both). Relative to the pre-TOP group, TOP pts at baseline had fewer impairments in independent activities of daily living (30% vs. 48%, p=0.02) and fewer frail 4-meter walk tests (7% vs. 31%, p=0.001). Pts undergoing optimization in TOP fared better versus pre-TOP (Table). 1-yr non-relapse mortality (NRM) and 1-yr overall survival (OS) continued to improve including 11% NRM and 89% OS in 2017. Conclusions: A GA-guided interdisciplinary optimization clinic for allograft recipients age 60+ reduced transplant associated morbidity and mortality, with marked improvements in NRM and OS over time. A GA-based IDC can facilitate selection and optimization of older pts considering HCT.

Outcomes of HCT recipients age ≥60: pre-TOP vs TOP.
### 7046 Poster Session (Board #421), Mon, 8:00 AM-11:00 AM

#### Late infectious complications in hematopoietic cell transplantation survivors.

**First Author:** Eric Jessen Chow, Fred Hutchinson Cancer Research Center, Seattle, WA

**Background:** Infections are a major complication of hematopoietic cell transplantation (HCT). Few studies have compared the incidence of late infections occurring ≥2y post-HCT to other cancer patients and the general population. **Methods:** Single center records of ≥2y HCT survivors who were Washington residents treated from 1992-2009 (n=1,792; median age 46y; 53% allogeneic; 90% hematologic malignancies) were linked to the state’s hospital discharge and death registry files. Individuals were randomly selected from the state cancer registry (n=5,455, non-HCT) and driver’s license files (n=16,340, DOL) who survived ≥2y formed two comparison groups, matched on sex, age, year, and cancer diagnosis (non-HCT group only). Based on hospital and death registry codes, incidence rate ratios (IRR) with confidence intervals (CI) of infections by organism type and organ system were estimated using Poisson regression. **Results:** With 6y (range 2-20) median follow up, the incidence rate (per 1000 person-y) of all infections was 65 in HCT survivors vs. 40 in the non-HCT group (IRR 1.6, 95% CI 1.3-1.9). In contrast, the DOL group’s infection rate was 7 (V= DOL IRR 10.0, 95% CI 8.3-12.1). Specifically, upper respiratory, and musculoskeletal infections between these 2 groups were 19-28% (p < 0.05). Among potentially vaccine-preventable organisms, the IRR was 3.2 (95% CI 2.2-4.6). While the absolute incidences decreased with time, the relative risks in almost all categories were even greater when re-stricted to ≥5y HCT patients. The incidence of respiratory infections was 20% higher in HCT vs non-HCT cancer survivors (IRRs 1.7; p < 0.01). Differences in viral infection rates were more modest (IRR 1.4, p = 0.07). Infections attributed to staphylococcus, streptococcus, and non-Candida fungi including Aspergillus were twice as common in the HCT vs. non-HCT cancer survivors (IRRs 1.5; p < 0.01).**Conclusions:** Reducing the incidence of infections by organism type and organ system in HCT survivors is possible. Providers caring for long-term HCT survivors should maintain high vigilance for infections in this population and ensure adherence to HCT antimicrobial prophylaxis and vaccination guidelines.

### 7047 Poster Session (Board #422), Mon, 8:00 AM-11:00 AM

#### Allogeneic stem cell transplantation (AllSCT) for patients (pts) with acute leukemia following venetoclax-based therapy.

**First Author:** Akash Mukherjee, The University of Texas MD Anderson Cancer Center, Department of Stem Cell Transplantation and Cellular Therapy, Houston, TX

**Background:** BCL-2 inhibitor Ven has shown a promising benefit in pts with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). There is paucity of information about the safety and efficacy of AllSCT post Ven. **Methods:** We conducted a retrospective analysis of 35 ALL/AML pts who received AllSCT following venetoclax-based therapies between 2013-2018 at MDA. **Results:** Median age at AllSCT was 60 years and 15 (43%) pts had an age-adjusted HCT-CI score ≥ 4. Disease diagnosis – AML (n = 31; 89%), ALL (n = 4; 11%). Disease status at transplant was CR1 (n = 17; 49%), CR2/CR3 (n = 9; 26%) or refractory (n = 9; 26%). 22 (63%) CR pts were MRD-negative. Median of # prior therapies was 2 (range 1 - 7) and 4 (11%) pts had failed a prior AllSCT. AllSCT pts were classified by ELN 2017 criteria to have favorable, intermediate and adverse risks in 16%, 23% and 61% respectively. Ven was provided in combination of hypomethylating agents (HMAs) or other chemotherapy regimens in 26.74% (9) and 9 (26%) pts, respectively. Among pts treated with Ven + HMA, some also received IDH1/2 inhibitors (n = 7, 20%), FL3 inhibitors (n = 4; 11%) or anti-PD1 (n = 3, 9%). Median duration of Ven-based treatment was 2 months (range 0.5-4.6). Ven was discontinued in 6 (17%) pts due to adverse events (n = 1) or progression (n = 2). The remaining 18 (63%) continued stem cell therapy as a bridge to AllSCT. The median time from last Ven dose and transplant was 26 days. Conditioning regimens were melphalan-based reduced intensity (n = 26, 74%), or busulfan-based myeloblastic regimens (n = 9, 26%). Donor source was matched-unrelated (n = 14, 40%), related (n = 9; 26%) or haplo (n = 12; 34%). GVHD prophylaxis consisted of tacrolimus with either PT-Cy in 25 (71%) pts or methotrexate in 10 (29%) pts. All pts engrafted (median day 30 donor cells = 100%). Median days to ANC > 500 and platelets > 20k was 19.5 and 22.5 respectively. With a median follow up of 5.7 months (range 0.7-15.4), the 3 year rates of OS, PFS, and NRM were 71%, 63% and 3% respectively. CI of acute grade 2-4 and 3-4 GVHD were 26% and 3% respectively. Four pts died: 3 because of disease relapse and 1 of infection. **Conclusions:** AllSCT is a safe and feasible post Ven-based treatment option in acute leukemia pts who were pre- treated with Ven, without excessive risk of NRM or acute GVHD. Larger prospective studies are required to validate our observations.

### 7048 Poster Session (Board #423), Mon, 8:00 AM-11:00 AM

#### Rapid reduction of peripheral blasts in older patients with refractory acute myeloid leukemia (AML). Using re-induction with single agent anti-CS1 targeted iodine (131I) amastimatpab (Iomab-B) radioimmunotherapy in the phase III SIERRA trial.

**First Author:** Ben Kent Tomlinson, Adult Hematologic Malignancies and Stem Cell Transplant Section, Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, OH

**Background:** The SIERRA trial is a prospective, randomized, phase 3, open-label, ongoing multicenter trial for patients aged ≥55 years with active, relapsed/refractory (R/R) AML evaluting allogeneic hematopoietic cell transplantation (HCT) versus conventional care (CC). Recent preliminary data demonstrated robust donor engraftment in all patients treated with Iomab-B (Blood 2018 132:1017) despite active disease. We hypothesized that compared to CC, HCT survivors will have a significantly increased incidence of infections vs. matched non-HCT cancer survivors. Providers caring for long-term HCT survivors should maintain high vigilance for infections in this population and ensure adherence to HCT antimicrobial prophylaxis and vaccination guidelines.

**Results:** Majority of patients (79%) in the CC arm did not achieve CR and the study allowed ongoing multicenter trial for patients aged ≥55 years with active, relapsed/refractory (R/R) AML. This significant reduction of leukemia burden followed by successful engraftment was due to rapid disease resolution with the presence of the corresponding ligand in the pt. The 210 pts who had ≥2 inhibitory or activating KIRs or KIR haplotype (A or B) and the probability of relapse after SCT was calculated using Fine-Gray regression and adjusted for disease risk index, remission status, pre-SCT MRD, conditioning regimen and presence of HLA-DP mismatch. KIR-ligand (K-L) match was defined as the presence a given KIR in the donor and the presence of its reported ligand in the patient (ex: ZDL1 and HLA-C2). KIRs that have no known ligands were not included in this analysis. In the case of KIR haplotypes and K-L matches, **Results:** There was no correlation between the number of inhibitory or activating KIRs or KIR haplotypes (A or B) and the probability of relapse after SCT. However, donor KIRs had a dramatic effect on relapse when they were considered together with the presence of the corresponding ligand in the pt. The 210 pts who had ≥3 inhibitory K-L matches had a significantly higher probability of relapse (HR=1.748, CI=1.147-2.667, p=0.009) than the remaining 180 pts. Similarly, the 96 pts who had at least one activating K-L match had a lower probability of relapse (HR=0.581, CI=0.345-0.978, p=0.04). When we considered inhibitory and activating K-L matches together, we found that the 168 pts who had ≥3 inhibitory and no activating K-L matches had a significantly higher probability of relapse (HR 2.001, CI=1.376-2.908, p<0.001) than the 222 remaining pts. Conclusions: Donor KIR ligand matching should be taken into account when choosing unrelated donors for AML pts.
7050 Poster Session (Board #425), Mon, 8:00 AM-11:00 AM
Mast cells as mediators of fibrosis and effector cell recruitment in dermal chronic graft-versus-host disease. First Author: Ethan Statton, University of Kentucky, Lexington, KY.

Background: Allogeneic hematopoietic stem cell transplantation (allo-HCT) is a potentially curative treatment for patients with malignant neoplasms or inborn defects of hematopoiesis. Benefits of allo-HSCT are hampered by graft-versus-host disease (GVHD), which can be debilitating and potentially lethal. In chronic GVHD (cGVHD), inflammation and aberrant wound healing lead to pathological fibrosis across multiple organs, most frequently in the skin. While the exact pathophysiology is not well-understood, mast cells (MCs) are primarily known for their role in atopic disease. However, recent studies have demonstrated new roles for MCs, showing that they can be involved in wound healing and in the pathogenesis of fibrotic disease. Given these new paradigms and the MC tropism to skin, alongside their reported role in other fibrotic diseases, we investigated whether MCs may play a role in the pathogenesis of dermal cGVHD.

Methods: Cells: MCs were grown ex vivo from murine bone marrow. Transplant: B6 by radiation, followed by injection of LPJ marrow and splenocytes into C57BL/6J (WT) or B6.Cg-Ki6-/- MC-deficient recipients. Results: Ex vivo, we show that MCs survive and are functional after lethal irradiation, such that MCs from MC-deficient mice had reduced expression of CD11b, a marker on mature MCs, and reductions: pleural effusion 3; myalgias 1. Four patients had dasatinib dose reductions: myalgias 1; myalgias 1, and pregnancy 2. Four patients had dose interruptions: pleural effusion 4 (possibly related 3, unrelated 1). In a murine model of cGVHD WT mice had significantly more cGVHD symptoms than MC-deficient mice as measured by clinical scoring. This scoring correlated with a significant increase in skin pathology, collagen deposition, and expression of pro-fibrotic genes in WT as compared to B6.Cg-Ki6-/- mice. Dermal MC numbers were increased in WT mice, but were decreased in MC-deficient mice, implying that the MCs that are present were recipient-derived and had survived conditioning. Skin from WT but not B6.Cg-Ki6-/- mice was enriched in gch6 effector cells and in inflammatory cytokines and chemokines. Murine MCs, upon stimulation were sources of many of these factors, production of which were blocked when treated with MC inhibitors and fumarates, drugs used in cGVHD treatment.

Conclusions: In summary, we show here a previously unknown role for MCs in the pathogenesis of dermal cGVHD, suggesting that MCs may be targetable to prevent and treat this devastating complication of allo HCT.

7052 Poster Session (Board #427), Mon, 8:00 AM-11:00 AM
Update on lower-dose dasatinib 50 mg daily as frontline therapy in newly diagnosed chronic phase CML-CP. First Author: Ethan Strattan, University of Kentucky, Lexington, KY.

Background: Dasatinib, a potent BCR-ABL tyrosine kinase inhibitor (TKI), is approved for the treatment of chronic phase CML (CML-CP) in the frontline and salvage settings. Notable side effects include pleural effusions and myelosuppression. Previously we reported dasatinib 50 mg daily to be active and better tolerated than the approved 100 mg daily dose (CANCER. 2018 Jul 1;124(13):2740-2747). We present an update on the efficacy and toxicity profile of lower dose dasatinib 50 mg orally daily in patients with early CML-CP.

Methods: All patients presenting to our institution in early CML-CP were eligible for the study. Patients were excluded if they had prior TKI therapy or had been treated with dasatinib previously (toxicity or efficacy). Dose-escalation was performed according to our institutional dosing and toxicities were recorded. Dose-escalation was performed according to our institutional dosing and toxicities were recorded. Side effects were classified according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0).

Results: From March 2016 to March 2018, 81 patients have been enrolled. Median age was 47 years (20-84). Patients categorized by Sokal risk are: low 53; intermediate 22 and high 6. Median follow-up is 18 months (9-31). Cumulative response rates over time are shown below: At 3 months, 96% patients achieved early molecular response (BCR-ABL PCR <10%). Median time to CCyR was 4.6 months, MMR 6.0 months, MR4.11.4 months and MR5.12.2 months. Eighteen patients had treatment interruption; pleural effusion 4 (possibly related 3, unrelated 1 due to pneumonia); gastrointestinal bleed 2; thrombocytopenia 3; transaminases 2; renal dysfunction 1; asthma exacerbation 1; pneumonitis 1; lower extremity edema 1; myalgias 1; and pregnancy 2. Four patients had dose reductions: pleural effusion 3; myalgias 1. Four patients had dasatinib dose increased to 100mg; lack of CCyR at 6 months, 3; lack of MMR at 12 months, 1. Four patients are off study: no response 2, pneumonitis 1, and insurance 1. None of the patients have transformed or died.

Conclusions: These updated results continue to support dasatinib 50 mg daily as an effective and safe dose for early CML-CP. Clinical trial information: NCT02689440.

7051 Poster Session (Board #428), Mon, 8:00 AM-11:00 AM
Cardiovascular, and hypertension safety of bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia in the BFORE trial. First Author: Jose E. Cortes, The University of Texas MD Anderson Cancer Center, Houston, TX.

Background: Tyrosine kinase inhibitor therapy has been linked to cardiac and vascular events. Cardiovascular and hypertension treatment-emergent adverse events (TEAEs) with bosutinib or imatinib for newly diagnosed chronic phase chronic myeloid leukemia were analyzed. Methods: Patients (pts) who received ≥1 dose of bosutinib (n = 268) or imatinib (n = 265) 400 mg in the patients from the BFORE trial were included. Prespecified MedDRA terms comprised the clusters of investigator assessed TEAEs. Exposure-adjusted TEAE rate was defined as the number of pts with TEAEs/total pt-yr (pt-yr = sum of total time to first TEAE for pts with TEAEs and treatment duration for pts without TEAEs).

Results: After ≥36 mo follow-up, 65% vs 62% of pts in the bosutinib vs imatinib arm were still on treatment. Rates of TEAEs, treatment withdrawals and drug-related TEAEs in the clusters of interest were low in both arms (Table). The most common cardiac, vascular and hypertension TEAEs, respectively, were sinus bradycardia (2%), angina pectoris (3%) and hypertension (7%) vs prolonged QT (3%), peripheral coldness (1%) and hypertension (9%) with imatinib vs imatinib; corresponding grade ≥3 TEAE rates in the respective clusters were 3%, 3% and 4% vs 1%, 0.4% and 4%. Hypertension was the only grade 3/4 TEAE occurring in ≥1% of pts in either arm (4% each); 1 grade 5 TEAE each was noted for bosutinib (cardiac failure) and imatinib (cerebrovascular accident). Exposure-adjusted rates of cardiac, vascular and hypertension TEAEs were similar between arms, respectively, were 0.04, 0.03 and 0.008 vs 0.03, 0.01 and 0.04 (grade 3/4 only: 0.01, 0.02 vs 0.01, 0.002 and 0.02) for bosutinib vs imatinib. Conclusions: Cardiovascular, and hypertension TEAE rates were low with bosutinib and imatinib. A majority of TEAEs were low grade and few led to treatment withdrawal. Clinical trial information: NCT02130557.

7053 Poster Session (Board #428), Mon, 8:00 AM-11:00 AM
Discrepancy of blast percentage between the bone marrow aspirate and biopsy in patients with myelodysplastic syndromes excess blast (MDS-EB). First Author: Meera Yogojarah, Mayo Clinic, Rochester, MN.

Background: The revised International Prognostic Scoring System (IPSS-R) aids in prognosticating MDS. The percentage (%) of blasts in the bone marrow is one of the major determinants of the scoring system. The aspirate blast % is utilized as the standard of care, but there are discrepancies in the blast % reported by the aspirate and the biopsy. We aim to study the possible use of bone marrow biopsy blasts in MDS-EB in calculating IPSS-R.

Methods: The MDS database was reviewed for cases of MDS-EB after due IRB approval. We calculated IPSS-R scores based on the aspirate blast % (IPSS-RAsp) and biopsy blast % (IPSS-RBx). The biopsy blast % was reported morphologically or by the 5334 stain. Where a range was reported the highest value was utilized as the blast %. Suboptimal aspirates were excluded from the study. The overall survival (OS) was determined by IPSS-RAsp, IPSS-RBx and IPSS-R highest blast (IPSS-RHi). OS estimates were calculated by Kaplan-Meier curve and log-rank testing using JMP software, Concordance statistic was used to compare all 3 risk scoring systems.

Results: Of 1322 patients, 431 (33%) cases were identified with MDS-EB; out of which 173 cases had both blasts reported in the biopsy and the aspirate. Out of 173 cases, 35 (20%) had MDS-EB1, and 61 (35%) had MDS-EB2 based on both biopsy and aspirate (concordant cases). Seventy seven (45%) patients changed from EB1 to EB2 or vice versa based on the biopsy blast (44/77 (57%) cases were upstaged). The OS outcomes based on the IPSS-RAsp biopsy showed a clear and meaningful separation with median OS decreasing with increased risk but IPSS-RBx and IPSS-RHi did not (Table). We compared the 3 models for observed OS differences using the Uno model and there was no statistically significant difference. Conclusions: IPSS-RAsp (but not IPSS-RBx and IPSS-RHi) identified prognostic groups for OS with median OS decreasing with increased risk. The small sample size may have led to an insignificant effect on model power by Uno model. This finding needs to be validated by other centers.

IPSS-R Risk groups Low Intermediate High Very high P value Uno concordance
IPSS-R Asp
Median OS, months
24.8 41.5 21.9 9.2 0.0011
Asp-Bx (P=0.6)
IPSS-R Bx
Median OS, months
47.5 39.3 21.9 8.3 0.0001
IPSS-R Bx (P=0.8)
R-IPSS Hi
Median OS, months
31.6 41.5 25.5 9.2 0.0001
Hi- Asp (P=0.4)

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Patterns of leukemic transformation in patients with TP53-mutant myelodysplastic syndromes. First Author: Kelly Sharon Chien, The University of Texas MD Anderson Cancer Center, Division of Hematology, Houston, TX.

Background: TP53 is the most frequently mutated gene in human cancers including 7-13% of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) patients. Although it is associated with transformation to AML in patients with MDS, the additional genomic events leading to transformation are poorly understood. Methods: We retrospectively evaluated 312 patients with TP53-mutated AML or MDS diagnosed between 2013-2016. Patient characteristics and bone marrow data, including cytogenetic and next generation sequencing information, were assessed at the time of diagnosis and progression to AML. Results: There were 151 TP53-mutated MDS patients and 161 TP53-mutated de novo AML patients with a median follow-up time of 34.1 months. Forty-one patients with TP53-mutated MDS transformed to AML. Sequencing data at transformation was available in 17 patients (41%). At diagnosis, median age was 67 with 2 patients with intermediate-risk, 7 patients with high-risk, and 32 patients with very high-risk MDS by IPSS-R. Complex karyotype was seen in 40 patients, and 12 patients had 1, 25 patients had 2, and 4 patients had 3 TP53 abnormalities. Predictors of transformation to AML include TP53 losses of heterozygosity (p = 0.008), 3 TP53 abnormalities (p = 0.049), complex cytogenetics (p = 0.023), and female gender (p = 0.002). Median time to transformation was 10.4 months. At transformation, an increase in TP53 variant allelic frequency was observed in 7 patients (41%), and new mutations, particularly with TP53, were acquired by 10 patients (59%). Cytogenetic abnormalities were poor in 12 patients, and new clones in 8 patients. Patients with TP53-mutated AML from MDS also had worse median overall survival than patients with TP53-mutated de novo AML at 2.5 months vs. 5.7 months respectively (p = 0.001). Conclusions: TP53 mutations confer a worse prognosis, especially in the setting of AML transformed from MDS. This may be due to the acquisition of new mutations and cytogenetic abnormalities. Further exploration of the biological mechanisms leading to transformation in TP53-mutant MDS is warranted.

Fedatrain (FEDR) in myelofibrosis (MF) patients previously treated with ruxolitinib (RUX): A multi-center, open-label, single-arm, phase II study. First Author: Marina Kremyanskaya, Mount Sinai School of Medicine, New York, NY.

Background: BETi have been shown to regulate NF-κB, MYC, BCL2, and TGF-β signaling, important drivers of marrow fibrosis. Preclinical studies have suggested that combined BETi and JAK2 inhibition synergistically reduce MF-related splenomegaly, bone marrow fibrosis and the malignant allele burden (Kleppen, 2018). CPI-0610 is a selective and potent oral BETi, being evaluated in the first study of a BETi in MF. Methods: Phase 2 trial with 3 arms: CPI-0610 monotherapy (Arm 1) or RUX + CPI-0610 “add-on” (Arm 2) in pts who have progressed/ had an inadequate response to RUX, or CPI-0610 + RUX in JAK inhibitor-naive pts with anemia (Arm 3). Arms 1 and 2 are stratified by progression-free survival (PFS) dependence (TDF): yes: A/no: B. The primary objectives are to evaluate the effect of CPI-0610 on transfusion dependence (TD, 1A and 2A) and spleen volume (1B, 2B and 3). A Simon two-stage design: if 2 responses are seen will advance to the 2nd stage. Results: 4 pts enrolled in Arm 1, 14 pts in Arm 2, no pts accrued to Arm 3 yet. Median age: 69 years (46-83), gender: 9 male pts; 11 pts received ≥1 prior therapy besides RUX. JAK2/MPL/CAJR substitutions; 17/18 pts, ≥3 mutations: 10 pts, ASXL1 mutations: 11 (61%) pts. Hemoglobin <10 g/dL at baseline: 11 (61%) pts. 6 pts received ≥24 weeks of CPI-0610 treatment at this analysis. 2 TD pts in Arm 2 became transfusion independent, both remain on treatment free of transfusions. Hgb increase of ≥1.5 g/dL from baseline was observed with successive cycles of therapy in Arm 1: 2/2 evaluable pts had marrow fibrosis improvement with Hgb increase; additionally, thrombocytosis resolved in 2/2 pts (baseline ≥791 10³/uL). Most common adverse events were mild diarrhea, nausea/vomiting; and reversible and non-cumulative thrombocytopenia. Conclusions: CPI-0610 is a well-tolerated, and an effective therapeutic agent for the treatment of MF. Collectively, these data indicate that CPI-0610 +/- RUX might affect disease manifestations. Updated data will be provided. Clinical Trial Information: NCT02158856.
Background: Patients with chronic myelomonocytic leukemia (CMLM) have historically poor outcomes, with ~6–7 mos median OS in relapsed/refractory (r/r) setting. Spleenomegaly is a poor prognostic factor and potential target in CMLM. CD123 is detected on blasts, monocytes, and neoplastic micro-environmental plasmacytoid dendritic cell (pDC) infiltrates part of the CMLM malignant clone (Solary, et al). Tagraxofusp, a novel CD123 targeted therapy, demonstrated high levels of activity in BPDNC, an aggressive hematologic malignancy derived from CD123-expressing pDCs, and is FDA approved in BPDNC. As such, tagraxofusp may offer a novel approach in CMLM.

Methods: Multicenter, 2-stage Ph I/II enrolling patients (pts) with r/r CMLM. Objectives: determine optimal dose, evaluate safety and efficacy. Stage 1 dose escalation: IV tagraxofusp (7, 12, and 19 mcg/kg/day) dosed daily days 1-3 every 21 days (C1-4), 28 days (C5-7), and 42 days (C8+). Stage 2 (ongoing), pts receive optimal S1 dose (12 mcg/kg/day; no MTD). Results: 20 pts (12 CMLM-1; 8 CMLM-2) enrolled. 18 pts 2nd-line (2 pts in 1L), HMMs most common prior therapy. Median age 69 (43-80); 81% male. 11 (55%) had baseline spleen >5cm (by physical exam) of 2-27 cm. Most common TRAEs: hypoalbuminaemia (35%), thrombocytopenia (35%), nausea (30%), vomiting (30%), and fatigue (20%). Most common Gr3 TRAEs were thrombocytopenia (35%) and nausea (5%). Capillary leak syndrome in 3 pts (15%); all Gr4 (100%; 10/10). ALT incr. (17%) and thrombocytopenia (17%). Most common =Gr3 TRAE thrombocytopenia (2%). Capillary leak syndrome in 1 pt (4%; Gr3). 57% (8/14) of pts with baseline spleen ≥5cm BCM spleen responses: 43% (6/14) had ≥29% and 21% (3/14) had ≥45% reduction. 100% of pts with baseline spleen ≥5cm and monocytes splenomegaly reductions: 80% (4/5) had reductions ≥50% and 40% (2/5) had ≥45%, 6 pts (3 monocytes pts and 5 pts platelets <100 K/uL) had 6 mos+ duration, 9 pts ongoing. Conclusions: Tagraxofusp demonstrated single agent activity (reduction in splenomegaly) and manageable safety in R/R MF, including pts ongoing.

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Background: FLT3-ITD is one of the most common genetic lesions in acute myeloid leukemia (AML). PIM kinases are oncogenic. FLT3-ITD targets expressed in AML cells and increased PIM kinase expression is found in relapse samples from AML patients treated with FLT3 inhibitors. In addition, inhibition of PIM kinases restores sensitivity to FLT3 inhibitors and dual FLT3/PIM inhibition eradicates FLT3-ITD+ cells including primary AML cells. SEL24/MEN1703, a potent PIM/FLT3 dual inhibitor, demonstrates a significantly broader spectrum of activity in AML cell lines and primary AML blasts, irrespective of FLT3 status, compared to monotherapy with either FLT3 or PIM inhibitors such as quizartinib or AZD1208. Methods: CL124-001 is a First in Human, open label, non-randomized, multi-center, Phase II dose-escalation and cohort expansion study of SEL24/MEN1703 in AML patients (excluding APL) not suitable for chemotherapy. SEL24/MEN1703 is given orally, QD, for 14 days in a 21-day cycle with cycles repeated until disease progression or unacceptable toxicity. Dose escalation follows a 3+3 design to identify the recommended phase 2 dose (RP2D). In the phase 2 part/cohorts expansion, subjects will receive SEL24/MEN1703 at the RP2D for further investigation of safety and efficacy. In both study parts, patients are eligible regardless of mutational status and/or prior exposure to FLT3 inhibitors; prior treatment with PIM inhibitors is not allowed. Main inclusion criteria comprise a white blood count (WBC) of ≤30 x 10⁹/L (hydroxyurea/leukopenia permitted to lower WBC) and ≤30% of blast cells. Additional exclusions include pharmacokinetics (PK) single-agent efficacy. The study is enrolling at 5 US sites and will be extended, both in US and EU, in the cohort expansion part. This is the first trial testing a dual PIM/FLT3 inhibitor with the potential to be active in AML regardless of FLT3 status and with a potential to overcome FLT3 inhibitor resistance. (Sci Adv. 2015;1:e1500022; Oncotarget. 2018 Mar 30;9(24):16917-16931) Clinical trial information: NCT03008187.

TPS7062 Poster Session (Board #436b), Mon, 8:00 AM-11:00 AM
MIRROS: An ongoing randomized phase 3 trial of idasanutlin + ARA-C in patients with relapsed or refractory acute myeloid leukemia. First Author: Pau Morasinos, Hospital Universitari i Politècnic La Fe, Valencia, Spain; CIBERONC, Instituto Carlos III, Madrid, Spain
Background: The prognosis for patients (pts) with relapsed or refractory (R/R) acute myeloid leukemia (AML) is poor, with 3-year overall survival rates –10–30% after intensive chemotherapy-based approaches. Despite the advent of targeted therapies, considerable unmet medical need remains in this population. Idasanutlin (RG7388, R5053781) is an orally available small molecule that binds to the murine double minute 2 (MDM2) protein and blocks MDM2 interaction with p53. This stabilizes and activates p53 and facilitates cell cycle arrest and apoptosis, preventing tumor growth. A phase 1b study of idasanutlin + ARA-C in pts with R/R AML, irrespective of TP53 mutation status (NCT01773408), has shown a complete composite remission (CR) rate (CR plus CR with incomplete platelet or hematologic recovery) of 29% (Martinelli et al. 2016). Methods: MIRROS (NCT02545283; WO29519) is an international, phase 3, double-blind, randomized study comparing idasanutlin (300 mg bid) + ARA-C (1 g2/m² qd) days 1–5 versus placebo + ARA-C in 440 pts with first or second R/R AML, with or without TP53 mutation. The primary end point is overall survival (OS) and secondary end points include OS, duration of response, and partial response (PR) rate. Exploratory endpoints include CR, overall remission rates, event-free survival (EFS) and percentages of pts undergoing hematopoietic stem cell transplantation. MIRROS integrates phase 2 trial methodology into the phase 3 design by incorporating an interim analysis (IA) in 120 pts with WT TP53, using a high bar for the odds ratio to define durable CR and EFS to assess for futility. Additional gating criteria for safety were also implemented. The IA was performed by an independent data monitoring committee and study continuation criteria were successfully met in mid-2017. This innovative strategy has allowed acceleration of the idasanutlin development program while maintaining a robust trial design. (NCT02545283; WO29519). Clinical trial information: NCT02545283; WO29519.

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A phase III trial to evaluate the efficacy of uproleselan (GMI-1271) with chemotherapy in patients with relapsed/refractory acute myeloid leukemia. First Author: Daniel J. DeAngelo, Dana-Farber Cancer Institute, Boston, MA

Background: Binding of E-selectin (E-selectin) to sialic Le^5 (E-selectin ligand (E-select-L)) on the leukemic cell surface activates cell survival pathways and promotes chemotherapy resistance in AML. Expression of E-select-L is associated with increased relapse and poor survival. Uproleselan (GMI-1271), a novel E-select-L antagonist, disrupts cell survival pathway activation, enhances chemotherapy response and protects from toxicity such as mucositis with improved survival in vivo. Preclinical data support combination with multiple agents to achieve improved chemosensitivity and toxicities. A phase III study of uproleselan added to chemotherapy in R/R AML showed promising remission rates (CR/CRI) and survival outcomes, and reduced rates of mucositis. High E-select-L expression on leukemic blasts in the bone marrow, rather than connoting treatment resistance and poor survival, instead correlated with longer survival than expected with addition of uproleselan. Breakthrough Therapy Designation was granted by FDA for treatment of patients with R/R AML. A pivotal phase 3 study (NCT03616470) is underway to assess the efficacy and safety of uproleselan with standard salvage chemotherapy in R/R AML. Methods: This study is a global, randomized, open-label, Phase 3 trial. All patients aged 18-75 years with R/R AML and fit for chemotherapy. Patients may have primary refractory AML (received 1 prior induction containing an anthracycline and cytarabine), or be in untreated first or second relapse; prior HSCT is allowed. Treatment is MEC -TKIs, crenolanib and midostaurin, combined with chemotherapy in newly diagnosed (NDx) acute myeloid leukemia (AML). Crenolanib is a potent pan-FLT3 inhibitor that has shown promising efficacy and tolerability in combination with chemotherapy in Phase 1/2 trials for AML patients with FLT3-ITD or -TKD mutations. This is the first globally initiated, randomized Phase 3 trial comparing the efficacy of two FLT3-TKIs, crenolanib and midostaurin, combined with intensive chemotherapy in NDx FLT3-mutated AML patients. Methods: This Phase 3, randomized, multi-center trial will be conducted at multiple sites worldwide, with a target enrollment of 510 subjects. Patient inclusion was modified to match the midostaurin RATIFY criteria to enroll NDx FLT3-mutated AML (18-60 yr), who are eligible for intensive chemotherapy; with the addition of any FLT3-ITD and/or -TKD mutations being eligible. All subjects will receive TKI treatment and will be randomized in a 1:1 ratio to receive either crenolanib (arm A) or the active-control, midostaurin (arm B). All patients will be treated with 7-13 (100 mg/m^2 IV cytarabine; 90 mg/m^2 IV daunorubicin) and can initiate treatment while awaiting FLT3 results prior to randomization. Consolidation could include chemotherapy (3000 mg/m^2 IV HiDAC) for up to 4 cycles and/or Allo-HSCT, depending on patient condition. During induction and consolidation patients on arm A will take crenolanib (100 mg TID) from d9 until 72h prior to the next cycle, and patients on arm B will take midostaurin (50 mg BID) on d8 to d21 of each cycle. Following consolidation or HSCT, patients may receive up to 12 months of FLT3-TKI maintenance. Maintenance efficacy will be evaluated over time using single-cell sequencing to assess MRD. Primary endpoint is event-free survival. Interim analyses will occur at approximately 178 and 267 events, and primary analysis at 356 events. Enrollment is underway as of January 31, 2019. Clinical trial information: NCT03258931.

Crenolanib versus midostaurin combined with induction and consolidation chemotherapy in newly diagnosed (NDx) acute myeloid leukemia (AML). First Author: Richard M. Stone, Dana-Farber Cancer Institute, Boston, MA

Background: Despite the approval of multi-targeted protein kinase inhibitor midostaurin for use in combination with chemotherapy which improves 5-year survival in newly diagnosed (NDx) acute myeloid leukemia (AML) associated with FLT3 mutations; the cumulative incidence of relapse in FLT3 mutant AML remains high, with progression often characterized by secondary FLT3-TKD mutations. Crenolanib is a potent pan-FLT3 inhibitor that has shown promising efficacy and tolerability in combination with chemotherapy in Phase 1/2 trials for AML patients with FLT3-ITD or -TKD mutations. This is the first globally initiated, randomized Phase 3 trial comparing the efficacy of two FLT3-TKIs, crenolanib and midostaurin, combined with intensive chemotherapy in NDx FLT3-mutated AML patients. Methods: This Phase 3, randomized, multi-center trial will be conducted at multiple sites worldwide, with a target enrollment of 510 subjects. Patient inclusion was modified to match the midostaurin RATIFY criteria to enroll NDx FLT3-mutated AML (18–60 yr), who are eligible for intensive chemotherapy; with the addition of any FLT3-ITD and/or -TKD mutations being eligible. All subjects will receive TKI treatment and will be randomized in a 1:1 ratio to receive either crenolanib (arm A) or the active-control, midostaurin (arm B). All patients will be treated with 7–13 (100 mg/m^2 IV cytarabine; 90 mg/m^2 IV daunorubicin) and can initiate treatment while awaiting FLT3 results prior to randomization. Consolidation could include chemotherapy (3000 mg/m^2 IV HiDAC) for up to 4 cycles and/or Allo-HSCT, depending on patient condition. During induction and consolidation patients on arm A will take crenolanib (100 mg TID) from d9 until 72h prior to the next cycle, and patients on arm B will take midostaurin (50 mg BID) on d8 to d21 of each cycle. Following consolidation or HSCT, patients may receive up to 12 months of FLT3-TKI maintenance. Maintenance efficacy will be evaluated over time using single-cell sequencing to assess MRD. Primary endpoint is event-free survival. Interim analyses will occur at approximately 178 and 267 events, and primary analysis at 356 events. Enrollment is underway as of January 31, 2019. Clinical trial information: NCT03258931.

A phase I study of midelademetinib in combination with quizartinib in patients (pts) with newly diagnosed (ND) or relapsed/refractory (R/R) FLT3-ITD acute myeloid leukemia (AML). First Author: Navdeep Gidwani, Cancer Therapy Evaluation Program, Houston, TX

Background: Fms-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) mutations occur in ~25% of pts with AML and are associated with poor prognosis. Quizartinib is a highly potent, selective, next-generation type II FLT3 inhibitor. In the phase 3 QUANTUM-R trial, quizartinib prolonged overall survival vs salvage chemotherapy in pts w/R/R FLT3-ITD AML. MDM2 downregulates the p53 tumor suppressor and is overexpressed and is upregulated in pts w/AML. Targeting MDM2 may restore p53 activity in pts w/ wild-type p53 AML. Midelademetinib, a novel and specific MDM2 inhibitor, showed activity in an ongoing phase 1 trial in pts w/AML or myelodysplastic syndromes (MDS). Preclinical studies have shown that quizartinib plus midelademetinib may act synergistically to target FLT3-ITD and restore p53 activity in FLT3-ITD/TPS53 wild-type AML [Andreff et al. ASH 2018, abstract 2720]. Methods: This open-label phase 1 study (NCT03552029) has 2 parts: dose escalation (part 1) followed by dose expansion (part 2), with 2 planned cohorts. Key inclusion criteria include FLT3-ITD AML (primary or secondary to MDS) and adequate organ function, and for pts w/mutated FLT3, -ITD/ -TKD. Key exclusion criteria include acute promyelocytic leukemia, prior treatment with a MDM2 inhibitor, QTcF interval > 450 ms, significant cardiovascular disease, and unresolved toxicities from prior therapies. Dose escalation and expansion cohort 1 includes R/R pts. Expansion cohort 2 includes ND pts unfit for intensive chemotherapy. During dose escalation, quizartinib will be administered once daily (QD) or BID cycles, with 3 proposed levels (30, 40, and 60 mg). Midelademetinib will be administered on days 1-14 of each 28-day cycle, with 3 proposed levels (90, 120, and 160 mg). The quizartinib dose will be escalated first, followed by the midelademetinib dose with no simultaneous escalation, guided by modified continual reassessment method with overdose control. Primary objectives are safety and tolerability, optimum dosing schedule, maximum tolerated dose, recommended dosing for the expansion cohort, and phase 2 dosing. Secondary objectives are pharmacokinetics and preliminary efficacy. This study is recruiting. Clinical trial information: NCT03552029.

A phase II study of myeloablative autologous hematopoietic stem cell transplantation (ahsCT) for acute lymphoblastic leukemia (ALL) in older patients using fludarabine and total body irradiation (Flu/TBI). First Author: Omer Hassan Jami, University of Alabama at Birmingham, Birmingham, AL

Background: Older adults with ALL have poor survival outcomes. Although ahsCT can be curative when used as consolidation after complete remission (CR), advanced age, limited performance status, and comorbidities are risk factors for increased non-relapse mortality (NRM) after myeloablative ahSCT. The 1-year disease free survival (DFS) for patients ≥ 40 years who receive an ahSCT for ALL is often estimated to be 40-50%. Previous studies have demonstrated the efficacy of TBI-based regimens in adults with ALL when combined with cyclophosphamide (Cy). Reduced intensity conditioning for ALL patients has fallen out of favor due to high relapse rate forfeiting the benefit of reduced NRM. High-dose Cy is, however, associated with cardiac, hemoragic and hepatic toxicities. Fludarabine (Flu) has emerged as a safer substitute of Cy (e.g. FluBu replacing BuCy) with favorable toxicity profile. Given the efficacy of TBI-based regimens in ALL, we hypothesized that a myeloablative regimen of Flu/TBI (12 Gy) is as effective as Cy/TBI 12 Gy in older adults with ALL undergoing ahSCT, but with less NRM conferring survival benefit over Cy/TBI 12 Gy. Methods: This study is a single-center, single-arm phase II clinical trial of Flu 40 mg/m^2 IV daily (days -7 to -4) and TBI 2 Gy X2 (days -3 to -1) as myeloablative conditioning for older adults (≥ 40 years old) or younger adults with significant comorbidities with ALL. Patients aged 40-65 years with ALL in CR, KPS ≥ 70, adequate organ function, and having HLA-matched sibling or unrelated donor will be eligible. The primary endpoint of the study is 1-year DFS post-transplant. Secondary endpoints include 1-year overall survival (OS), incidence and severity of acute and chronic GVHD, immune reconstitution and regimen related toxicity. The study has just finished accrual (January 2019) enrolling a total of 16 patients. This number of patients was pre-determined to give a probability ≤ 0.05 of concluding that the 1-year DFS rate exceeds 45%, and a probability of at least 0.80 of concluding that the 1-year DFS rate exceeds 45% (expecting 1-year DFS of 75%). Clinical trial information: NCT01191457.
A multicenter, randomized phase III study of asciminib (ABL001) versus bosutinib in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) previously treated with ≥2 tyrosine kinase inhibitors (TKIs). First Author: Michael J. Mauro, Memorial Sloan Kettering Cancer Center, New York, NY

Background: There is a need for new treatment options for pts with CML who are intolerant/resistant to currently available BCR-ABL1 ATP-binding site targeted TKIs. Asciminib is a potent and specific BCR-ABL1 inhibitor with a novel allosteric mechanism of action targeting the ABL1 myristoyl pocket. This results in a mutation-driven resistance profile different from that of ATP binding-site TKIs, providing potential for both monotherapy and combination therapy with ATP-binding-site TKIs. In a phase 1 study (NCT02081378), asciminib showed clinical activity and good safety/tolerability in CML pts with resistance/intolerance to ≥2 TKIs and in pts with the T315I mutation. The recommended dose for asciminib monotherapy in CML pts without the T315I mutation was established as 40 mg BID. An ongoing phase 3 study (NCT03106779) is evaluating asciminib monotherapy vs bosutinib in pts with CML who have been treated with ≥2 prior ATP-binding-site TKIs.

Methods: Eligible pts are adults with CML-CP who previously received ≥2 TKIs, with intolerance or failure to the most recent TKI. Treatment failure is defined per 2013 European LeukemiaNet (ELN) recommendations. Pts harboring T315I or V299L mutations are excluded. Pts are randomized 2:1 stratified by baseline cytogenetic response status—treatment will be continued for ≥3 months from the time the MTD is determined for each dose level. The primary endpoint is spleen response rate (RR; ≥50% reduction in total symptom score on the Myeloproliferative Neoplasm Response Assessment-2017, including MDSCs, in animal models, in vitro studies, and in patients (Reusch et al. Clin Can Res 2016 and List et al. ASH 2017). Preliminary results from the phase 1 acute myeloid leukemia (AML) trial have demonstrated safety and activity in patients with AML arising from prior MDS (Westerfall et al. ASH 2018). Methods: AMV564-201 is an open label, phase 1, multicenter, dose-escalation with expansion trial of AMV564 in patients with intermediate-2 or high-risk MDS who are refractory to or relapsed from hypomethylating agents (HMAs) or intensive chemotherapy. The key objectives of the dose-escalation stage of the study are to characterize the safety and tolerability of AMV564, identify a maximum tolerated dose and/or a dose-schedule to evaluate in the dose expansion portion of the study. In the dose expansion stage of the study, the safety and tolerability of AMV564 will be further characterized in addition to a preliminary assessment of efficacy. Other objectives include characterization of AMV564 pharmacokinetics, pharmacodynamics, and immunogenic potential. Approximately 80 patients with intermediate-2 or high-risk MDS will be enrolled. The Dose Escalation Stage will include up to approximately 30 patients, depending on the dose at which the MTD is determined for each schedule, and approximately 50 additional patients will be enrolled in the Expansion Stage. AMV564 will be administered daily as a continuous intravenous (CIW) infusion over a period of 24 hours for 14 days in each cycle. Each cycle will be approximately 4 weeks. A lead-in dose regimen will be utilized for all patients treated at dose levels at or above 50 mcg/day. Patients will receive up to 4 cycles of AMV564 treatment at the assigned dose level. Clinical trial information: NCT03516591.

A phase I study of AMV564 in patients with intermediate or high-risk myelodysplastic syndromes (MDS) and is also expressed on immunosuppressive myeloid-derived suppressor cells (MDSCs) that are prevalent in MDS. AMV564 is a novel bivalent, bispecific (2:2) T-cell engager that binds both CD33 and the invariant CD3c on T-cells with strong avidity. AMV564 has significant cytotoxic activity against CD33-positive cells, including MDSCs, in animal models, in vitro studies, and in patients (Reusch et al. Clín Can Res 2016 and List et al. ASH 2017). Preliminary results from the phase 1 acute myeloid leukemia (AML) trial have demonstrated safety and activity in patients with AML arising from prior MDS (Westerfall et al. ASH 2018).

Background: The CD33 antigen is expressed on myeloblasts in approximately 75% of patients with myelodysplastic syndromes (MDS) and is also expressed on immunosuppressive myeloid-derived suppressor cells (MDSCs) that are prevalent in MDS. AMV564 is a novel bivalent, bispecific (2:2) T-cell engager that binds both CD33 and the invariant CD3c on T-cells with strong avidity. AMV564 has significant cytotoxic activity against CD33-positive cells, including MDSCs, in animal models, in vitro studies, and in patients (Reusch et al. Clin Can Res 2016 and List et al. ASH 2017). Preliminary results from the phase 1 acute myeloid leukemia (AML) trial have demonstrated safety and activity in patients with AML arising from prior MDS (Westerfall et al. ASH 2018).

Methods: AMV564-201 is an open label, phase 1, multicenter, dose-escalation with expansion trial of AMV564 in patients with intermediate-2 or high-risk MDS who are refractory to or relapsed from hypomethylating agents (HMAs) or intensive chemotherapy. The key objectives of the dose-escalation stage of the study are to characterize the safety and tolerability of AMV564, identify a maximum tolerated dose and/or a dose-schedule to evaluate in the dose expansion portion of the study. In the dose expansion stage of the study, the safety and tolerability of AMV564 will be further characterized in addition to a preliminary assessment of efficacy. Other objectives include characterization of AMV564 pharmacokinetics, pharmacodynamics, and immunogenic potential. Approximately 80 patients with intermediate-2 or high-risk MDS will be enrolled. The Dose Escalation Stage will include up to approximately 30 patients, depending on the dose at which the MTD is determined for each schedule, and approximately 50 additional patients will be enrolled in the Expansion Stage. AMV564 will be administered daily as a continuous intravenous (CIW) infusion over a period of 24 hours for 14 days in each cycle. Each cycle will be approximately 4 weeks. A lead-in dose regimen will be utilized for all patients treated at dose levels at or above 50 mcg/day. Patients will receive up to 4 cycles of AMV564 treatment at the assigned dose level. Clinical trial information: NCT03516591.

Background: Myelofibrosis (MF) is a serious life-threatening condition characterized by splenomegaly, constitutional symptoms, and shortened survival. Ruxolitinib (RUX) is currently the only approved drug for treatment (Tx) of Intermediate- (Int-) or High-risk MF. RUX discontinuation rates are high, mainly due to lack of response, loss of efficacy, intolerance, and drug-induced cytopenias, resulting in an important unmet medical need for a JAK2 inhibitor that is effective after RUX failure. FEDRATINIB (FEDR) is an oral, JAK2-selective inhibitor that produces substantial spleen volume reduction (SVR) and improves constitutional symptoms as initial therapy of MF (Pardanani, 2015) and in pts resistant to or intolerant of RUX (Harrison, 2017). Methods: This multicenter, open-label, single-arm study (NCT03755518) is enrolling adult pts with primary, post-polycthemia vera, or post-essential thrombocythemia MF; Dynamic International Prognostic Scoring System (DIPSS) Int- or High-risk disease; splenomegaly; eCOG PS ≤2; and platelet counts ≥50 × 10^11/L. Pts must have received prior RUX Tx for ≥3 mo or during ≥28 days of RUX therapy were RUX-intolerant (developed RBC transfusion dependence; ≥2 units/mo for 3 mo) or grade ≥3 thrombocytopenia, anemia, hematoma/hemorrhage). Pts receive continuous FEDR 400 mg QD in 28-day cycles. Spleen volume is assessed by MRI/CT scan at screening, after cycles 3, 6, and 12, and at end of treatment. Primary endpoint is spleen response rate (RR; ≥35% SVR from BL by cycle 6 end). Secondary endpoints include duration of spleen RR, spleen size reduction, rate and duration of symptom response (≥50% reduction in total symptom score on the Myelofibrosis Symptom Assessment Form), and safety. Risk mitigation strategies for gastrointestinal adverse events and Wernicke encephalopathy are evaluated. Exploratory endpoints include survival, patient-reported outcomes, and biomarkers of FEDR efficacy and biochemical activity. The study will enroll ~110 pts. Assuming a spleen RR of 35%, the study will have ~90% power to detect the lower bound of the 95% CI that excludes 20%. Enrollment is ongoing. Clinical trial information: NCT03755518.

TPS7070 Poster Session (Board #440b), Mon, 8:00 AM-11:00 AM

A phase I study of AMV564 in patients with intermediate or high-risk myelodysplastic syndromes. First Author: Guillermo Garcia-Manero, The University of Texas MD Anderson Cancer Center, Houston, TX
TRANSCEND CLL 004: Minimal residual disease (MRD) negative responses after lisocabtagene maraleucel (Liso-Cel; JCAR017), a CD19-directed CAR T cell product, in patients with relapsed/refractory chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (CLL/SLL). First Author: Tanya Siddiqi, City of Hope National Medical Center, Duarte, CA

Background: Eradication of MRD in CLL patients may be necessary for deep and durable responses. We assessed safety, pharmacokinetics, and efficacy of liso-cel, an investigational, anti-CD19 CAR T cell product administered as a defined composition of CD4+CD19+ CAR T cells, in the ongoing phase 2 TRANSCEND CLL 004 study. Methods: Eligible pts had CLL/SLL, received ≥2 prior lines of therapy (including Bruton’s tyrosine kinase inhibitors [BTKi]) unless medically contraindicated, and had ECOG PS ≤1. Post lymphodepleting chemotherapy, pts received liso-cel infusion at either dose level (D1L) = $5 \times 10^7$ to $10^8$ or D2L = $10^8$ to $10^9$ total CAR+ T cells. Pts were monitored for dose-limiting toxicities (DLTs). Response was assessed by iwCLL 2008 criteria. MRD was assessed by flow cytometry in blood ($10^{-4}$) and by NGS in bone marrow (BM; $10^{-6}$). Results: At data cutoff, 16 pts received liso-cel: D1L, n = 6; D2L, n = 10. 75% of pts had high-risk features (IP3 mutation, complex karyotype, or del17p); 100% had prior ibrutinib and 50% had prior venetoclax. Median number of prior lines of therapy was 4.5 (2–11). There was 1 DLT of grade (G) 4 hypertension (D2L). The most common G3/4 treatment-emergent adverse events were cytopenias (thrombocytopenia, 75%; anemia, 69%; neutropenia, 63%; leukopenia, 56%). 1 pt had G3 cytokine release syndrome (CRS); 3 pts had G3 neurologic events (NE). Best overall response rates (ORRs) in 15 evaluable pts was 87% (13/15). 7 pts (47%) achieved complete remission with/without MRD and 50% had prior venetoclax. Conclusions: The median follow-up was 16 days (4–30). Conclusions: In this study of heavily pretreated pts with standard- and high-risk CLL/SLL and previous ibritumomab treatment, liso-cel-related toxicities (ie, CRS and NEs), were manageable. Pts rapidly achieved CR/CRi and uMRD. Additional follow-up will be presented. Clinical trial information: NCT03331198.

7501 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Effect of fixed-duration venetoclax plus obinutuzumab (VenG) on progression-free survival (PFS), and rates and duration of minimal residual disease negativity (MRD–) in previously untreated patients (pts) with chronic lymphocytic leukaemia (CLL) and comorbidities. First Author: Kirsten Fischer, Department I of Internal Medicine and Center of Integrated Oncology Cologne Bonn, University Hospital, Cologne, Germany

Background: The multinational, open-label, phase 3 CLL14 trial compared fixed-duration targeted VenG treatment with chlorambucil-obinutuzumab (ClbG) in previously untreated pts with CLL and comorbidities. Here we present endpoint analyses with particular emphasis on MRD– and PFS. Methods: Pts with a CIRS score ≥6 and/or an estimated creatinine clearance <70 mL/min were randomized 1:1 to receive equal duration treatment with 12 cycles (C) of standard Clb or Ven 400 mg daily in combination with G for first 6 C. Primary endpoint was PFS. MRD– in peripheral blood (PB) or bone marrow (BM) 3 months (mo) after treatment completion was a key secondary endpoint. MRD was analyzed serially from C4 every 3 mo by an allele-specific oligonucleotide polymerase chain reaction assay (ASO-PCR; cut-off, $10^{-4}$) and by next generation sequencing (NGS; cut-offs, $10^{-4}, 10^{-5}, 10^{-6}$). Results: 432 pts were enrolled; 216 in each treatment group (intent-to-treat population). After 29 mo median follow-up, superior PFS was observed with VenG vs ClbG (HR 0.35; 95% CI 0.23–0.53; P < 0.0001). MRD– by ASO-PCR was significantly higher with VenG vs ClbG in both PB (76% vs 35% [P < 0.0001]) and BM (57% vs 17% [P < 0.0001]) 3 mo after treatment completion. Overall, 75% of VenG MRD-negative pts in PB were also MRD-negative in BM vs 49% in the ClbG group. Landmark analysis for this timepoint by PB MRD status showed that MRD– was associated with longer PFS. Higher MRD– rates were achieved early and were more sustainable with VenG: 81% (VenG) vs 27% (ClbG) of pts were MRD-negative 12 mo after treatment completion; HR for MRD conversion 0.36 (95% CI 0.21–0.60). Median time-off-treatment: 19 mo. MRD– rates by NGS confirmed these results: 78% (VenG) vs 34% (ClbG) of pts had MRD– at <10^{-4}, 31% vs 4% at <10^{-5} and 35% vs 15% at ≥10^{-6}–10^{-5}, respectively. Conclusions: Fixed-dose VenG induction deepened (<10^{-6} in 1/3 of pts), high, and long lasting MRD– rates (with a low rate of conversion to MRD+) 1 year after treatment initiation in previously untreated pts with CLL and comorbidities, translating into improved PFS. Clinical trial information: NCT02242942.

7502 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Effect of fixed-duration venetoclax plus obinutuzumab (VenG) on progression-free survival (PFS), and rates and duration of minimal residual disease negativity (MRD–) in previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) and comorbidities. First Author: Kirsten Fischer, Department I of Internal Medicine and Center of Integrated Oncology Cologne Bonn, University Hospital, Cologne, Germany

Background: The national trial, open-label, phase 3 CLL14 trial compared fixed-duration targetedVenG treatment with chlorambucil-obinutuzumab (ClbG) in previously untreated pts with CLL and comorbidities. Here we present endpoint analyses with particular emphasis on MRD– and PFS. Methods: Pts with a CIRS score ≥6 and/or an estimated creatinine clearance <70 mL/min were randomized 1:1 to receive equal duration treatment with 12 cycles (C) of standard Clb or Ven 400 mg daily in combination with G for first 6 C. Primary endpoint was PFS. MRD– in peripheral blood (PB) or bone marrow (BM) 3 months (mo) after treatment completion was a key secondary endpoint. MRD was analyzed serially from C4 every 3 mo by an allele-specific oligonucleotide polymerase chain reaction assay (ASO-PCR; cut-off, $10^{-4}$) and by next generation sequencing (NGS; cut-offs, $10^{-4}, 10^{-5}, 10^{-6}$). Results: 432 pts were enrolled; 216 in each treatment group (intent-to-treat population). After 29 mo median follow-up, superior PFS was observed with VenG vs ClbG (HR 0.35; 95% CI 0.23–0.53; P < 0.0001). MRD– by ASO-PCR was significantly higher with VenG vs ClbG in both PB (76% vs 35% [P < 0.0001]) and BM (57% vs 17% [P < 0.0001]) 3 mo after treatment completion. Overall, 75% of VenG MRD-negative pts in PB were also MRD-negative in BM vs 49% in the ClbG group. Landmark analysis for this timepoint by PB MRD status showed that MRD– was associated with longer PFS. Higher MRD– rates were achieved early and were more sustainable with VenG: 81% (VenG) vs 27% (ClbG) of pts were MRD-negative 12 mo after treatment completion; HR for MRD conversion 0.36 (95% CI 0.21–0.60). Median time-off-treatment: 19 mo. MRD– rates by NGS confirmed these results: 78% (VenG) vs 34% (ClbG) of pts had MRD– at <10^{-4}, 31% vs 4% at <10^{-5} and 35% vs 15% at ≥10^{-6}–10^{-5}, respectively. Conclusions: Fixed-dose VenG induction deepened (<10^{-6} in 1/3 of pts), high, and long lasting MRD– rates (with a low rate of conversion to MRD+) 1 year after treatment initiation in previously untreated pts with CLL and comorbidities, translating into improved PFS. Clinical trial information: NCT02242942.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
7504 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Sintilimab for relapsed/refractory (r/r) extranodal NK/T-cell lymphoma (ENKTL): A multicenter, single-arm, phase 2 trial (ORIENT-4). First Author: Rong Tao, Department of Hematology, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: ENKTL account for more than 20% of the peripheral T-cell lymphomas in Asia. Patients with r/r ENKTL have a poor prognosis after failing an L-asparaginase-based regimen, and the median overall survival is less than 6 months.

The overexpression of PD-L1 induced by EBV infection is a potential mechanism for ENKTL to evade immune surveillance. Several phase I studies of PD-1 antibodies in r/r ENKTL have demonstrated potential efficacy. Sintilimab, a fully human anti-PD-1 monoclonal antibody, has a safety profile consistent with other approved PD-1 antibodies and was approved for r/r classical Hodgkin lymphoma in China in 2018. This multicenter, single-arm, phase 2 study aims to validate the efficacy and safety of sintilimab monotherapy in patients with r/r ENKTL in China.

Methods: Patients with pathologically confirmed r/r ENKTL were enrolled. Sintilimab was given 200 mg IV Q3W, until PD, death, unacceptable toxicity, or withdrawal from the study. Treatment beyond PD is allowed. Tumor response evaluation was performed by both PET-CT and CT/MRI with contrast. The primary endpoint was objective response rate based on LUCANO 2014 criteria. Data cut-off date for this analysis was February 2, 2019.

Results: From August 31, 2017 to February 7, 2018, a total of 28 patients were enrolled: 60.7% male, and the median age was 65 (range: 19-87) years. Sixty-eight percent of patients were stage IV and 89.3% were ECOG PS 0-1. All patients had failed an L-asparaginase-based regimen. The median lines of previous therapy were 3 (range: 1-12). 76.8% of patients received prior radiotherapy and 7.1% had failed HSCT. Median duration of therapy was 14.04 (range: 1.4-17.3) months and 19 patients are still receiving sintilimab. Sixty-eight percent (19/28, 95% CI: 47.6%-84.1%) of patients achieved primary response (CR+PR), including 4 patients who experienced PD prior to having a response. DCR was 85.7%, including 5 patients who experienced PD before SD or response. The 1-year OS rate was 82.1% and the median OS has not been reached. Most TRAEs were G1-2 (62.4%) and no patients discontinued treatment due to AEs. The most common TRAEs were neutropenia (46.4%) and anemia (46.4%) in patients who had no concurrent treatment for anemia. Sintilimab is a novel, next-generation PI3Kδ inhibitor with unique inhibition of casein kinase-1 (CK1ε) and a differentiated tolerability profile compared to earlier PI3Kδ inhibitors (Burris et al, 2018). This registration-directed study evaluates the efficacy and safety of sintilimab in pts with r/r ENKTL and could be a promising treatment option for these patients. Early disease progression observed by PET-CT in this study could be pseudoprogression as it did not correlate with poor outcome, which warrants further investigation.

Clinical trial information: NCT03228836.

7506 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Umbilalisib monotherapy demonstrates efficacy and safety in patients with relapsed/refractory marginal zone lymphoma: A multicenter, open label, registration directed phase II study. First Author: Nathan Hafele Fowler, The University of Texas MD Anderson Cancer Center, Department of Lymphoma/Myeloma, Houston, TX

Background: Rituximab (RTX) alone or with chemotherapy has substantially improved outcomes for patients (pts) with marginal zone lymphoma (MZL), but relapse is common, particularly in pts who are negative for FLIPI or C-Score. Umbilalisib is a novel, next-gen PI3Kδ inhibitor with unique inhibition of casein kinase-1ε (CK1ε) and a differentiated tolerability profile compared to earlier PI3Kδ inhibitors (Burris et al, 2018). This registration-directed study evaluates the efficacy and safety of umbilalisib in pts with rel/ref (R/R) MZL.

Methods: Pts who had histologically confirmed MZL, ECOG PS ≤2, and ≥1 prior therapy including ≥1 anti-CD20 mAb-containing regimen. Pts received umbilalisib 800 mg orally once daily until PD or unacceptable toxicity. The primary endpoint was overall response (ORR) as assessed by independent review (IRC) per 2007 IWG criteria. ORR by investigator assessment is reported here, and ORR by IRC per 2017 IRC criteria. Secondary endpoints included duration of response (DOR), PFS, and safety. Results: 69 pts were enrolled; we report on the first 38 who are eligible for at least 6 months of follow-up as of the data cut-off. Among the 38 pts; extranodal (n = 23), nodal (n = 8), and splenic (n = 7). Median age was 67 years (range, 34-81). Median # of prior systemic therapies was 2 (range, 1-5). Seven pts (18%) had monotherapy RTX only, and 26 (68%) had at least one anti-CD20 mAb-containing chemotherapy. Median follow-up was 9.6 mos; ORR was 55% (4 CRs and 17 PRs). Eleven pts (29%) had stable disease (SD) of which 6 of these SD pts remained on study ranging from 7-12 mos. The clinical benefit rate (CR+PR+SD) was 84%, and 91% of pts with at least 1 post-baseline scan were progression-free at 6 mos. Median time to initial response was 2.7 mos, while median DOR was not reached (95% CI: 8.4-NR). The 12-month PFS was 71%. The most common all causality (<20%) adverse events (AE) of any grade included: diarrhea (45%), nausea (29%), fatigue (26%), headache (26%), cough (24%), and decreased appetite (21%). The most common Grade 3/4 events were neutropenia (8%), febrile neutropenia (5%), and diarrhea (5%). As of the cutoff date 38 pts had received treatment thus far: 30 pts with single-agent umbilalisib is active and well tolerated in pts with R/R MZL, achieving durable responses with chemotheraphy-free therapy. Clinical trial information: NCT02793583.

7507 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Rituximab maintenance for patients with diffuse large B-cell lymphoma in first complete remission: Results from a randomized HORIZON-Mono Lymphoma Group Phase III study. First Author: Ely J. Lugtenburg, Erasmus MC Cancer Institute, Department of Hematology, Rotterdam, Netherlands

Background: This randomized phase III trial assessed whether intensification of rituximab (R) during the first 4 cycles of R-CHOP can improve outcome of diffuse large B-cell lymphoma (DLBCL) patients compared with standard R-CHOP. Patients in complete remission (CR) after induction treatment were randomized between rituximab maintenance and observation. Intensification of rituximab was not more effective than standard R-CHOP, showing similar CR-rates and progression free survival after induction (ASCO 2016 # 7504). Here, we report the results of the second randomization for rituximab maintenance therapy. Methods: Patients in CR after R-CHOP were randomized between 24 months of rituximab maintenance and observation. Secondary endpoints included overall survival (OS) and adverse events (AEs). Conclusions: R-CHOP was compared to rituximab maintenance therapy. The 3-year OS rate was 79% for rituximab maintenance versus 74% for observation. This difference was not statistically significant, with a hazard ratio of 0.83 (95% confidence interval 0.57-1.19, p = 0.31, adjusted for age and aa-IP). The second endpoint OS was also not significantly different (85% versus 83% at 5 years). No clinical subgroup benefited from rituximab maintenance. Toxicity was mild. Among patients who received rituximab maintenance CT Regimen 4 of the 3 and 4 AE was reported in 93% and 87% of patients respectively. Infection was the most frequent AE, a grade 3 infection occurred in 6% of patients. Neutropenia was seen in 1% (grade 3) and 3% (grade 4) of patients. Conclusions: Rituximab maintenance therapy provides no additional benefit for DLBCL patients in first CR after R-CHOP. Clinical trial information: www.trialregister.nl NTR1014.
NCT02636322. 

cytotoxic-free combination of rituximab 375 mg/m², ibrutinib 560 mg, 

With chemotherapy.

Ibrutinib (ibr), a first-in-class, once-daily Bruton

Background:

Medical Center, Rochester, NY

First Author: Paul M. Barr, University of Rochester Medical Center, Rochester, NY

Background:

First Author: Jason Westin, The University of Rochester, MN

Oral Abstract Session, Toe, 9:45 AM-12:45 PM

Smart start: Final results of rituximab, lenalidomide, and ibrutinib lead in 

7508 

Poster Session Discussion; Displayed in Poster Session (Board #263), Mon, 8:00 AM-11:00 AM, Discussed in Poster Session Discussion, Mon, 11:30 AM-1:00 PM

Outcomes with rituximab plus bendamustine (R-Benda), dexamethasone, rituximab, cyclophosphamide (DRC), and bortezomib, dexamethasone, rituximab (BDR) as primary therapy in patients with Waldenstrom macroglobulinemia (WM), First Author: Jithma P. Abyekoon, Department of Internal Medicine, Mayo Clinic, Rochester, MN

Background: Waldenstrom macroglobulinemia (WM) is a rare lymphoma for which scant comparative data exist to guide frontline therapy. Herein, we compared commonly used regimens in WM. R-Benda, DRC, and BDR in 

7509 

7510 

Poster Discussion Session; Displayed in Poster Session (Board #264), Mon, 8:00 AM-11:00 AM, Discussed in Poster Session Discussion, Mon, 11:30 AM-1:00 PM

Final analysis from RESONATE: Six-year follow-up in patients (pts) with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) on ibrutinib. First Author: Paul M. Barr, University of Rochester Medical Center, Rochester, NY

Methods:

Pts were randomized to receive oral ibr 420 mg daily until PD or intravenous ofa for up to 2 years. Long-term efficacy endpoints were determined. Results: Among 391 pts randomized to receive ibr (n=195) or ofa (n=196), 86% and 79%, respectively, were in the genomic high-risk population (del(17p), del(11q), TP53 mutation, and/or unmutated IGHV). At final analysis, median follow-up was 64 mo (range, 0.3-72) on ibr. Of pts randomized to ofa, 68% crossed over to receive ibr. Significant sustained PFS benefit was observed with ibr vs ofa, with median PFS 44.1 vs 8.1 mo (HR 0.15; 95% CI 0.11-0.20; P=0.0001) and was consistent across baseline subgroups. Median PFS in genomic high-risk population was 44.1 vs 8.0 mo on ibr vs ofa (HR 0.11, 95% CI 0.08-0.15). ORR with ibr was 88% (CR/CRI in 1%). Initial ibr treatment conferred better OS than ofa when censored for crossover (HR 0.64; 95% CI 0.42-0.98). Median duration of ibr was 41 mo (range 0.2-71); 41% of pts received ibr >4 yrs. AE profile with ibr remained consistent with prior reports. Cumulatively during long-term ibr therapy, all-grade ≥3 hypertension and atrial fibrillation occurred in 21% (9%) and 12% (6%) of pts, respectively; major hemorrhage occurred in 10%. Most common reasons for ibr discontinuation (DC) prior to study closure were PD (37%) and AEs (16%); DC due to AEs occurred in 6%, 3%, 6%, and 4% of pts during 1-2, 3-4, 5-6, and 7+ yrs of ibr, respectively. Conclusions: With up to 6 years of follow-up, extended ibr treatment showed sustained efficacy in pts with R/R CLL, including in pts with high-risk genomic features. Safety remained acceptable with low rates of DC due to AEs, and with no new safety signals in long-term follow-up. These results establish the durability and 

Poster Session Discussion; Displayed in Poster Session (Board #265), Mon, 8:00 AM-11:00 AM, Discussed in Poster Session Discussion, Mon, 11:30 AM-1:00 PM

Second cancer incidence in CLL patients receiving BTK inhibitors. First Author: David Alan Bond, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: Patients (pts) with chronic lymphocytic leukemia (CLL) suffer morbidity and mortality from CLL and increased risk for second primary neoplasm (SPN). BTK inhibitors (BTKi) are highly effective for the treatment (tx) of 

7511 

Poster Abstract Session, Tue, 9:45 AM-12:45 PM

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7512 Poster Discussion Session; Displayed in Poster Session (Book #266), Mon, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-1:00 PM

Results of the PI3Kδ inhibitor ME-401 alone or with rituximab in relapsed/refractory (R/R) follicular lymphoma (FL). First Author: Andrew David Zelenetz, Memorial Sloan Kettering Cancer Center, New York, NY

Background: ME-401, a potent and selective oral PI3Kδ inhibitor, is being evaluated in a Phase 1b study in patients (pts) with R/R B-cell malignancies (NCT02914938); 70 pts were treated; we report here results in FL. Methods: Pts with ECOG ≤2, no prior PI3Kδ therapy and progression of disease (POD) after ≥2 prior therapies were initially enrolled in a dose escalation phase (60-180 mg) then in 60 mg expansion cohorts as monotherapy or in combination with rituximab. ME-401 was given initially on a daily continuous schedule (CS) until POD or unacceptable toxicity. An intermitted schedule (IS) on days 1-7 of a 28-day cycle was then evaluated after 2 cycles (n = 18) or ≥3 cycles (n = 9) of CS. Toxicity was managed by switch to IS or POD IS managed by switch to CS. Results: 48 FL pts received ME-401 alone (n = 39) or with rituximab (n = 9). Median age 64.6 yrs. (range 38-81), median prior therapies 2 (range 1-10), 30 had ≥3 prior therapies and 25 were POD24. 28 pts remain on therapy with median follow-up of 9.3 months (range 0.5-22.5) and 20 discontinued: 9 POD, 4 adverse events (AEs), 4 withdrew consent, and 3 for stem cell transplant. Delayed (≥ Cycle 2) grade 3 immune related AEs (irAEs), primarily diarrhea/colitis and rash, reported in 9/30 (30%) on CS and 6% (4 of 67) on IS. irAEs were managed by switch to CS. Conclusions: 48 FL pts managed to IS can be salvaged by switch to CS. Results: 48 FL pts received ME-401 alone (n = 39) or with rituximab (n = 9). Median age 64.6 yrs. (range 38-81), median prior therapies 2 (range 1-10), 30 had ≥3 prior therapies and 25 were POD24. 28 pts remain on therapy with median follow-up of 9.3 months (range 0.5-22.5) and 20 discontinued: 9 POD, 4 adverse events (AEs), 4 withdrew consent, and 3 for stem cell transplant. Delayed (≥ Cycle 2) grade 3 immune related AEs (irAEs), primarily diarrhea/colitis and rash, reported in 9/30 (30%) on CS and 6% (4 of 67) on IS. irAEs were managed by switch to CS. Results: 48 FL pts managed to IS can be salvaged by switch to CS.

7514 Poster Discussion Session; Displayed in Poster Session (Book #268), Mon, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-1:00 PM

Efficacy and time to next treatment following lenalidomide/rituximab (R2) or rituximab/placebo in patients with R/R indolent NHL (AUGMENT). First Author: John G. Gribben, Centre for Haematopoietic Oncology, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom

Background: Relapse is expected in treated indolent lymphoma patients, and an unmet need exists to prolong remission with effective therapies. Lenalidomide + rituximab (R2) may improve the efficacy of the next therapeutic intervention. Methods: The AUGMENT phase III study evaluated patients with R/R FL grade 1-3a (82%) and MZL (18%) after ≥1 prior systemic therapy (not rituximab refractory). Randomization was 1:1 to R2 (lenalidomide PO 20 mgid, d1-21/28 X12 cycles + rituximab [RIW] 275 mg/m2 wk 1, d1, 8, 15, 22 and 29-36 d1) and RIW placebo (same dose schedule). The primary endpoint was POY by IWG. Response was scored according to: POY, AEs were scored according to CTCAE v.5.0. Conclusions: These analyses suggest that R2 (vs R/placebo) prolonged time to response. R2 is active with a tolerable safety profile in patients with R/R FL and MZL, and in patients refractory to rituximab. Clinical trial information: NCT01998655.

7513 Poster Discussion Session; Displayed in Poster Session (Book #267), Mon, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-1:00 PM

MAGNIFY: Phase IIIb interim analysis of induction R2 followed by maintenance in relapsed/refractory indolent non-Hodgkin lymphoma. First Author: David Jacob Andorsky, Rocky Mountain Cancer Centers, US Oncology Research, Boulder, CO

Background: Standard treatment is lacking for patients with relapsed indolent NHL (iNHL). PI3Kδ inhibitors reported a median PFS of < 1 y in R/R NHL. The immunomodulatory agent lenalidomide shows enhanced activity with rituximab (ie, R2), which recently reported a 39.4-mo median PFS in R/R NHL patients (AUGMENT; Leonard. ASH 2018:445). Methods: MAGNIFY is a multicenter, non-registrational phase IIIb trial in patients with R/R FL grade 1-3a and MZL designed to determine the optimal duration of lenalidomide. Lenalidomide 20 mg/d PO for 12 cycles + rituximab 375 mg/m2 wk 1 and q4w×4 (R2) followed by 1:1 randomization in patients with stable disease or better to continued R2 vs rituximab maintenance. These analyses evaluate the primary end point of ORR by 1999 IWG criteria for induction R2 in efficacy-evaluable patients receiving ≥1 treatment with baseline/post-baseline assessments. Results: At a median 1.7 mo follow-up, 370 patients (80% FL grade 1-3a; 20% MZL) were enrolled with a median age of 66 y, 83% stage III/IV disease, and a median of 2 prior therapies (95% prior rituximab-containing). Efficacy-evaluable patients showed a 73% ORR and 45% CR (Table). Median TTR was 2.7 mo, median DR was 36.8 mo, and median PFS was 36.0 mo. 142 of 370 patients have been randomized and entered maintenance. The most common all-grade AEs were 48% fatigue, 40% neutropenia, 35% diarrhea, 30% nausea, and 29% constipation. Grade 3/4 AE neutropenia was 34%; all other grade 3/4 AEs were <6%. Continued R2 therapy is active with a tolerable safety profile in patients with R/R FL and MZL, and in patients refractory to rituximab. Clinical trial information: NCT01998655.

7515 Poster Discussion Session; Displayed in Poster Session (Book #269), Mon, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-1:00 PM

Lisocabagene maraleucil (lisocel)-treatment of patients (pts) with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) and secondary CNS lymphoma: Initial results from TRANSCEND NHL 001. First Author: Jeremy S. Abramson, Massachusetts General Hospital Cancer Center/Harvard Medical School, Boston, MA

Background: No clinical studies have yet evaluated CAR T cell therapies in pts with relapsed NHL who have secondary CNS lymphoma. We report data from this pt subgroup receiving lisocel (UCAR-JACO17), an investigational, anti-CD19 CAR T cell product administered as a defined composition of CD4+/CD8+ CAR T cells, in the phase 1 TRANSCEND NHL 001 study. Methods: Eligible pts had confirmed B-cell NHL with R/R disease after ≥2 prior lines of therapy. Pts with secondary CNS lymphoma could enroll if, or if developed on study, could continue to receive lisocel. After lymphodepleting chemotherapy, lisocel was administered at 1 of 2 dose levels (DL): DL1 = 50 × 10^6 to DL2 = 100 × 10^6 total CAR+ T cells. Efficacy was evaluated per the Lugano criteria. Pts achieving a complete response could be retreated with lisocel upon subsequent progressive disease. Results: Of 232 pts enrolled, 5 pts withdrew consent due to heavy CAR+ T cells or other causative effect on cognition (n = 5), or were lost to follow-up (n = 3). All other AEs were managed per ISF. Conclusions: These analyses suggest that R2 (vs placebo) prolonged time to subsequent therapy and is associated with longer PFS2, enabling greater response to next therapy. Although patient numbers were modest, it is hypothesized that patients who received R2 were generally more responsive to subsequent therapy than those treated with placebo. Clinical trial information: NCT01959001.

Response to next treatment after R2 and Rplus.

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<th>Treatment (R2 vs Rplus)</th>
<th>ORR, %</th>
<th>CR, %</th>
<th>Median TTR, mo (95% CI)*</th>
<th>Median DO, mo (95% CI)*</th>
<th>Median PFS, mo (95% CI)*</th>
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<td>Single agent chemos (n = 8/14)</td>
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<td>38</td>
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7516 Poster Discussion Session; Displayed in Poster Session (Board #270), Mon, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-1:00 PM

Safety and preliminary efficacy in patients (pts) with relapsed/refractory (R/R) mantle cell lymphoma (MCL) receiving lisocabtagene maraleucel (Liso-cell) in TRANSCEND NHL 001. First Author: Michael Wang, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Most pts with MCL relapse after first-line immunotherapy, with poor responses to salvage therapy. We report initial dose-finding results from pts with R/R MCL treated with liso-cell (UCAR017), an investigational, anti-CD19 CAR T cell product administered as a defined composition of CD4+ and CD8+ CAR T cells, in the ongoing phase 1 TRANSCEND study. Methods: Eligible pts had confirmed MCL (cyclin D1 expression, t[11;14]) with R/R disease after ≥1 prior lines of therapy. After lymphodepleting chemotherapy, liso-cell was administered at 1 of 2 dose levels (DL): DL1 = 50 × 10^6 or DL2 = 100 × 10^6 total CAR+ T cells. Results: At data cutoff, 9 pts (DL1, n = 6; DL2, n = 3) had received liso-cell. The median (range) age was 66 (58–78) years; 7 pts were male. Histologies included blastoid (n = 3) and pleomorphic (n = 1) variants. 8 pts had documented Ki67 > 30% (40%–80%); 1 pt had TP53 mutation. Pts had received a median of 5 (2–7) prior therapies; 3 pts had received prior hematopoietic stem cell transplant. All 9 pts had prior brutinib; 4 had a better response of progressive disease on brutinib. 6/9 pts (67%) received bridging chemotherapy. 4/9 pts (44%) had serious treatment-emergent adverse events (TEAEs). 5/9 pts (56%) had grade (G) 3/4 TEAEs, primarily anemia, neutropenia, and hypophosphatemia (22% each). 3/9 pts (33%) had cytokine release syndrome (CRS); 4/9 pts (44%) had neurotoxicity with step-fractionation in these pts, despite escalation of the Cycle 1 Day 15 dose to 20 mg, with a median to time to relapse of 54 days (IQR 16–120). Results: Pre-axi-cel pt characteristics: median lines of therapy were 4 (range 2–11), 86% were Stage III/IV and 22% were ECOG >1. Following relapse, 60% (n=61) were biopsied and 70% (43/61) had CD19 expression measured. Thirty percent (13/43) were CD19 negative by: IHC (3/13), flow (2/13) or both (8/13). Seventy percent (n=71) received salvage therapy for PD. Median lines of salvage therapy was 1 (range 0–4). The most common therapies were Lenalidomide-based (30%), checkpoint inhibitors (30%), chemotherapy (20%) and radiation (10%). First salvage therapy ORR by regimen: checkpoint inhibitors = 24%, lenalidomide regimen = 20% and chemotherapy = 11%. One pt reported allogeneic transplant. Twelve pts enrolled on clinical trial, with one receiving 2nd CAR-T. Median OS following relapse was 108 days (95% LCL 71). Nineteen pts relapsed <3 months after axi-cel and did not receive therapy with median OS 17 days (95% CI 7–49); 33 pts relapsed <3 months and received therapy with 114 day median OS (95% LCL 82). In contrast, 30 pts who relapsed >3 months post axi-cel and received therapy had estimated median OS ≥ 220 days (95% LCL 81). Conclusions: Patients with LBL relapsing less than 3 months following axi-cel have extremely poor outcomes supporting the development of novel therapies. Therapy for relapse >3 months appears promising. JYS and SD contributed equally; AAP, DBM and BTH contributed equally.

7517 Poster Discussion Session; Displayed in Poster Session (Board #272), Mon, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-1:00 PM

Outcomes in large B-cell lymphoma progressing after axicabtagene ciloleucel (Axi-cell): Results from the U.S. Lymphoma CART-T Consortium. First Author: Jay Y. Spiegel, Stanford University, Stanford, CA

Background: Axi-cell, an anti-CD19 CART cell therapy, achieved 83% ORR, 58% CR rate, with 39% PFS at 2 years in patients (pts) with relapsed refractory large B-cell lymphoma (LBCL) on the ZUMA-1 study (Locke, Lancet Oncology 2018). Data from a 17-center consortium showed response rates were similar in 274 pts treated with commercial axi-cell (Nastoupil, ASH 2018). Here, we performed retrospective analysis of outcomes in pts with progressive disease (PD) after axi-cell. Methods: Response status was determined by Cheson 2014 and reported as date of radiologic relapse. 274 pts were infused by December 26, 2018 with maximum follow-up of 14 months; 116 pts had PD as of Feb 1, 2019. Breakdown sites provided additional data, totaling 85% (n=199) with a median to time to relapse of 54 days (IQR 16–120). Results: Pre-axi-cel pt characteristics: median lines of therapy were 4 (range 2–11), 86% were Stage II/III and 22% were ECOG >1. Following relapse, 60% (n=61) were biopsied and 70% (43/61) had CD19 expression measured. Thirty percent (13/43) were CD19 negative by: IHC (3/13), flow (2/13) or both (8/13). Seventy percent (n=71) received salvage therapy for PD. Median lines of salvage therapy was 1 (range 0–4). The most common therapies were Lenalidomide-based (30%), checkpoint inhibitors (30%), chemotherapy (20%) and radiation (10%). First salvage therapy ORR by regimen: checkpoint inhibitors = 24%, lenalidomide regimen = 20% and chemotherapy = 11%. One pt reported allogeneic transplant. Twelve pts enrolled on clinical trial, with one receiving 2nd CAR-T. Median OS following relapse was 108 days (95% LCL 71). Nineteen pts relapsed <3 months after axi-cel and did not receive therapy with median OS 17 days (95% CI 7–49); 33 pts relapsed <3 months and received therapy with 114 day median OS (95% LCL 82). In contrast, 30 pts who relapsed >3 months post axi-cel and received therapy had estimated median OS ≥ 220 days (95% LCL 81). Conclusions: Patients with LBL relapsing less than 3 months following axi-cel have extremely poor outcomes supporting the development of novel therapies. Therapy for relapse >3 months appears promising. JYS and SD contributed equally; AAP, DBM and BTH contributed equally.

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428s Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia

Safety.

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*excluding progressive disease
Safety and efficacy of PD-L1 inhibitor durvalumab with R-CHOP or R2-CHOP in subjects with previously untreated, high-risk DLBCL. First Author: Grzegorz S. Nowakowski, Mayo Clinic, Rochester, MN

Background: We report results of a phase 2, open-label study of durvalumab (durva) in combination with R-CHOP or R2-CHOP (R-CHOP + lenalidomide) in previously untreated, high-risk diffuse large B-cell lymphoma (DLBCL). Methods: Subjects (≥18 y; ECOG 0–2) with previously untreated, high/high-intermediate risk DLBCL (IPI 3–6/NCCN-IPi ≥4) were stratified to R-CHOP (Arm A, GCB DLBCL) or R2-CHOP for 6–8 cycles (Arm B, ABC DLBCL) based on cell of origin identified by gene expression followed by durva consolidation up to month 12 from start of induction. After FDA placed clinical holds on trials including combination therapy with checkpoint inhibitors and immunomodulatory agents, the study was revised to include both ABC and GCB in Arm A (durva + R-CHOP). The primary endpoint was complete response rate (CR) at end of induction; secondary endpoints were rate of subjects continuing to consolidation, safety, and response in biological.

Results: A total of 46 subjects were treated (safety: A/B, n=43/3); median age, 62/66 y; male, 61%/67%; ECOG 2, 19%/33%; Arm A: ABC; Stage IV, 79%/33%; bulky disease: 49%/67%; double/triple-hit lymphoma, 30%/33%. As of Aug 2, 2018, 30/3 (A/B) had completed induction therapy, and 19 subjects (A) were ongoing. CR (95% confidence interval) at end of induction was (A) 54% (37%-71%) and (B) 67% (9%-99%); 68%/67% (A/B) continued to complete therapy and were progression free at month 12. Safety profile was as expected for the combinations of the regimen with no new safety signal identified. Frequent treatment-emergent adverse events (TEAEs; ≥25%: A+B) included fatigue (61%), neutropenia (52%), peripheral sensory neuropathy (50%), nausea (46%), diarrhea (28%); constipation, decreased appetite, insomnia, pyrexia (24% each); grade 3/4 TEAEs occurred in 84%/100% of subjects (A/B), and 3 subjects (2/1) died with no death related to study treatment. Follow-up for efficacy and safety is ongoing. Conclusions: Durva + R-CHOP combination therapy is safe and continues encouraging response rates in subjects with high-risk DLBCL including double-hit lymphoma. Clinical trial: NCT0303520.
Outcomes of stem cell transplant in patients with Richter transformation.

First Author: Yucai Wang, Mayo Clinic, Rochester, MN

Methods: Cirm 600 mg was selected for further evaluation. A randomized phase 2 trial comparing C+Ibr and Ibr monotherapy in R-CLL was conducted.

Results: The combination of C+Ibr was well-tolerated and showed a similar response rate compared to Ibr monotherapy. The median progression-free survival (PFS) was 14.6 months in the C+Ibr group and 11.6 months in the Ibr monotherapy group. The overall response rate (ORR) was 79% in the C+Ibr group and 62% in the Ibr monotherapy group. The complete response rate (CR) was 48% in the C+Ibr group and 32% in the Ibr monotherapy group. The median duration of response was 25.0 months in the C+Ibr group and 22.8 months in the Ibr monotherapy group. The median time to treatment failure (TTF) was 24.2 months in the C+Ibr group and 18.4 months in the Ibr monotherapy group. The median overall survival (OS) was 40.1 months in the C+Ibr group and 32.6 months in the Ibr monotherapy group. The results were consistent with the known safety profile of Ibr and the combination of C+Ibr was well-tolerated.

Conclusions: The combination of C+Ibr is associated with improved PFS, ORR, CR, duration of response, TTF, and OS compared to Ibr monotherapy in R-CLL patients. The combination of C+Ibr is a promising treatment option for R-CLL patients.

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7528

Poster Session (Board #282), Mon, 8:00 AM-11:00 AM

Long-term follow-up of previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) treated with ofatumumab (OFA) and chlorambucil (CHL): Final analysis of the phase 3 COMPLEMENT 1 trial. First Author: Fritz Offner, University Zieheinken Gent, Belgium

Background: Previously in the COMPLEMENT 1 study, treatment with OFA and CHL in pts with untreated CLL had shown a significant improvement in the progression-free survival (PFS) compared with CHL alone, and was well tolerated. Here, we report the final overall survival (OS) analysis of the 5-year (y) follow-up, updated investigator-assessed PFS and safety from the study.

Methods: 910 treated pts, not fit for fludarabine-based therapy (due to advanced age or co-morbidities) were randomized 1:1 to OFA+CHL or CHL alone. Pts in OFA+CHL arm received OFA (Cycle 1: 300 mg day (d) 1, 1000 mg d8; subsequent cycles: 1000 mg d1) in addition to CHL (10 mg/m2, d1-7) for 3 to 12 cycles of 28 d each. Pts in CHL arm received CHL only. Results: Overall, 447 pts were randomized to OFA+CHL (n = 222) or CHL (n = 226); 168 (76%) and 164 (73%) pts completed the scheduled treatments, respectively. Baseline characteristics were similar in both arms. The investigator-assessed median PFS was 23.4 months (mos) in the OFA+CHL arm and 14.7 mos in the CHL arm (HR: 0.61 [95% CI 0.49, 0.76], p < 0.001). Median OS could not be estimated for the OFA+CHL arm, and 14.7 mos in the CHL arm (HR: 0.66 [95% CI 0.56, 0.77], p < 0.001). Median OS rate (95% CI) at 5 y was 68.5% (61.5%, 74.5%) in the OFA+CHL arm, and 65.7% (58.6%, 71.9%) in the CHL arm. Post-treatment anti-cancer therapy following discontinuation was received by a greater proportion of pts in the CHL (65%) vs. OFA+CHL (56%), and started earlier in the CHL arm (48 vs 57 d). 84 (39%) pts in the OFA+CHL arm and 99 (44%) pts in the CHL arms died during the study with 5-on-treatment deaths in each group. Grade ≥3 adverse events were seen in 64% and 48% of pts in the OFA+CHL vs. CHL arms, respectively, most common being ≥5% in either arm) neutropenia (26% vs. 15%), thrombocytopenia (5% vs. 10%), pneumonia (9% vs. 5%), and anemia (5% vs. 5%). Conclusions: This 5-y survival follow-up analysis supported the results from primary analysis with an estimated 12% (not significant) and 39% risk reduction in OS and PFS, respectively, in the OFA+CHL arm compared with the CHL arm. No new safety concerns were observed in the OFA+CHL arm. Clinical trial information: NCT01748189.

7529

Poster Session (Board #283), Mon, 8:00 AM-11:00 AM

Occurrence of other cancers in patients with chronic lymphocytic leukemia and mutations in protection of telomeres 1 (POT1) gene. First Author: Matteo Molica, University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX

Background: Mutations in POT1 gene in CLL lead to uncapping of the telomeric ends, causing fusion events and chromosomal aberrations. POT1 is mutated in approximately 4% of pts with CLL. Recent studies reported germline variants in POT1 in pts with familial CLL and in familial malignant lymphomas. We evaluated pts characteristics and the presence of other cancers (OC) in pts with CLL with POT1 mutation seen at our institution.

Methods: We performed next generation sequencing (NGS)-based analysis for the detection of mutations in 29 genes frequently mutated in pts with CLL using blood and/or bone marrow samples containing a minimum of 10% clonal B-cells from 1467 pts diagnosed with CLL. Clinical characteristics, prognostic factors (FISH and IGH status), personal and familial history of OC were collected in pts with POT1 mutations. Results: Mutations in POT1 were found in 52 of the 1467 pts studied (3.5%). Pts with POT1 mutation were young (median age 59 years), commonly presented with early stage disease (Binet stage A 69% vs B/C 31%; p<0.0046 and Rai stage G1 65% vs II-IV 35%; p<0.043) and predominantly male (37 male vs 15 female). According to FISH, the more frequent abnormalities were del13q (33%), no abnormalities (25%) and del11q (21%). IGHV status was more commonly unmutated (69%). The most frequent DNA mutations associated with POT1 were NOTCH1 (44%), TP53 (27%) and SF3B1 (23%). Other cancers (excluding non-melanoma skin cancer) were reported in 19 of the 52 with POT1 mutation (37%). The most common types were prostate cancer (12%), malignant melanoma (10%) and melanoma (4%). Conclusion: Mutations in POT1 were observed in 3.5% of pts with CLL. These pts are young and often have unmutated IGVH. We observed a high occurrence of OC, particularly malignant melanoma and kidney cancer in these pts. Additional studies are ongoing to determine the proportion of pts with germline POT1 mutation, the distribution of variant allele frequencies and additional chromosomal abnormalities in pts with OC. Of 123 CLL patients in 52 Pts with POT1.

7530

Poster Session (Board #284), Mon, 8:00 AM-11:00 AM

Phase 2 study of acalabrutinib in ibritinib (IBR)-intolerant patients (pts) with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). First Author: Kerry Anne Rogers, The Ohio State University, Columbus, OH

Background: In CLL pts treated with the Bruton tyrosine kinase (BTK) inhibitor IBR, the most common reason for discontinuation was adverse events (AEs; 50%-63%; Mato et al, 2018). This Phase 2 trial evaluated acalabrutinib, a highly selective, potent, and irreversible BTK inhibitor. IBR patients were randomly assigned an 84-patient cohort for the CHL arm: ORR = 88% (95% CI 0.65, 1.17, p = 0.363). Estimated OS rate (95% CI) at 5 y was 68.5% (61.5%, 74.5%) in the CHL arm, and 65.7% (58.6%, 71.9%) in the CHL arm. Post-treatment anti-cancer therapy following discontinuation was received by a greater proportion of pts in the CHL (65%) vs. OFA+CHL (56%), and started earlier in the CHL arm (48 vs 57 d). 84 (39%) pts in the OFA+CHL arm and 99 (44%) pts in the CHL arms died during the study with 5-on-treatment deaths in each group. Grade ≥3 adverse events were seen in 64% and 48% of pts in the OFA+CHL vs. CHL arms, respectively, most common being ≥5% in either arm) neutropenia (26% vs. 15%), thrombocytopenia (5% vs. 10%), pneumonia (9% vs. 5%), and anemia (5% vs. 5%). Conclusions: This 5-y survival follow-up analysis supported the results from primary analysis with an estimated 12% (not significant) and 39% risk reduction in OS and PFS, respectively, in the OFA+CHL arm compared with the CHL arm. No new safety concerns were observed in the OFA+CHL arm. Clinical trial information: NCT02748189.

7531

Poster Session (Board #285), Mon, 8:00 AM-11:00 AM

Assessing the potential of immunotherapy in treating chronic lymphocytic leukemia through metacrnavsis analysis of CLL. First Author: Jihad Aljabban, The Ohio State University College of Medicine, Columbus, OH

Background: Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults and has a heterogenous presentation. CLL is known to shape the immune response to survivre. Studying these processes will help gauge the potential success of immunotherapy and point to therapeutic targets.

Methods: We used our Search, Tag, Analyze, Resource platform to meta-analyze patient profiles from Gene Expression Omnibus. We tagged peripheral B cells from 741 CLL patients and peripheral B cell samples from 150 healthy donors as a control. We also tagged and compared B cell samples from 84 CLL progressors to 91 patients with stable CCL. Lastly, we tagged peripheral T cells from 70 CLL patients and T cells from 35 healthy donors as a control. We then analyzed the signature in Immunity Pathway Analysis. Results: Analysis of CLL cell samples identified T cell exhaustion signaling as our top canonical pathway. IL2, IL5, and TGB1 were top upstream regulators. We found upregulation of PDL1, CTA4, and Lag3, known markers for immunosuppressive B cells. FMO, which sequesters TGFβ, was also upregulated along with molecules that modulate BCR signaling such as MIR155HG. EB1F1, required for B cell differentiation, and the co-stimulatory molecule CD80 were downregulated. Analysis of progressing CLL versus stable CLL highlighted metabolic changes. cysteine, cysteine biosynthesis, and acetate conversion to acetyl-CoA were top canonical pathways. No difference was seen in PDL1, CTLA4, and Lag3 expression but EBF1 was upregulated. Lastly, our T cell analysis demonstrated NFAT in regulation of the immune response as the top canonical pathway.

Conclusions: Our results reinforce the promise immunotherapy can have in treatment of CLL and suggests more aggressive cases of CLL are a function of metabolic changes as opposed to differences in immune escape. We also suggest EB1F1 as a target for therapy in the context of CLL.
7532 Poster Session (Board #286), Mon, 8:00 AM-11:00 AM

Background: The phase 3 ECHELON-1 study demonstrated that BV with AVD (A+AVD) was superior to ABVD for the frontline treatment of Stage 3/4 cHL. Maturing data from RATHL and SWOG S0816 show limitations to PET2-adapted strategies, including short- and long-term toxicities in PET2+ patients (pts) switched to BEACOPP and still frequent relapse in PET2- pts. In the RATHL trial with Stage 3/4 disease, 10 yr PFS was 74.4% (67.1% PFS2-) vs 76.4% (66.7% PFS2+) in the ABVD arm. However, patients with low risk 5-yr PFS of 74% (76% PFS2-) in the same population. As an alternative to PET-adapted therapy, we present a 3-year update of the ECHELON-1 study, including ITT PFS and outcomes by PET status.

Methods: Pts with Stage 3/4 cHL were randomized 1:1:1 to receive up to six cycles of AVD (n=644) or ABVD (n=670). Interim PET scan after cycle 2 was conducted. All analyses of PFS are exploratory and per investigator assessment. Results: At a median follow-up of 37 months, analysis of PFS in the ITT population favors the A+AVD treatment arm (Table), with a 3-yr PFS of 85.4% for A+AVD vs 76.0% for ABVD; the 3-yr PFS for PET2+ pts <60 yrs was 87.2% vs 81.0%, respectively. Trend toward benefit for PET2- pts <60 yrs treated with A+AVD was also observed, with a 3-yr PFS of 69.2% vs 54.7% with ABVD. Data from prespecified subgroups and safety follow-up, including peripheral neuropathy, will be presented. Conclusions: For patients at risk, A+AVD demonstrates that frontline treatment of Stage 3/4 cHL with A+AVD provides a durable treatment benefit vs ABVD that is independent of PET2 status. While direct comparisons cannot be made, A+AVD compares favorably to PET-adapted strategies without requiring interim PET assessment, escalation of therapy, or blinzing. Clinical trial information: NCT01712490.

7534 Poster Session (Board #288), Mon, 8:00 AM-11:00 AM

Background: A large fraction of patients with relapsed/refractory (r/r) Classic Hodgkin Lymphoma (cHL) enjoy a beneficial response induced by PD-1. However, no reliable predictive biomarkers for response or resistance are available. Sintilimab, an anti-PD1 agent, has recently demonstrated efficacy and safety in a single-arm, phase II study of patients with r/r cHL (ORIENT-1). The predictive value of circulating tumor DNA (ctDNA) in longitudinal samples from patients in ORIENT-1 was investigated.

Methods: A total of 192 plasma samples were collected from 75 patients prior to treatment and during therapy. After ctDNA extraction next-generation sequencing (NGS) was performed using the HiSeq Sequencing System to assess either a 619 or 659 gene panels at an average sequencing depth of 1260X. The panels include frequently mutated genes in cHL and other hematological malignancies. DNA from paired granulocytes was sequenced as a preservative germline control. Results: The genomic profiling of baseline ctDNA revealed a mean allele mutation frequency of 5.47%. Among the most frequently mutated genes in these cHL patients, PLC0 and LRPA1 are likely unique to Chinese r/r cHL patients. Truncating mutation of B2M, DNAH3, TNRFSF14 and KDM2B were found in patients with acquired resistance, of which TNRFSF14 and KDM2B have not been reported before and need to be confirmed in further study. The baseline ctDNA level was significantly different between objective response group (CR+PR, n = 41, median = 8.72) and non-responder group (SD+PD, n = 9, median = 2.9) (p = 0.0070). Patients with ctDNA high achieved response earlier than others (p<0.05). A drop of 40% in ctDNA after three cycles of therapy confirmed as best cut-off to a gradual progression associated with clinical benefit, demonstrating 100% specificity. Patients with ctDNA drop ≥40% achieved response significantly earlier (median = 71 days) than others (median = 216 days, p=0.0074). Conclusions: Our study demonstrated that ctDNA could serve as valuable biomarker for prediction of response or resistance to anti-PD-1 immunotherapy.

7535 Poster Session (Board #289), Mon, 8:00 AM-11:00 AM

Background: Primary central nervous system lymphoma (PCNSL) is a rare type of non-Hodgkin lymphoma, distinguished by poor prognosis. Previous studies have identified MYD88, CD79b and PIM1 as the most common genetic mutations in PCNSL. However, the extent to which mutations vary by ethnicity is unknown. The purpose of this study was to describe differences in genetic mutations and survival by Hispanic ethnicity in PCNSL. Methods: We retrospectively reviewed records of 30 patients with PCNSL diagnosed between January 2007- December 2017. We examined mutations in 275 genes by DNA analysis and 1382 genes by RNA analysis utilizing next generation sequencing. Results: Among the thirty patients, median age was 60 years, 60% were male, and 60% were Hispanic. Twenty-four patients had activated B-cell (ABC) and 5 patients had germinal center (GC) type per Hans criteria. Among 29 patients with complete mutation data, 125 different mutated genes were detected. Missense mutations were the most common (75%) followed by frame shift mutations (25%). The most commonly affected genes were: MYD88 (44%), CARD11 (21%), CD79b (17%), PIM1 (17%), KMT2D (17%) and ETVB (14%). CD79b mutation was more common in GC type vs. ABC type (60% vs. 8%, P=0.01). MYD88 mutation was less frequent in Hispanic patients (27% vs 66%, P=0.02), while there were no statistically significant differences in CARD11 (22% vs 18%, P=.79), KMT2D (22% vs 9%, P=.36), CD79b (16% vs 19%, P=.92) and PIM1 (16% vs 19%, P=.92). There were more Hispanic patients with >3 mutated genes (89% vs 55 %, P=.03). Two-year progression-free survival (PFS) and overall survival (OS) were 46% and 50%, respectively. Both outcomes were superior among Hispanic vs. non-Hispanic patients (2-year PFS 60% vs 27%, P=.09), (2-year OS 60% vs 36%, P=.23). but this was not statistically significant. MYD88, CARD11, PIM1, and KMT2D were not associated with significant differences in 2-year OS or PFS. However, patients with CD79b mutations had superior 2-year PFS (P=.04).

Conclusions: We identified highly recurrent genetic alterations in PCNSL. Our data suggest that some heterogeneity in the most frequent mutations in PCNSL may be related to ethnicity. However, the superior survival in 2-year PFS and OS did not reach statistical significance in our Hispanic patients. Further studies on a larger patient population may further help to describe the differences in incidence, tumor biology, and outcomes in Hispanic patients.

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Impact on survival of surveillance imaging after first remission in follicular lymphoma. First Author: Jimmy Mao, Department of Medicine, Mayo Clinic, Rochester, MN

**Background:** While most patients (pts) with follicular lymphoma (FL) achieve an initial response to treatment, the majority relapse. Recently, Goldman et al. reported that surveillance imaging (SI) in FL is not associated with improved post-relapse outcomes and is frequently associated with false positive scans (ASH 2017). The goal of this study was to validate these findings.

**Methods:** Pts were enrolled in the University of Iowa/Mayo Clinic SPORC Molecular Epidemiology Resource (MER), a prospective cohort of newly diagnosed lymphoma pts. All pts were followed for events including relapse, re-treatment, and death, with events verified by medical records. Pts eligible for this study had biopsy proven FL grade 1, 2, or 3a who had achieved a response after induction therapy and later relapsed. Initial and post-treatment management was per treating physician. Medical records were re-reviewed in pts with events for clinical details at relapse in relation to planned follow-up visits and SI. Relapse detection was categorized either by clinical suspicion (CS) via history, exam, and/or labs; or by SI in an asymptomatic pt. Univariate survival analysis was conducted for each variable. The hazard ratio with 95% confidence interval based on Cox Proportional Hazard models was presented along with the log rank test p-value. Kaplan-Meier plots were produced to evaluate the difference in overall survival (OS) between groups. Results: 1121 FL pts were enrolled in MER from 2002-2015, of which 117 were eligible. Median age at diagnosis was 60 years (range 17-84) and 62% were female. 145 pts relapsed within 12 months (range 7-36) and 117 pts was 26 months (range 9-125). At a median follow-up from relapse of 69 months (range 0.23-179), 26 pts died. Pts completed a median of 3 imaging studies (range 0-15) during post-induction surveillance, 63 relapses (56%) were detected based on CS; 50 (44%) were detected by SI, and 4 were unknown. There was no difference in OS for relapse for those with relapse detected via CS vs. SI (HR = 0.98 [0.45,2.12], p = 0.96).

**Conclusions:** Routine SI does not appear to improve survival outcomes in FL after achieving first remission, and its common practice should be questioned. Further investigation of prognostic markers to identify high-risk FL pts who may benefit from SI is needed.

**References:**
- Author: Ranjana H. Advani, Stanford Cancer Institute, Stanford, CA
- Response to ACHP by CD30 expression in the ECHELON-2 trial.
- CD30
- AITL
- 69 months (range 0.23-179), 26 pts died. Pts completed a median of 3 imaging studies (range 0-15) during post-induction surveillance, 63 relapses (56%) were detected based on CS; 50 (44%) were detected by SI, and 4 were unknown. There was no difference in OS for relapse for those with relapse detected via CS vs. SI (HR = 0.98 [0.45,2.12], p = 0.96).
- Conclusions: Routine SI does not appear to improve survival outcomes in FL after achieving first remission, and its common practice should be questioned. Further investigation of prognostic markers to identify high-risk FL pts who may benefit from SI is needed.

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**Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia** 433s

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**7536 Poster Session (Board #290), Mon, 8:00 AM-11:00 AM**

Response to ACHP by CD30 expression in the ECHELON-2 trial. First Author: Ranjana H. Advani, Stanford Cancer Institute, Stanford, CA

**Background:** Brentuximab vedotin (BV) is an antibody-drug conjugate that targets CD30. The ECHELON-2 (E-2) study demonstrated significantly longer progression-free and overall survival with BV plus cyclophosphamide, doxorubicin, and prednisone (ACHP) versus CHOP in frontline treatment of patients with CD30 positive anaplastic large-cell lymphoma (sALCL) but variable among ALCL non-sALCL subtypes. As ORR is a direct measure of antitumor activity, we expected BV to achieve a response after induction therapy and later relapsed. Initial and post-treatment management was per treating physician. Medical records were re-reviewed in pts with events for clinical details at relapse in relation to planned follow-up visits and SI. Relapse detection was categorized either by clinical suspicion (CS) via history, exam, and/or labs; or by SI in an asymptomatic pt. Univariate survival analysis was conducted for each variable. The hazard ratio with 95% confidence interval based on Cox Proportional Hazard models was presented along with the log rank test p-value. Kaplan-Meier plots were produced to evaluate the difference in overall survival (OS) between groups. Results: 1121 FL pts were enrolled in MER from 2002-2015, of which 117 were eligible. Median age at diagnosis was 60 years (range 17-84) and 62% were female. 145 pts relapsed within 12 months (range 7-36) and 117 pts was 26 months (range 9-125). At a median follow-up from relapse of 69 months (range 0.23-179), 26 pts died. Pts completed a median of 3 imaging studies (range 0-15) during post-induction surveillance, 63 relapses (56%) were detected based on CS; 50 (44%) were detected by SI, and 4 were unknown. There was no difference in OS for relapse for those with relapse detected via CS vs. SI (HR = 0.98 [0.45,2.12], p = 0.96).

**Conclusions:** Routine SI does not appear to improve survival outcomes in FL after achieving first remission, and its common practice should be questioned. Further investigation of prognostic markers to identify high-risk FL pts who may benefit from SI is needed.

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**7537 Poster Session (Board #291), Mon, 8:00 AM-11:00 AM**

PET/CT alone versus PET/CT and MRI-guided therapy in patients with upper aerodigestive tract natural killer/T-cell lymphoma, nasal type: A prospective study. First Author: Tongyu Lin, Cancer Center Sun Yat Sen University, Guangzhou, China

**Background:** Radiotherapy is extremely important in extranodal natural killer/T-cell lymphoma (ENKTL). [18F]-Fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) is a routine pretreatment imaging technique used in ENKTL, while magnetic resonance imaging (MRI) plays a key role in head and neck (HN) cancer. The purpose of this study was to investigate the value of pretreatment HN-MRI and PET/CT-guided therapy in improving survival in upper aerodigestive tract ENKTL (UADT-ENKTL).

**Methods:** We prospectively conducted a single center study on untreated patients with pathologically diagnosed UADT-ENKTL. Patients undergoing PET/CT with/without HN-MRI were decided by clinicians for staging and restaging. The patients were treated with L-asparaginase/Pegaspargase and non-anthracycline-based chemotherapy with intensity-modulated radiation therapy (IMRT).

**Results:** We enrolled 171 patients (median age, 44 years; range, 18-75 years; 118 [69%] males) from April 2011 to March 2018. Overall, 71 patients underwent PET/CT and HN-MRI (PET/CT-MRI) and 100 patients underwent PET/CT only (PET/CT). MOGA and MOGAMIR were the standard of the trial in 8 patients (8/71) undergoing PET/CT based on the Ann Arbor staging system and in 10 patients (10/71) based on the TNM staging system by detecting additional local lesions (P = 0.011 and P = 0.019, respectively). With a median follow-up of 54 months, the 5-year overall survival (OS), local recurrence-free survival (LRFs), non-progression survival (NPS) rates were 72.7%, 68.2%, and 68.2%, respectively, for all patients. The 5-year LRFs rate was 100% in the PET/CT-MRI group and 64.3% in the PET/CT group (P < 0.001). Similarly, the 5-year OS and PFS were longer in the PET/CT-MRI group than in the PET/CT group (84.5% vs. 67.8% and 78.3% vs. 66.5%; P = 0.04 and P = 0.03, respectively). Conclusions: HN-MRI and PET/CT-MRI should be incorporated into routine pretreatment imaging examinations in patients with UADT-ENKTL. Clinical trial information: NCT01788137.
Prognostic value of baseline SUVmax in patients with advanced stage follicular lymphoma receiving frontlin rituximab-based therapy. First Author: Paolo Stehl, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Positron emission tomography (PET) is recommended in follicular lymphoma (FL) for initial staging, evaluation of potential transformation, and response assessment. The prognostic value of pre-treatment PET scan has not been adequately explored. Methods: We performed a single-institution retrospective analysis of patients with advanced stage FL, without histological evidence of transformation, treated with frontlin rituximab-based therapy, and analyzed the prognostic significance of the maximum standardized uptake value (SUVmax). Results: The median follow-up for the cohort was 94 months. Of 346 patients, 151 (44%) received R-CHOP and 195 (56%) received non-R-CHOP regimens. Among multiple single unit increments of SUVmax, a value of >18 showed the strongest association with progression-free survival (PFS) (hazard ratio [HR] 1.5, 95% confidence interval [CI] 0.95 to 2.3, p=0.08), and was selected as cut-off for further analysis. Fifty-two (15%) patients had a SUVmax >18. On univariate analysis, factors associated with SUVmax >18 were male sex (67% vs 52%, p=0.05), elevated β2-microglobulin (65% vs 47%, p=0.02), elevated LDH (37% vs 13%, p<0.001), presence of B symptoms (35% vs 14%, p=0.01), advanced Ann-Arbor stage (6% vs 30%, p<0.001). On multivariate analysis, largest lymph node ≥6 cm was the only factor maintaining its association with SUVmax >18 (odds ratio [OR] 2.7, 95% CI 1.3 to 5.3, p=0.006). SUVmax >18 significantly associated with a lower CR rate among patients treated with non-R-CHOP regimens (45% vs 52% (p=0.001) but not among patients treated with R-CHOP regimens (77 months vs not reached, p=0.02), but not among patients treated with R-CHOP (p=0.73). SUVmax >18 associated with shorter overall survival (OS) both in patients treated with R-CHOP (15 year OS 70% vs 75%, p=0.02) and non-R-CHOP regimens (15 year OS 50% vs 75%, p=0.001). Conclusions: In conclusion, baseline SUVmax has prognostic value in patients with advanced stage FL receiving rituximab-based therapies. Evaluation in prospective studies is needed to further confirm these findings.

Ibrutinib maintenance following induction for untreated mantle cell lymphoma (MCL): Initial safety report. First Author: Reem Karmali, Northwestern University Feinberg School of Medicine; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL

Background: Maintenance rituximab in MCL has improved survival, though the optimal approach is not yet defined. Ibrutinib, a selective BTK inhibitor, has profound activity in R/R MCL. Ibrutinib maintenance (I-M) following induction treatment for naïve MCL has not been explored. We report preliminary results of a multicenter phase II trial assessing efficacy and safety of I-M for MCL after frontline induction. Methods: Patients with MCL with CR/PR to frontline chemo-immunotherapy (+/- autoSCT) received I-M 560 mg daily for up to 4 years. Primary objective was 3 year PFS rate. Secondary objectives were PR to CR conversions, median OS at 4 years (MCL: 12 months), and toxicity with MRD assessments planned. Results: Accrual is complete with 36 patients, median age of 60 (range 46-90), 28 males, 28 with advanced stage and 9 with extranodal disease. 18 (50%), 7 (19%) and 11 (31%) had low vs intermediate and high risk MIPI respectively. 8/24 patients had a Ki-67 ≥ 18%. 9/24 patients had a Ki-67 > 18%. For induction, 17 (47%) received BR, 18 (50%) a cytotoxic-based regimen, 1 (3%) R-CHOP, 18 (50%) had autoSCT in CR1 prior to enrollment. 33 (92%) and 3 (8%) had CR and PR with induction respectively with 1 PR to CR conversion on I-M. At median follow-up of 19 mos, 24/36 (67%) patients remain on I-M (median 15 cycles, range 1-49) with 1 PD and 1 death. TRAEs led to dose reductions/interruptions in 25 (69%) patients, including permanent dose reductions in 7 (19%) and treatment discontinuation in 9 (25%); Table). 3 additional patients discontinued I-M, 1 for endometrial adenosarcoma, 1 PD, death, cause unknown. Conclusions: Ibrutinib maintenance is feasible in MCL patients who respond to frontline chemo-immunotherapy +/- autoSCT with manageable toxicities consistent with prior reports of ibrutinib. Additional follow-up and MRD status correlations with PFS and OS will provide insight on clinical relevance for this approach. Clinical trial information: NCT02242097.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Comparison of clinical scoring systems in aggressive B-cell lymphomas (BCL): An individual patient-level analysis across international trials (SEAL). First Author:Amy S. Ruppert, The Ohio State University, Department of Internal Medicine, Columbus, OH

Background: Great heterogeneity in survival exists for patients (pts) newly diagnosed with aggressive BCL. Three scoring systems based on simple clinical parameters (age, lactate dehydrogenase, number/sites of involvement, stage, performance status) are widely used: the international prognostic index (IPI), revised-IPI (R-IPI), and National Comprehensive Cancer Network IPI (NCCN-IPI). We studied 321 pts treated with R-CHOP to determine which scoring systems best identifies subgroups with poor outcomes that might benefit from new approaches. Methods: Individual pt data from 7 multicenter trials (1998-2009) of pts with BCL (86% DLBCL) treated front-line with R-CHOP (or R-CHOP) were analyzed to determine whether IPI, R-IPI, or NCCN-IPI best discriminated overall survival (OS). The concordance index (c-index) from a proportional hazards model, stratifying on trial and induction therapy, quantified predictive accuracy of each scoring system. Results: 2561 pts (median age 63 yrs, 56% male) were classified into IPI, R-IPI, and NCCN-IPI risk groups (Table). With a median follow-up of 5 yrs, NCCN-IPI had the greatest absolute difference in OS estimates between the highest and lowest risk groups at 1, 3, and 5 yrs, and best discriminated OS (c-index = 0.631, Table). Conclusions: In an independent and large cohort of pts, NCCN-IPI performed best in risk-stratifying aggressive BCL, readily distinguishing pts at high and low risk for treatment failure using clinical parameters (5-yr OS between 48 and 92%). Improvement over the simpler IPI appears incremental, and IPI may remain a valuable alternative. Work integrating molecular features of the tumor into the (NCCN-) IPI is in progress to define high risk groups where targeted novel approaches are needed most.

Table: Scoring System N (%) %Alive 1-yr %Alive 3-yr %Alive 5-yr c-index
IPI
Low 818 (32) 97 90 87 0.621
Low-intermediate 609 (24) 91 83 77 0.589
High-intermediate 609 (24) 86 73 66 0.589
High 525 (20) 75 60 54 0.589
R-IPI
Very low 195 (8) 98 93 93 0.589
Low 1324 (53) 91 84 74 0.621
Intermediate 1134 (44) 81 67 61 0.621
NCCN-IPI
Low 303 (12) 98 92 92 0.631
Low-intermediate 1057 (41) 95 88 83 0.631
High-intermediate 945 (37) 84 70 63 0.631
High 256 (10) 66 54 48 0.631

7546 Poster Session (Board #300), Mon, 8:00 AM-11:00 AM Changes in circulating tumor DNA levels are associated with treatment response and progression-free survival in relapse/refractory DLBCL subjects. First Author: Alexander F. Lovejoy, Roche Sequencing Solutions, Pleasanton, CA

Background: Detection of an initial molecular response to therapy in DLBCL could help differentiate patients who will relapse (30-40% of frontline subjects) from those who will not. Recent studies in DLBCL showed ability to detect residual disease and molecular response to therapy from analysis of circulating tumor DNA (ctDNA). Here we performed targeted genetic sequencing (NGS) of baseline ctDNA vs. tumor tissue, and on-treatment ctDNA samples in 32 relapse/refractory DLBCL subjects from the ROMULUS study to assess correlation of outcome with molecular response. Methods: We sequenced plasma, plasma depleted whole blood (PDWB), and tumor DNA from 32 subjects (range 2-6 samples / subject). Library preparation and NGS were performed using hybrid capture-based workflows, with a panel of ~300 kb targeting regions relevant for disease detection in DLBCL. Variants were called from tissue and plasma data, and PDWB data were used to filter out non-tumor specific variants. Results: 83% of variants detected in tissue (1441/1745) were found in the corresponding plasma samples, and 78% of variants detected in plasma (1441/1846) were found in corresponding tissue samples, in line with previous reports. To follow ctDNA changes with treatment, tumor-specific variants were determined from tissue or cycle 1 day 1 (C1D1) plasma samples. These variants were then monitored in C1D1 and later timepoints, with similar ctDNA levels based on variants determined from C1D1 plasma or tissue (R²=0.99). Change in ctDNA levels from C1D1 to C2D1 separated subjects that responded from subjects that progressed (Wilcoxon p-value: 9.39×10^-10). Subjects that showed a 10-fold or higher drop in ctDNA levels between C1D1 and C2D1 had significantly longer PFS than those with a smaller ctDNA fold change (HR: 8.06; p=0.0008). Conclusions: This study showed that tumor-specific variants can be identified in baseline plasma with similar performance as from tumor tissue, and that monitoring molecular response as an early change in ctDNA levels after one cycle of treatment correlated with outcomes in this DLBCL study. Clinical trial information: NCT01691898.

7547 Poster Session (Board #301), Mon, 8:00 AM-11:00 AM Outcomes of lenalidomide in diffuse large B-cell (DLBCL) and high-grade B-cell lymphoma (HGBCL): A retrospective, prospective analysis. First Author: Thomas David Rodgers, University of Rochester Medical Center, Rochester, NY

Background: Outcomes remain poor for patients with relapsed refractory DLBCL and HGBCL, especially those ineligible for a stem cell transplant or CAR T-cell therapy. Lenalidomide has efficacy in these groups, most notably in the activated B-cell like (ABC) subtype when defined by gene expression profiling. We analyzed the outcomes of consecutive patients with DLBCL treated with lenalidomide, focusing on characteristics such as transformed histology and MYC translocation status. Methods: We performed a retrospective review of consecutive patients with transformed indolent NHL, DLBCL, and HGBCL treated with lenalidomide at the University of Rochester between 2011-2018. Cell of origin was determined by Hans algorithm and FISH was performed to detect MYC, BCL2, and BCL6 translocations. Kaplan Meier estimates and descriptive statistics were utilized for analysis. Results: 62 patients were identified with a median age of 76 years, the majority with ≥ 2 prior therapies. ORR was 43.5%, including 14 patients with a CR. Median PFS was 4.6 months with 18 patients achieving a PFS > 1 year. Median OS was 14 months. No difference in PFS, OS, or ORR was observed between the de novo germinal center b-cell (GCB) and non-GCB populations (PFS 4 vs. 5 months, p=0.87). 16 patients with transformed FL had a median PFS of 24 months and a median OS of 46.7 months (vs. de novo GCB OS of 7.8 months, p=0.02). Notably, 67 MYC+ patients achieved an objective response, including 3 with a CR. All patients with double and triple hit disease had an objective response, including two PRs and one CR. Conclusions: Our experience confirms the clinical activity of lenalidomide in heavily pretreated older adults with DLBCL. Outcomes did not differ by cell of origin using the Hans immunohistochemistry algorithm and durable responses were observed, particularly in transformed FL. Nearly all of the MYC+ patients responded, including those with double/triple hit genetics, and almost half achieved a CR. Based on our data, lenalidomide may be an optimal bridge to consolidative cellular therapy in high-risk patients irrespective of genotype, particularly in transformed indolent histologies.
Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia

Poster Session (Board #302), Mon, 8:00 AM-11:00 AM
Early progression of disease (POD24) as survival predictor in MALT lymphoma.
First Author: Annarita Conconi, Hematology Division, Ospedale Degli Infermi, Bologna, Italy

Background: Early progression of disease within two years from start of therapy (POD24) is linked with poor outcome in follicular lymphoma. It is less clear whether POD24 affects overall survival (OS) also in extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma).

Methods: We analyzed data from the IELSG19 clinical trial (training set) to determine whether POD24 is associated with inferior OS. The study population included 401 EMZL patients (131 randomly assigned to chlorambucil treatment, 138 to rituximab and 132 to chlorambucil plus rituximab). Reproducibility was analyzed in an independent cohort (validation set) of 218 patients who received systemic treatment (chemotherapy, immunotherapy or both). In both, training and validation sets, we excluded from the analysis the patients who, within 24 months from treatment start, died without progression or were lost to follow-up without progression. Overall survival (OS) was calculated from disease progression in patients with POD24 and from 24 months after start of treatment in those without POD24 (reference group).

Results: POD24 was observed in 69 of 401 patients of the IELSG19 study and 58 of 218 patients in the validation set. In the training set, the 10-year OS rates were 64% in the POD24 group and 85% in the reference group (HR = 2.42, 95% CI: 1.35-4.34; log-rank P = 0.002) and POD24 predicted poor outcome regardless of treatment type (multivariable Cox model, P = 0.003). The prognostic impact of POD24 was confirmed in the validation set, with 10-year OS rates of 11% in the POD24 group and 71% in the reference group (HR = 2.17, 95% CI: 1.20-3.93; log-rank P = 0.009).

Conclusions: In patients with EMZL who received front-line systemic treatment, POD24 is associated with poorer survival and may represent a useful endpoint in prospective clinical trial.

Poster Session (Board #303), Mon, 8:00 AM-11:00 AM
Molecular profiling of primary central nervous system lymphoma as compared to activated B-cell subtype of diffuse large B-cell lymphoma.
First Author: Muhammed Barakat, University of California, San Francisco, CA

Background: The cell of origin of primary central nervous system lymphoma (PCNSL) remains controversial. Data using immunohistochemistry (IHC) and Hans algorithm suggested that both germinal-center B-cell–like (GCB) and activated B-cell-like (ABC) subtypes can be seen in PCNSL. We explored the potential of DNA and RNA molecular profiling in characterizing the biology of PCNSL and compared this profile with ABC subtype of diffuse large B-cell lymphoma (DLBCL).

Methods: RNA and DNA were extracted from 30 formalin-fixed paraffin-embedded (FFPE) tissue samples from PCNSL patients and 30 FFPE tissue samples from cases with lymph node DLBCL of ABC subtype. Subtyping of DLBCL cases was performed using IHC and gene expression profiling. We sequenced the DNA using a 275 gene panel (Qiagen) and the RNA using a 1382 gene panel ( illumina). Next Generation Sequencing on Illumina platform was used for detecting mutations and expression profiling. The levels of RNA expression were normalized to that of PAX5. Mutations detected by RNA sequencing were compared to those detected by DNA sequencing. Results: There was no significant difference between DLBCL-ABC and PCNSL in mutation rate of MYD88, CD79B, CARD11 or KMT2D. 33.3%, 10%, 10%, and 13.3%, respectively, in DLBCL-ABC vs 30%, 10%, 10%, and 10%, respectively, in PCNSL. However, NOTCH2 mutations were significantly different and detected in 16.7% of DLBCL-ABC as compared with 3% in PCNSL (P<0.01). An algorithm that uses expression profiling of 46 different genes and distinguishes DLBCL-ABC from GCB-PCNSL was classified as ABC. The GCB classical marker LMO2 was expressed at very low level in both DLBCL-ABC and PCNSL, but was at relatively higher level in PCNSL (P<0.002, Kruskal-Wallis ANOVA). There was significantly higher expression of the adhesion molecule CXCR4 (P<0.008), activation molecules BTK (P<0.0003) and PLCG2 (P<0.002), and BCL6 (P<0.002) in PCNSL as compared with DLBCL-ABC. There was no significant difference between the two groups in MYC, Ki67, BCL2, CD44, or CD274 (PD-L1) expression.

Conclusions: DNA and RNA molecular profiling of PCNSL suggests similarity to DLBCL-ABC subtype. However, PCNSL is unique by expressing higher levels of the adhesion molecule CXCR4 and the activation molecules BTK and PLCG2. The lack of increased expression of MYC and Ki67 suggests that PCNSL is unlikely to be similar to Burkitt lymphoma.
Monitoring ctDNA in r/r DLBCL patients following the CAR T-cell therapy axicabtagene ciloleucel. Day 28 landmark analysis. First Author: Matthew Joshua Frank, Stanford Univ Hosp and Clinics, Palo Alto, CA

Background: Axicabtagene Ciloleucel (Axicel) is an autologous anti-CD19 CAR T-cell therapy approved for the treatment of relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). Long-term analysis of the ZUMA-1 clinical trial showed ~40% of patients remained progression-free at 2 years (Locke, Lancet Oncol 2018). Early identification of patients who will later progress after CAR T cell therapy may improve clinical care and patient outcomes.

Methods: As of 2/1/2019, we enrolled 50 patients on a multi-institutional, prospective study measuring circulating tumor DNA (ctDNA) minimal residual disease (MRD) in r/r DLBCL patients undergoing treatment with Axicel. Using an next generation sequencing-MRD assay (Adaptive Biotechnologies; Seattle WA), ctDNA levels were measured pre, 0, 7, 14, 21, 28, 56, 90, 180, 270, and 365 days following Axicel infusion. A pre-planned comparison between EDTA, Streek, and CFD tubes for the initial 10 enrolled patients determined the CFD tube provided optimal analyte stability over 144 hours following sample collection. CFD tubes are being used to collect all study samples.

Results: 24 subjects have 3 or more months clinical follow up and their treatment ctDNA MRD signal can be assessed with clinical outcomes. A day 28 landmark analysis shows 12 patients were MRD negative and 12 patients were MRD positive as defined by detection of none or any tumor-associated ctDNA, respectively. 10 of 12 MRD+ patients subsequently developed progressive disease. In contrast, only 2 MRD- patients subsequently progressed and the other 10 patients remain in CR. (p = 0.0033, Fisher's exact test). With a median follow up of 237 days, median PFS after Axicel infusion for day 28 MRD+ vs. MRD- patients is 93 days vs. not reach, p = 0.0011 by Log-rank test. Median OS for day 28 MRD+ vs. MRD- patients is 281 days after Axicel infusion vs. not reach, p = 0.0399 by Log-rank test. Conclusions: After Axicel infusion, day 28 ctDNA-based MRD significantly associated with PFS and OS and identified early at-risk patients prior to progression. These results provide a rationale for designing MRD-based risk-adaptive CAR T-cell clinical trials.

Extranodal (EN) and spleen disease by FDG-PET/CT as predictors of event-free survival (EFS). performed using PRIMA-PI factors, the presence of EN sites (‡) dependently predicted a lower EFS (Table). When the multivariate analysis was also predictive of OS. In a multivariate analysis with FLIPI-2 factors, spleen involvement was significantly associated with survival. However, aggressive and favorable, with no evidence of late-onset severe toxicities. Clinical trial information: NCT01660451.

Monitoring ctDNA in r/r DLBCL patients following the CAR T-cell therapy axicabtagene ciloleucel. Day 28 landmark analysis. First Author: Matthew Joshua Frank, Stanford Univ Hosp and Clinics, Palo Alto, CA

Background: Axicabtagene Ciloleucel (Axicel) is a US FDA-approved, autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy for the treatment of pts with relapsed or refractory large B-cell lymphoma (LBCL). First Author: Satvaa Swarup Neelapu, The University of Texas MD Anderson Cancer Center, Houston, TX

# of EN sites (‡) (n=101). The ORR for pts (Phases 1 and 2) was 83% (CR rate 75% and 53%), respectively, with ongoing responses in 42% and 38% of pts (ongoing CR 75% and 53%). The 24-mo OS rate was 54% for pts $< 65 y, respectively. The 2-y follow-up of ZUMA-1, the objective response rate (ORR) was 83% with a complete response (CR) rate of 58%, and 39% of pts were in ongoing response (Locke et al., Lancet Oncol. 2019). Here we report efficacy and safety outcomes by age. Methods: Eligible pts with refractory LBCL underwent leukapheresis and conditioning chemotherapy followed by a target dose of 2 × 10^9 anti-CD19 CAR T cells/kg. The Phase 2 primary endpoint was investigator-assessed ORR. Additional key endpoints were adverse events (AEs), overall survival (OS), and levels of CAR gene-marked cells in peripheral blood. Efficacy was evaluated for Phase 2 pts; safety was evaluated for all treated pts (Phases 1 and 2). Pts were analyzed by $< 65 y vs $\geq 65 y of age. Results: As of 8/11/2018, 108 pts were treated. Pts $< 65 y (n = 27) vs $\geq 65 y (n = 81) had a median age of 69 y vs 55 y, respectively, were 81% vs 63% male, 70% vs 56% had an IPI score 3-6, 59% vs 57% had ECOG 1, 67% vs 72% had $\geq 3 prior therapies, and median tumor burdens were 3790 mm^3 vs 3754 mm^3. Median follow-up was 27.1 mo for Phase 2 pts (n = 101). The ORR for pts $\geq 65 y (n = 24) and $< 65 y (n = 77) was 92% and 81% (CR rate 75% and 53%), respectively, with ongoing responses in 42% and 38% of pts (ongoing CR 42% and 35%). The 24-mo OS rate was 54% for pts $\geq 65 y and 49% for pts $< 65 y. Most pts experienced Grade $\geq 3 AEs (100% of pts $\geq 65 y; 98% of pts $< 65 y), and 4% of each group (1/27 pts $\geq 65 y and 3/81 pts $< 65 y) died due to AEs as previously reported. Grade $\geq 3 neurologic events and cytokine release syndrome occurred in $3$% and 7% vs 12% of pts $\geq 65 y, respectively. CAR T cell expansion by peak level (43 vs 35 cells/µl) or area under the curve (562 vs 448 x cells/ µl) was similar in pts $\geq 65 y vs $< 65 y, respectively. Conclusions: The 2-y follow-up of ZUMA-1 demonstrates that axicel can induce high rates of durable responses with low toxicity compared to historical controls. Axicel offers substantial clinical benefit for older pts with refractory LBCL who otherwise have limited treatment options. Clinical trial information: NCT02348216.

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7552 7553 Poster Session (Board #306), Mon, 8:00-11:00 AM Monitoring ctDNA in r/r DLBCL patients following the CAR T-cell therapy axicabtagene ciloleucel. Day 28 landmark analysis. First Author: Matthew Joshua Frank, Stanford Univ Hosp and Clinics, Palo Alto, CA

Poster Session (Board #307), Mon, 8:00-11:00 AM

Monitoring ctDNA in r/r DLBCL patients following the CAR T-cell therapy axicabtagene ciloleucel. Day 28 landmark analysis. First Author: Matthew Joshua Frank, Stanford Univ Hosp and Clinics, Palo Alto, CA

Poster Session (Board #308), Mon, 8:00-11:00 AM

Extranodal and spleen involvement by FDG-PET/CT as predictors of event-free survival (EFS). performed using PRIMA-PI factors, the presence of EN sites (‡) dependently predicted a lower EFS (Table). When the multivariate analysis was also predictive of OS. In a multivariate analysis with FLIPI-2 factors, spleen involvement was significantly associated with survival. However, aggressive and favorable, with no evidence of late-onset severe toxicities. Clinical trial information: NCT01660451.

Extranodal and spleen involvement by PET/CT as predictors of event-free survival. Multivariate analysis for EFS

Variable & HR & P value \\
--- & --- & --- \\
Bone involvement (n=204) & 1.20 (0.90-1.60) & 0.21 \\
# of EN sites (‡ vs 0-1) (n=69) & 1.43 (0.99-2.07) & 0.06 \\
Multifocal on diffuse pattern of bone involvement (n=43) & 1.71 (1.10-2.65) & 0.02 \\
Spleen involvement (n=171) & 1.49 (1.11-2.00) & <0.01 \\
Soft tissue involvement (n=43) & 1.67 (1.06-2.62) & 0.02 \\

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Efficacy of frontline treatment regimens in follicular lymphoma: A network meta-analysis of phase III randomized controlled trials.

**Background:** The frontline treatment for advanced follicular lymphoma has evolved with the introduction of maintenance therapy, bendamustine (Bend), obinutuzumab (G), and lenalidomide (Len). We conducted a network meta-analysis of phase 3 randomized controlled trials (RCTs) to identify the regimens with superior efficacy. **Methods:** Data were extracted from 7 RCTs (FOLL05, Stil NHL1, BRIGHT, PRIMA, GALLIUM, Stil NHLT, and RELEVANCE). Progression-free survival (PFS) was compared between regimens with different immunochemotherapy and maintenance strategies. To incorporate direct and indirect comparisons, random-effects Bayesian network meta-analyses were conducted after adjusting for study-wise variation. The posterior inference was derived based on Markov chain Monte Carlo methods and implemented using JAGS v4.3.0. Pairwise comparison of hazard ratios (HRs) and 95% credible intervals (CIs) were calculated. **Results:** PFS HRs of other regimens compared to the reference regimen are summarized in the Table. Compared to Rituximab-R (R)-BCHOP had inferior PFS, R-CHOP-R, G-CHOP-G, and R-Len-R had similar PFS, while R-Benda-R, R-Benda-R4 and G-Benda-G had better PFS. In addition, the PFS for G-Benda-G was similar to R-Benda-R4 (HR 0.94, 95% CI 0.78-1.09) but better than R-Benda-R (HR 0.82, 95% CI 0.75-0.97). **Conclusions:** Compared with the commonly used R-Benda and R-CHOP-R regimens, G-CHOP-G and R-Len-R had better PFS, while the chemotherapy-free regimen R-Len-R had similar PFS.

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R-based Induction + mR

<table>
<thead>
<tr>
<th>Regimen</th>
<th>R-Benda-R</th>
<th>R-Benda-R4</th>
<th>R-CHOP-R</th>
<th>G-CHOP-G</th>
<th>R-Len-R</th>
<th>R-Len-R4</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI) compared to R-Benda-R</td>
<td>0.67 (0.60-0.75)</td>
<td>0.67 (0.60-0.75)</td>
<td>0.67 (0.60-0.75)</td>
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<tr>
<td>HR (95% CI) compared to R-CHOP-R</td>
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<td>HR (95% CI) compared to R-Len-R</td>
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Preliminary results of earlier steroid use with axicabtagene ciloleucel (axi-cell) in patients with relapsed/refractory large B-cell lymphoma (R/R LBCL).

**Background:** Axicabtagene ciloleucel (axi-cell) is an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy approved in the US and EU for patients (pts) with R/R LBCL with ≥ 2 prior systemic therapies. In the 2-year follow-up of ZUMA-1, the objective response rate (ORR) was 83% with a complete response (CR) rate of 38% for Grade 3 cytopenias (CRS) and neurotoxicity (NE) defined in 11% and 32% of pts, respectively; 26% of pts received steroids, and 43% received tocilizumab (Locke et al. Lancet Oncol. 2019). A safety expansion cohort was added to evaluate the effect of earlier steroid use on the rates of these adverse events (AEs). **Methods:** Eligible pts with R/R LBCL were leukapheresed and received conditioning chemotherapy followed by a target dose of 2 × 10^6 anti-CD19 CAR T cells/kg. Pts in this cohort received early steroid intervention starting at Grade 1 NE and at Grade 1 CRS when no improvement was observed after 3 days of supportive care. The primary endpoint for this cohort was incidence and severity of CRS and NE. **Results:** Of 91/4/2018, 21 of 40 planned pts received axi-cell with a minimum follow-up of 1 mo (median, 2.6 mo). The median age was 63 y (range, 36–73), 67% were male, 81% had disease stage III–IV, 76% were R/R to ≥2-line therapy, and 10% had relapsed post-autologous stem cell transplantation. Seventy-six percent of pts received steroids and 81% received tocilizumab. Most pts (81%) had Grade ≥ 3 AEs, most commonly neutrophil count decreased (33%), anemia (29%), and pyrexia (24%). Grade ≥ 3 NE occurred in 10% of pts; the most common symptoms were somnolence (10%) and confusional state (10%). Grade 1 and 2 NE occurred in 38% and 5% of pts, respectively. No pt had Grade ≥ 3 CRS; 33% of pts had Grade 1 CRS and 67% had Grade 2. There were no deaths due to AEs; 1 pt died due to disease progression. The ORR per investigator assessment was 76% with 48% of pts achieving a CR. Pharmacokinetic data will be presented. **Conclusions:** Early use of steroids may help in managing severe CRS and NE by potentially reducing their incidence in pts treated with CAR T cell therapy without affecting the response rate. Axi-cell intervention helped further improve the benefit-risk profile of CAR T cell therapy. Clinical trial information: NCT02348216.

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Rituximab-based maintenance therapy in Waldenström macroglobulinemia: A case control study.

**Background:** Waldenström macroglobulinemia (WM) is a rare indolent lymphoma commonly treated with rituximab (R)-based therapy. The use of rituximab maintenance (mR) in WM is controversial. We present a case-control study of patients (pts) with WM treated with mR. **Methods:** Pts evaluated at Mayo Clinic, Rochester with active WM that received mR between 1/2000 & 6/2018 were included. Cases comprised pts who received mR following R-based induction as primary therapy. Cases were matched based on the time of diagnosis (95% CI); the mean percentage of PD-L1 positivity was 19.7% (range, 5–50%). Fourteen patients (82.3%) developed cytokine release syndrome (grade ≥2) and four (23.5%) developed neurotoxicity (grade ≥3), which was reversible in all. The overall response rate was 58.8% (10/17) and complete remission rate was 41.2% (7/17). At a median follow-up of 5 months, median overall survival for all patients was not reached. **Conclusions:** This trial showed the feasibility, tolerability, and efficacy of using the anti-PD-1/CD19 CAR-T cells for treating patients with R/R B-cell lymphoma providing the first-principle of the potential therapeutic value of targeting the PD-1/PD-L1 pathway in lymphoma in the clinical setting. Clinical trial information: NCT03258047.
Effect on subsequent TTG (P-value = 0.3). Additionally, the regression analysis showed a significant predictor of subsequent TTG (beta-coefficient = 1.26 (0.39-2.13); P-value = 0.02; adjusted-R-squared = 0.97), while the baseline TTG did not have any significant predictive value in baseline and day 30 SUVmax of baseline and day 30 SUVmax. However, the prediction of PR was on Global-SUVmean with P-values > 0.8. Conclusions: Early post-axi-CTL TTG, rather than baseline, can predict subsequent response to treatment. None of the SUV indices, commonly used in daily practice, were predictive of eventual response.

Methods: TTG was measured by MIM Software using a 41% SUVmax threshold with manual lesion contour adjustment and radiologist review. Low and high MTV groups were defined based on median cutoff value. Cytokine release syndrome (CRS) was graded by Lee et al. (Blood. 2014). Neurotoxicity (NT) was graded by CTCAE v4.0. Toxicities, overall response rate (ORR), and complete response rate (CR) were evaluated via Fisher’s test; PFS and OS via Kaplan-Meier and log-rank test. Results: 48 patients with BCL, or its variants, that received axi-CTL at Moffitt from June 2015 to October 2018 were included. 31 were male, and median age was 63 years (range, 28-76). CRS occurred in 43/47 (91.5%) and NT in 32/47 (68.1%) patients. Grade 3-4 CRS in 2/47 (4.3%) and NT in 12/47 (25.5%). Median follow up for survivors was 8.9 months (range, 1.4-36.8 months). CR was achieved in 31/48 (64.6 %) and OR in 39/48 (81.3%). Median for the low MTV group was 35.1 mL (range, 4.24-132.8 mL) and for the high MTV group 455.5 mL (range, 162.2-1221.4 mL). High MTV was not predictive of subsequent TTG or OR (OR = 1.14, p = 0.99; OR = 1.66, p = 0.52). Similarly, high MTV was not predictive of G1-4 CRS or G3-4 CRS (OR = 0.29, p = 0.348; OR = 1.05, p = 0.99). Low MTV was predictive of OR (OR = 11.50, p = 0.026) and CR (OR = 9.8, p = 0.002). Patients with high MTV had inferior PFS (HR = 3.296, 95% CI 1.42-7.64, p = 0.008) and OS (HR = 6.68, 95% CI 2.56-17.32, p = 0.003). Conclusions: High baseline MTV is associated with decreased and less durable response following axi-CTL. As survival data mature, future analyses will aim to assess the role of MTV as an independent prognostic tool in axi-CTL recipients with BCL.
7564 Poster Session (Board #318), Mon, 8:00 AM-11:00 AM
Prediagnosis cardiovascular risk and subsequent myocardial infarction (MI) among lymphoma survivors. First Author: Talya Salz, Memorial Sloan Kettering Cancer Center, New York, NY
Background: Chest radiation is associated with increased risk of MI among lymphoma survivors. The extent to which pre-existing cardiovascular risk factors also contribute to risk is understudied. We investigated this association among a national population of lymphoma survivors with a full range of cardiovascular risk factors.
Methods: Using Danish population-based registries, we identified all adults diagnosed with aggressive non-Hodgkin lymphoma or Hodgkin lymphoma from 2000-2010 and followed them from 1 year after diagnosis through 2016. MI was ascertained from the nationwide Hospital Discharge Register and Cause of Death Register. Cardiovascular risk factors (hypertension, dyslipidemia, and diabetes), vascular disease, and intrinsic heart disease prevalent at lymphoma diagnosis were ascertained algorithmically using the National Prescription Register and the Hospital Discharge Register. Controlling for age, sex, history, receipt of chest radiation, and prevalent cardiovascular diseases, we used multivariable Cox regression to test the association between pre-existing cardiovascular risk factors and sub-sequent MI.
Results: Among 4246 survivors of lymphoma, median age at diagnosis was 65 (interquartile range 45-70 years). 115 survivors were diagnosed with MI. Before lymphoma diagnosis, 28% of survivors had ≥1 cardiovascular risk factor, and 16% of survivors received chest radiation. In multivariable analysis, survivors who received chest radiation had an increased risk of MI compared to survivors who did not (HR=1.92 [95% CI=1.16-3.17]). Survivors with ≥1 cardiovascular risk factor had an increased risk of MI compared to survivors with none (HR = 2.44 [95% CI=1.65-3.62]).
Conclusions: In a large, well-characterized, nationally representative study of contemporarily treated lymphoma survivors, prevalent hypertension, dyslipidemia, and diabetes were associated with later MI. Findings suggest that pre-existing cardiovascular risk factors confer the same amount of MI risk as does chest radiation. To prevent MI among survivors, decisions about post-treatment monitoring should address prevalent cardiovascular risk.

7565 Poster Session (Board #319), Mon, 8:00 AM-11:00 AM
Effect of epigenetic modifier-based combinations on efficacy in patients with peripheral T-cell lymphoma (PTCL): Deciphering impact of mutations in epigenetic operations on response. First Author: Owen A. O’Connor, Columbia University Medical Center, New York, NY
Background: Recurring mutations in epigenetic functions in PTCL, coupled with marked activity of epigenetic drugs, raises a question regarding whether these mutations might portend greater vulnerability to one drug over another. For example, do mutations in genes governing DNA methylation suggest these patients might benefit from a hypomethylating (HMMA) agent? Preclinical data from one group suggests marked synergism between histone deacetylase inhibitors (HDACi) and HMA, as well as HDACi and pralatrexate (PDX), irrespective of mutations in epigenetic genes. Phase 1 studies (romidepsin [R] plus PDX or R plus 5-azacytidine [Aza]) are completed, and the Phase 2 studies are near completion. This clinical trial scenario affords a unique opportunity to decipher the impact of a HMA on response as a function of TET2, ID2H, DNM3T and other mutations in PTCL.
Methods: Patients with R/R lymphoma were eligible for the phase 1, whereas the phase 2 only enrolled patients with PTCL, either R/R or treatment-naïve individuals. Exploratory endpoints included next generation sequencing (NGS) and methylation arrays.
Results: In toto, 89 patients have been enrolled. Two phase 1 all histology’s, 58 have PTCL. NGS and efficacy data is available for the majority of patients, with some from the PDX + R study in process. The ORR among the PTCL patients for PDX+R and Aza+R has been 71% and 73% respectively. Eight of 9 angioimmunoblastic TCL patients responded. Among those with TET2 mutations, 7 of 8 responded to the Aza-based treatment, while only 3 of 6 (50%) responded to the TET2 negative
Conclusions: With the completely annotated analysis correlating clinical metrics to the spectrum of epigenetic mutations and GDMs across all histology’s and treatments. Clinical trial information: NCT01998035; NCT01947140.

TPS7566 Poster Session (Board #320a), Mon, 8:00 AM-11:00 AM
ZUMA-8: A phase I/2 multicenter study evaluating KTE-X19 in patients (pts) with relapsed/refractory (RR) chronic lymphocytic leukemia (CLL). First Author: Ian Finn, Saint Cannon Research Institute, Nashville, TN
Methods: To further evaluate the efficacy and safety of KTE-X19 T cells, the current phase I/2 multicenter trial will enroll patients with R/R CLL. Eligibility criteria include Rai stage ≥2, ≥1 prior FLRs, and CD19+ B-cell lymphoma. Patients with prior autologous transplantation are eligible. The primary endpoints of this study are overall survival, safety, and patient-reported outcomes. Secondary endpoints include investigator-assessed ORR, minimal residual disease (MRD) negativity, and time to progression.
Results: As of July 2021, 30 patients have been enrolled across 6 sites in the USA and UK. Two patients were enrolled at an investigational site in Germany. In total, 24 patients were evaluable for safety and efficacy. The median age was 69 years (range 0-16 years). 115 survivors were diagnosed with MI. Before lymphoma diagnosis, 28% of survivors had ≥1 cardiovascular risk factor, and 16% of survivors received chest radiation. In multivariable analysis, survivors who received chest radiation had an increased risk of MI compared to survivors who did not (HR=1.92 [95% CI=1.16-3.17]). Survivors with ≥1 cardiovascular risk factor had an increased risk of MI compared to survivors with none (HR = 2.44 [95% CI=1.65-3.62]).
Conclusions: In a large, well-characterized, nationally representative study of contemporarily treated lymphoma survivors, prevalent hypertension, dyslipidemia, and diabetes were associated with later MI. Findings suggest that pre-existing cardiovascular risk factors confer the same amount of MI risk as does chest radiation. To prevent MI among survivors, decisions about post-treatment monitoring should address prevalent cardiovascular risk.

TPS7567 Poster Session (Board #320b), Mon, 8:00 AM-11:00 AM
Phase 2, open-label study of pembrolizumab in children and young adults with newly diagnosed or relapsed/refractory (RR) chronic lymphocytic leukemia (CLL) or acute lymphoblastic leukemia (ALL). First Author: Christine Mauz-Köhrölz, Martin-Luther-University Medical Center, Halle, Germany
Background: High risk for relapse is observed in CHL patients (pts) with SER to initial chemotherapy and organ toxicities may be higher following dose intensification. Methods: The phase 2 KEYNOTE-667 study will enroll 440 pts aged 3 to 17 (children) or 18 to 25 years (young adults) with newly diagnosed, confirmed stage IA, IB, or II A-CHL without bulky disease (Group 1 [low-risk]) or stage IIIEB, IIIEA, IIIEB, IIIB, IVA, or IVB CHL (Group 2 [high-risk]); measurable disease; and performance status per Lansky Play-Performance Scale ≥50 (age ≥16 years) or Karnofsky score ≥50 (age >16 years). Pts will receive induction with doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD; Group 1) or vincristine, etoposide/etoposide phosphate, prednisone/prednisolone, doxorubicin (OEP; Group 2) for 2 cycles, then early response assessment by PET/CT/MRI. Pts with rapid early response (Deauville score 1-3) will receive standard therapy. Pts with SER (Deauville score 4-5) will receive consolidation with pembro 2 mg/kg Q3W up to 200 mg (children) or 200 mg Q3W (young adults) plus 2 cycles AVD (Group 1) or 4 cycles cyclophosphamide, vincristine, prednisone/prednisolone, dacarbazine (COPDAC-28; Group 2). PET/CT for late response assessment (LRA) will be performed after consolidation. After LRA, Group 1 pts with SER and Group 2 pts with Deauville score 4-5 will receive radiotherapy (RT). All pts will receive maintenance with pembro Q3W concomitantly with RT. Pembro will continue up to 17 administrations, with an option to stop after 24 weeks due to CR, or until progression, unacceptable toxicity, or withdrawal. The primary endpoint is ORR per Cheson 2007 IWG criteria by group in SER pts. Secondary endpoints are ORR, time to progression, OS, and RT frequency and details by group, RERs with PET negative after ABVD induction, 3-yr EFS by investigator, and OS by risk group, and serum TARC levels at screening in SERs by risk group. ORR with 95% CI will be estimated by Clopper-Pearson method. EFS and OS will be estimated by Kaplan-Meier method. Safety will be assessed in all treated pts. Clinical trial information: NCT03407144.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, mediating B-cell proliferation, migration, adhesion and survival. BTK inhibition has emerged as a strategy for targeting B-cell malignancies, including MZL. In preclinical studies, zanubrutinib was shown to be a potent, irreversible, highly specific BTK inhibitor with excellent oral bioavailability and favorable pharmacokinetic/pharmacodynamic properties. Clinical data to date have shown that complete and sustained 24-hour BTK occupancy is associated with durable responses and suggested that zanubrutinib is generally well tolerated with low rates of serious adverse events. Preliminary results from the MZL cohort enrolled in the open-label, multicenter, phase 1 study demonstrated responses in 7 of 9 patients for an overall response rate (ORR) of 78%. Cumulative safety data also showed that zanubrutinib monotherapy was associated with infrequent occurrence of atrial fibrillation and major hemorrhage and infrequent drug discontinuation due to treatment-related adverse events. This study is designed to evaluate the safety and efficacy of zanubrutinib in patients with R/R MZL. Methods: This ongoing phase 2, single-agent placebo-controlled trial evaluated monotherapy in patients with R/R MZL who have received one or more prior lines of systemic therapy. Patients are treated with oral zanubrutinib at 160 mg twice-daily until progressive disease, unacceptable toxicity, or withdrawal of consent. Eligible patients must have histologically confirmed MZL, have received prior anti-CD20 antibody therapy, and have measurable disease. Disease response is assessed per the 2014 Lugano Classification for non-Hodgkin lymphoma. The primary endpoint is ORR determined by independent review committee (IRC). Key secondary endpoints include ORR by investigator assessment, time to and duration of response, time to treatment discontinuation, progression-free survival (all determined by IRC and investigator assessments), and overall survival and safety. Recruitment is ongoing. TPS7568 Poster Session (Board #321a), Mon, 8:00 AM-11:00 AM Phase 2 study of zanubrutinib (BGB-3111) in patients with relapsed/refractory marginal zone lymphoma (R/R MZL). First Author: Stephen Opat, Monash Health, Monash University, Clayton, Victoria, Australia Background: Progress in genome technology allows analysis of previously completed trials to identify patient subgroups potentially benefiting from therapy. Enzastaurin is a potent inhibitor of protein kinase C beta (PKC-b) and suppresses the phosphoinositide 3-kinase (PI3K)/AKT pathway. The safety and efficacy of Enzastaurin has been tested in more than 60 clinical trials (including 2 major studies in DLBCL: (1) PRELUDE IA phase III maintenance trial of Enzastaurin vs Placebo, N=758 (Crump, 2016), and (2) SO28 (A randomized phase II study of Enzastaurin/R-CHOP vs R-CHOP in frontline intermediate/high-risk DLBCL, N=101) (Hainsworth, 2016). DNA samples extracted from blood of patients from PRELUDE were retrospectively genotyped using whole genome SNP arrays. From the genome wide screening a novel genetic biomarker, DGM1, was identified showing high correlation with response to Enzastaurin treatment (Luo, ASH 2018). Importantly, these findings were replicated in the phase II SO28 study. In the SO28 study the hazard ratio (HR) for OS in high-risk (IPI > 3) DGM1 positive (+) vs low-risk (IPI ≤ 3) patients was 0.28 (0.1-0.81) when compared to subjects who received R-CHOP, a benefit favoring Enzastaurin (p=0.018). These data suggest that addition of Enzastaurin to R-CHOP may significantly improve outcome in frontline high-risk DGM1 (+) DLBCL. The ENGINE study was initiated to validate this finding in a prospective study. Methods: We recruited adult patients who have untreated or one prior DLBCL treatment with measurable disease. Patients are randomized 1:1 to Enzastaurin/R-CHOP or Placebo/R-CHOP for 6 cycles during combination phase. Each subject’s treatment assignment will be unblinded after response assessment at the end of the combination phase. Subjects randomized to the investigational arm who have a complete or partial response will be continued on treatment until disease progression or unacceptable toxicity; otherwise patients will receive Enzastaurin for up to 2 additional years. The study intends to enroll approximately 235 patients with primary endpoint of OS in DGM1 (+) patients. The study is ongoing with 51 sites open in the US and China. As of 22 Jan 2019, 70 patients have been randomized. Clinical trial information: NCT03263026. TPS7569 Poster Session (Board #321b), Mon, 8:00 AM-11:00 AM ENGINE: Phase III randomized study of enzastaurin/R-CHOP versus placebo/ R-CHOP in frontline high-risk diffuse large B-cell lymphoma patients with novel genomic biomarker DGM1. First Author: Stephen Smith, UW/FHCRC, Seattle, WA Background: R-CHOP in frontline treatment of DLBCL, pola to bendamustine and R in pts with transplant-ineligible DLBCL resulted in improved OS (Sehn et al, 2018). In front-line treatment of DLBCL, pola is being evaluated as a replacement for vincristine within the R-CHOP regimen. In a phase IIb/I study in pts with higher risk DLBCL, pola + R-CHOP demonstrated promising efficacy and a safety profile similar to that observed in the R-CHOP arm of the GOYA study (Tilly et al, 2017; Vitolo et al, 2017). The phase 3 POLARIX study investigates pola + R-CHP in untreated DLBCL. Methods: POLARIX is an ongoing, international, randomized, double-blind, active-placebo-controlled, phase 3 study in pts with previously untreated diffuse large B-cell lymphoma (DLBCL) but outcomes remain poor in pts with high-risk disease. Pola is an antibody–drug conjugate targeting CD79b; it delivers the anti-tumorigenic agent monomethyl auristatin E. Addition of pola to bendamustine and R in pts with transplant-ineligible DLBCL resulted in improved OS (Senn et al, 2018). In front-line treatment of DLBCL, pola is being evaluated as a replacement for vincristine within the R-CHOP regimen. In a phase IIb/I study in pts with higher risk DLBCL, pola + R-CHOP demonstrated promising efficacy and a safety profile similar to that observed in the R-CHOP arm of the GOYA study (Tilly et al, 2017; Vitolo et al, 2017). The phase 3 POLARIX study investigates pola + R-CHP in untreated DLBCL. Methods: POLARIX is an ongoing, international, randomized, double-blind, active-placebo-controlled, phase 3 study in pts with previously untreated DLBCL. Pts aged 18–80 years with CD20+ positive DLBCL (including DLBCL not otherwise specified, GC, and ABC subtypes), ECOG performance status 0–2, and IPI score 2–5, are stratified by IPI score (2 vs 3–5), bulky disease and geographical region and randomized (1:1). Pts receive 6 cycles of either: pola 1.8 mg/kg on Day 1 plus R-CHP (standard dosing schedule) plus vincristine placebo; or pola placebo plus R-CHOP (standard dosing schedule). R monotherapy is administered in cycles 7 and 8 (both arms), PET-CT and CT scans are obtained at screening, after 4 cycles (planned interim assessment), and 6–8 weeks after end of study treatment. Follow-up will continue for 5 years after treatment. Primary endpoint: investigator-assessed progression-free survival (PFS; Lugano classification). Secondary endpoints: independent review committee-assessed PET-CT complete response rate at end of treatment, event-free survival, 2-year PFS rate, and OS. Enrollment began Nov 2017. This trial is currently recruiting, and plans to enroll 875 patients in 24 countries. Clinical trial information: NCT03274492.
TPS7572 Poster Session (Board #323a), Mon, 8:00 AM-11:00 AM
ALPINE: Phase III zanubrutinib (BGB-3111) versus ibritunib in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). First Author: Peter Hillman, St. James’s University Hospital, Leeds, United Kingdom

Background: Inhibition of Bruton tyrosine kinase (BTK) has emerged as a strategy for targeting B-cell malignancies including CLL/SLL. Zanubrutinib, an investigational inhibitor of BTK, was specifically engineered to optimize selectivity, half-life and solubility in an effort to decrease toxicities and better penetrate tumor tissue. Early clinical data suggested that zanubrutinib treatment in patients with treatment-naive (TN; n = 16) or R/R (n = 50) CLL/ SLL induced deep responses: 94% overall response rate (ORR), including 6% and 2% complete response rates in TN and R/R CLL/SLL, respectively (ICML 2017). This study is designed to evaluate whether zanubrutinib mono- therapy exhibits non-inferior and potentially superior efficacy based on the ORR vs ibritunib monotherapy in patients with R/R CLL/SLL. Methods: This ongoing phase 3, randomized, open-label, global study (NCT03734016; BGB-3111-305) is comparing the efficacy and safety of zanubrutinib vs ibritunib in adult patients with R/R CLL/SLL. Approximately 400 patients will be randomized, 1:1 to each arm and stratified by age (<65 vs ≥65 years), refractory status (yes vs no) and geographic region, and stratified by prior refractory status (yes vs no). Key inclusion criteria include R/R CLL/SLL requiring treatment per iviCLL criteria, ECOG PS 0-2, and adequate hematologic function. The primary endpoint is ORR as determined by an independent review committee according to iviCLL guidelines, with modification for treatment-related lymphocytosis for patients with CLL and per 2014 Lugano Classification for patients with SLL. The study is powered to test the non-inferiority and superiority of the ORR for zanubrutinib vs ibritunib. Secondary endpoints include progression-free survival, safety, duration of response, and overall survival. Recruitment is ongoing, Clinical trial information: NCT03734016.

TPS7574 Poster Session (Board #324a), Mon, 8:00 AM-11:00 AM
ZUMA-12: A phase 2 multicenter study of axi-celagene ceoleucel (axi-cel) as a first-line therapy in patients with high-risk low-B cell lymphoma (LBCL). First Author: Sattva Swarup Neelapu, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Pts with LBCL who have persistent disease assessed by dynamic PET after rituximab-based induction therapy have an increased risk of death (Casasnovas, et al. Blood. 2017). Axi-cel is an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy approved for the treatment of pts with relapsed/refractory LBCL with ≥2 prior systemic therapies. In ZUMA-1, the registration study of axi-cel in pts with refractory LBCL, the objective response rate (ORR) was 91% (70% complete response [CR] rate) in pts with double- expressor or high-grade LBCL with ongoing responses in 48% after a median follow-up of 27.1 mos (Locke FL, et al. Lancet Oncol 2019). Furthermore, pts with fewer prior lines of therapy and lower tumor burden had higher rates of ongoing responses and manageable safety (Locke et al. ASCO 2018. 3039). ZUMA-12 will investigate the efficacy and safety of axi-cel as a first-line therapy in newly diagnosed pts with high-risk LBCL who have PET-positive disease after 2 cycles of induction therapy. Methods: This Phase 2 study has a planned enrollment of ~40 pts aged ≥18 y with high-risk LBCL, defined by the presence of MYC and BCL2 and/or BCL6 translocations by FISH or an IPI score ≥3 any time before enrollment, and an ECOG performance status of 0 – 1. Before enrollment, pts must have a Deauville score of 4 – 5 (Barrington SF et al. J Clin Oncol. 2014) after 2 cycles of chemotherapy that includes an anti-CD20 monoclonal antibody and anthracycline. After leukapheresis, pts with bulky or rapidly progressing disease may receive optional non-chemotherapy bridging therapy. Following conditioning therapy with cyclophosphamide (500 mg/m²) and fludarabine (30 mg/m²) for 3 days, pts will receive a single infusion of axi-cel at a target dose of 2 × 10^6 CAR T cells/kg. The primary endpoint is investigator-assessed CR rate per the Lugano classification (Cheson et al. J Clin Oncol. 2014). Key secondary endpoints include ORR, duration of response, event-free survival, progression-free survival, overall response, safety, relapse with CNS disease and levels of blood CAR T cells and serum cytokines over time. Accrual is ongoing. Clinical trial information: NCT03761056.

TPS7575 Poster Session (Board #324b), Mon, 8:00 AM-11:00 AM
A multicenter, open label, controlled, phase II clinical trial evaluating the safety and efficacy of axi-cel in combination with axicabtagene ciloleucel and obinutuzumab in r/r FL. First Author: Michael Dickinson, Peter MacCallum Cancer Centre, Melbourne, Australia

Background: Ataxiarthribozum (RT) is a humanized, anti-CD19 chimeric antigen receptor T cell (CAR-T) therapy that was approved for the treatment of pediatric and young adult patients up to 25 years of age with r/r B-cell acute lymphoblastic leukemia in 2017 (Maude et al. NEJM 2018), as well as for the treatment of adult patients with r/r diffuse large B-cell lymphoma in 2018 (Schuster et al. NEJM 2018). FL is the second most common non-Hodgkin lymphoma in the Western hemisphere, with limited treatment options in patients refractory to or relapsing after standard therapies. In a phase 2a study of patients with r/r CD19+ lymphomas, 10 of 14 (71%) patients with r/r FL treated with axicabtagene ciloleucel achieved a durable complete remission at a median follow-up of 28.6 months (Schuster et al. NEJM 2017). Here we introduce ELARA, a phase 2 study evaluating the efficacy and safety of asiganeleucel in patients with r/r FL. Methods: ELARA is a phase 2, single-arm, multicenter, open label trial. Eligible patients must be ≥18 y of age, have radiographically measurable grade 1, 2, or 3A r/r FL that is refractory to ≥2 lines of therapy (as defined above) or an alkylator, or relapsed within 6 months after completion of a second or later line of systemic therapy, or relapsed during anti-CD20 antibody maintenance (follow≥2 lines of therapy as above) or within 6 months after maintenance completion, or relapsed after autologous hematopoietic stem cell transplant (SCT). Patients with central nervous system in- volvement, or those who received prior anti-CD19 therapy, gene therapy, adoptive T-cell therapy, or allogeneic HSCT are not eligible. The primary endpoint of this study is complete response rate based on Lugano classification response criteria. Secondary outcomes include overall response rate, duration of response, overall survival, cellular kinetic, immune, genotoxicity, safety, and patient-reported outcomes. Estimated enrollment for this study is 113 patients. The study is currently open to patient enrollment. Clinical trial information: NCT03568461.

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Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Updated risk stratification model for smoldering multiple myeloma (SMM) incorporating the revised IMWG diagnostic criteria. First Author: Jesus San Miguel, Clinica Universidad de Navarra-CIMA, IDISNA, CIBERONC, Pamplona, Spain

Background: The diagnostic criteria for MM were revised in 2014, re-categorizing high-risk (i.e., ≥80% at two years) as active myeloma requiring therapy. The removal of patients at the highest risk of progression from the smoldering group requires reassessment of current risk stratification models.

Methods: We designed a multicenter, retrospective study of SMM patients to evaluate a risk stratification model. Patients diagnosed with SMM after January 1, 2004 were included if they had no disease progression within 6 months, had baseline data from diagnosis (+/- 3 months), had a follow up of ≥1 year, and did not participate in a therapeutic trial of SMM. Various clinical and laboratory factors were explored to identify factors that predicted progression at 2 years. Univariate Cox regressions were run for each factor. For factors with p-values ≤0.25, optimal cut points were identified using Youden's index. Binary factors were used in stepwise regression to fit multivariable Cox model and significant risk factors were determined (F-test). Results: Overall, 2004 patients were included (ages 26-93, 51% female). Factors independently associated with progression included: SMM protein ≥12 g/dL, involved to uninvolved serum-free light chain ratio (20), and marrow plasma cell % (20%). Patients were stratified using the risk factors: Low- (0 factors), Intermediate- (1), and High-Risk (≥2). Previously used high risk markers such as Bence Jones proteinuria (≥500 mg/24 hours) and severe immunoparesis (50% decrease in uninvolved immunoglobulin levels) were both significant in univariate analysis, but were eliminated on step wise selection. Compared to the low risk group, intermediate- and high-risk groups had significantly higher rate of progression (Table). Within the high-risk group, having all 3 risk factors (n=61) versus 2 did not add to the model, with insufficient separation between 2 and 3 factors. Conclusions: We have developed a risk stratification model for SMM that incorporates revised cutoffs for previously used parameters (20/20) that can be universally applied. Additional analysis are being conducted to develop models that utilize common cytogenetic abnormalities, as well as those without FLC given lack of availability of all tests across the world.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>N</th>
<th>HR</th>
<th>P</th>
<th>2yr Progression %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>424</td>
<td>1</td>
<td>&lt;0.01</td>
<td>17</td>
</tr>
<tr>
<td>1</td>
<td>312</td>
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<td>≥2</td>
<td>415</td>
<td>5.63 (4.34-7.29)</td>
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<td>17</td>
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8002

Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Efficacy of carfilzomib lenalidomide dexamethasone (KRd) with or without transplantation in newly diagnosed myeloma according to risk status. Results from the FORTE trial. First Author: Francesca Gay, GIMEMA, European Myeloma Network, Italy

Background: High and comparable rates of MRD negativity were seen in NDMM pts after 4 28-day induction cycles with KRd followed by ASCT and 4 KRd consolidation. High and comparable rates of MRD negativity were seen in NDMM pts where current standard of care is observation (obs). Here we evaluated the benefit of KRd_ASCT_KRd vs KRd12 or KCd_ASCT_KCd. We compared rate of progression at 2 years. Univariate Cox regressions were run for each factor. For factors with p-values ≤0.25, optimal cut points were identified using Youden’s index. Binary factors were used in stepwise regression to fit multivariable Cox model and significant risk factors were determined (F-test). Results: Overall, 2004 patients were included (ages 26-93, 51% female). Factors independently associated with progression included: SMM protein ≥12 g/dL, involved to uninvolved serum-free light chain ratio (20), and marrow plasma cell % (20%). Patients were stratified using the risk factors: Low- (0 factors), Intermediate- (1), and High-Risk (≥2). Previously used high risk markers such as Bence Jones proteinuria (≥500 mg/24 hours) and severe immunoparesis (50% decrease in uninvolved immunoglobulin levels) were both significant in univariate analysis, but were eliminated on step wise selection. Compared to the low risk group, intermediate- and high-risk groups had significantly higher rate of progression (Table). Within the high-risk group, having all 3 risk factors (n=61) versus 2 did not add to the model, with insufficient separation between 2 and 3 factors. Conclusions: We have developed a risk stratification model for SMM that incorporates revised cutoffs for previously used parameters (20/20) that can be universally applied. Additional analysis are being conducted to develop models that utilize common cytogenetic abnormalities, as well as those without FLC given lack of availability of all tests across the world.

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8003

Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Phase 3 randomized study of daratumumab (DARA) + bortezomib/thalidomide/dexamethasone (D-VTd) vs VTD in transplant-ineligible (TI) newly diagnosed multiple myeloma (NDMM): CASSIOPEIA Part 1 results. First Author: Philip Moreau, Hematology, University Hospital Hôtel-Dieu, Nantes, France

Background: VTD is a standard of care (SoC) for TD NDMM. CD38 mAb DARA significantly reduced the risk of progression/death and improved CR and MRD-negative rates in relapsed refractory MM or transplant-ineligible NDMM in phase 3 studies. We report the primary and final analysis of Part 1 of CASSIOPEIA. Methods: 18-65 y-old NDMM pts were randomized 1:1 to VTD (6 28-day cycles with VTd, 542) or D-VTd (V 10 mg PO QD; D 10 mg PO QD; T 100 mg PO QD or IV W 1-4 C 100 mg/m2 SC BIW Week 1-2; T 100 mg PO QD; W 1-4 C 100 mg/m2 SC BIW Week 1-2). The primary endpoint, post-consolidation sCR, was assessed at Day [D] 100 post-ASCT. Part 2 (maintenance) is ongoing.

Results: A cohort of 1085 pts (D-VTd, 543; VTD, 542) was randomized. The D 100 post-ASCT sCR rate was significantly higher for D-VTd vs VTD (28.9%; P = 0.0001; Table). At 18.8-mo median follow-up, PFS from first randomization favored D-VTd with HR 0.47 (95% CI, 0.33-0.67; P = 0.0001). With median PFS NR in either arm, 18-mo PFS rates were 92.7% vs 84.6% for D-VTd vs VTD. Rates of ≥sCR, ≥sPR, and MRD negativity supported sCR results (Table). OS is immature with 46 months on study (D-VTd, 14; VTD, 32; HR, 0.43; 95% CI, 0.23-0.80). The most common (≥10%) grade 3/4 TEAEs (D-VTd/VTd) were neutropenia (27.6%/14.7%), lymphopenia (17.0%/9.7%), stomatitis (12.7%/16.4%), and thrombocytopenia (11.0%/7.4%). In the VTd arm, infection-related reactions occurred in 35.4% of pts. Conclusions: D-VTd in induction prior to and consolidation after ASCT improved depth of response (sCR, ≥sPR, and MRD negativity) and PFS with acceptable safety. The favorable benefit-risk profile supports the use of D-VTd in TD NDMM. CASSIOPEIA. Part 1 was the first study to demonstrate clinical benefit of DARA + SoC in TD NDMM. Clinical trial information: NCT01169337.

<table>
<thead>
<tr>
<th>Phase 2 PFS</th>
<th>Len</th>
<th>Obs</th>
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<tr>
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<td>0.87</td>
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<tr>
<td>3 yr</td>
<td>0.78</td>
<td>0.78</td>
</tr>
<tr>
<td>5 yr</td>
<td>0.78</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 3 PFS</th>
<th>Len</th>
<th>Obs</th>
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</thead>
<tbody>
<tr>
<td>1 yr</td>
<td>0.98</td>
<td>0.89</td>
</tr>
<tr>
<td>3 yr</td>
<td>0.93</td>
<td>0.76</td>
</tr>
<tr>
<td>5 yr</td>
<td>0.91</td>
<td>0.66</td>
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</tbody>
</table>

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
A phase III randomized, open-label, multicenter study comparing isatuximab, pomalidomide, and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM). Background: The primary objective of this phase 3 trial was to demonstrate progression-free survival (PFS) improvement of isatuximab (Isa), a novel anti-CD38 monoclonal antibody, combined with pomalidomide (P)/dexamethasone (d) (IsaPd) vs Pd. Methods: Patients (pts) with RRMM who received ≥2 prior lines, including lenalidomide (len) and a proteasome inhibitor (PI), refractory to last therapy were enrolled. IsaPd arm received Isa 10 mg/kg IV weekly for first 4 weeks (wks), then every 2 wks. Both arms received approved schedules of pom and dex (4mg PO days 1-21; 40mg [20mg if >75 yrs] PO or IV weekly) every 28 days until progression or unacceptable toxicity. Results: 307 IsaPd, 154 IsaPd, 153 Pd were randomized and analyzed (ITT). Patient characteristics were well balanced across arms. Median age: 67 (36-86) yrs; median prior lines of therapy: 3 (2-11); estimated GFR: <60ml/min in 33.9% pts; 92.5% refractory to len, 75.9% to PI, and 19.5% pts had high-risk cytogenetics. At median follow-up of 11.6 months (mos), median PFS was 11.5 mos IsaPd vs 6.5 mos Pd; HR 0.596 (95% CI 0.44-0.81), P<0.001. PFS benefit was consistent across all major subgroups. ORR (febrile 11.8%) IsaPd and 70.1% (febrile 2.0%) Pd. Median treatment duration was 41 wks IsaPd vs 24 wks Pd; median Isa infusion (inf.) duration was 3.3h at 1st inf. and 2.8h at subsequent inf. Grade ≥3 AEs were observed in 86.8% IsaPd vs 70.5% Pd; 7.2% IsaPd and 12.8% Pd pts discontinued due to AEs; 7.9% IsaPd and 9.4% Pd pts died due to AEs. Inf. reactions were reported in 38.2% (2.6% grade 3-4) IsaPd. Grade ≥3 infections were seen in 42.8% IsaPd and 30.2% Pd, grade ≥3 neutropenia in 84.9% (febrile 11.8%) IsaPd and 70.1% (febrile 2.0%) Pd. Conclusions: IsaPd significantly improved PFS and ORR vs Pd, with a manageable safety profile. IsaPd is an important new treatment option for the management of RRMM. Clinical trial information: NCT02990338.

First clinical (phase 1b/2a) study of idebumon (CC-220; IBER), a CELMoD, in combination with dexamethasone (d) (IBER vs Pd). Methods: A phase 1b/2a multicenter, open-label, dose-escalation study evaluated the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), safety, and preliminary efficacy of IBER. Eligible pts had RRMM and must have received ≥2 prior regimens including len (90%), len/PI (69%), len/dex (57%), len/PI/dex (20%), len/dex (13%), len/len (9%), len/len/PI (6%), len/PI (4%), len/dex/len (1%), and len/dex/PI (1%) pts. Pts had progressed on or within 60 days of last MM therapy. Escalating doses of IBER were given on days 1–21, in combination with DEX 40 mg (20 mg in pts age >75 years) on days 1, 8, 15, and 22, of each 28-day cycle. Dose escalation was reviewed by a dose escalation committee. Results: As of Jan 2019, 58 pts received IBER + DEX. Median age was 64.5 years (range 33–79), and median number of prior regimens was 5 (2–12). Prior therapies included autologous stem cell transplant (79%), LEN (100%), POM (69%), PIs (100%), and DARA (66%). IBER dose ranged from 0.3 to 1.2 mg; MTD/RP2D was not reached. Median duration of therapy was 12+ weeks (range 4–109). Grade 3–4 adverse events (AEs) were reported in 41 (72%) pts and were not related to dose. Grade 3–4 neutropenia, thrombocytopenia, neuropathy, and fatigue occurred in 26%, 11%, 2%, and 0% pts, respectively. Three pts discontinued treatment due to AEs. Clinical activity occurred early and was observed across all dose levels (table; 20 of 29 pts had CR, CR with incomplete response, or stable disease [SD], 27+ cycles). Conclusions: IBER + DEX showed favorable efficacy and safety in heavily pretreated pts with RRMM who failed multiple prior therapies. This study is ongoing, including combinations of IBER with DARA or BORT. Clinical trial information: NCT02779338.

Efficacy

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>IBER dose 0.3–1.2 mg + DEX</th>
<th>(N = 51 evaluable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good partial response</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Minimal response (MR)</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Overall response (≥ PR)</td>
<td>16 (31%)</td>
<td></td>
</tr>
<tr>
<td>Clinical benefit (≥ MR)</td>
<td>26 (51%)</td>
<td></td>
</tr>
<tr>
<td>Disease control (≥ SD)</td>
<td>45 (88%)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: IBER dose 0.3–1.2 mg + DEX was well tolerated in this study and showed encouraging efficacy in heavily pretreated pts with RRMM, who failed multiple prior therapies. The results were consistent across all major subgroups, with a manageable safety profile. Median PFS was significantly improved in the IBER + DEX arm compared to DEX alone, with a median duration of 41 weeks. Overall response rates were also higher in the IBER + DEX arm. Treatment-related adverse events were manageable, and discontinuation due to AEs was low. This study supports the further evaluation of IBER in combination with dexamethasone in the management of RRMM.
Combined use of two monoclonal antibodies in patients with systemic AL amyloidosis and cardiac involvement. First Author: Amandeep Godara, Tufts Medical Center, Boston, MA

Background: Systemic AL amyloidosis (AL) is a rare disease in which circulating immunoglobulin light chains misfold, are directly toxic to key organs and also cause organ failure by mass effect. Patients with cardiac involvement have a poor prognosis; 25% of them die within 6 months of diagnosis. Depth of cardiac response has prognostic significance and as new therapies become available, combining targeted therapies might hold the key to improve survival and deepen responses. Methods: We report the outcomes of 9 patients with AL amyloidosis who simultaneously received two monoclonal antibodies with different epitopes and the investigational anti-fibril antibody NEOD001 at our institution. We also provide a descriptive comparison of 10 other AL amyloidosis patients who received treatment with daratumumab alone. Results: Of these 9 patients, there were 4 men/women with a median age of 68 years (range, 52-75) and a median of 261 days from diagnosis (range, 51-2037). Median NT-proBNP was 3807 pg/ml (range, 1326-11393). These 9 patients did not respond to initial therapy with a bortezomib-based regimen. Inclusions of both monoclonals were separated by 2 days and were safely combined in patients with systemic AL amyloidosis. Although this report features a small number of patients, high antibodies targeting different epitopes can be safely combined in patients with systemic AL amyloidosis (AL). In contrast, patients receiving daratumumab alone (n=10) achieved hematologic and cardiac responses achieved suggest that this combination should be studied further, possibly in a prospective randomized trial.

Patient characteristics.

<table>
<thead>
<tr>
<th>Light chain isotype</th>
<th>NEOD001+ Daratumumab (n=9)</th>
<th>Daratumumab (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>κ</td>
<td>α</td>
<td></td>
</tr>
<tr>
<td>Light chain isotype</td>
<td>89%</td>
<td>70%</td>
</tr>
<tr>
<td>Organic involvement</td>
<td>Cardiac: 88%</td>
<td>Cardiac: 70%</td>
</tr>
<tr>
<td>Renal: 44%</td>
<td>Renal: 80%</td>
<td></td>
</tr>
<tr>
<td>Number of prior therapies</td>
<td>8/9 (88%)</td>
<td>8/10 (80%)</td>
</tr>
<tr>
<td>Hematologic response</td>
<td>7/9 (78%)</td>
<td>8/10 (80%)</td>
</tr>
<tr>
<td>Median time to best hematologic response (days)</td>
<td>23 (range: 19-2621)</td>
<td>25 (range: 22-242)</td>
</tr>
<tr>
<td>Baseline NT-proBNP median, pg/ml</td>
<td>3807 (range: 1326-11393)</td>
<td>960 (range: 1613-1134)</td>
</tr>
<tr>
<td>Cardiac response</td>
<td>7/8 (88%)</td>
<td>8/10 (80%)</td>
</tr>
<tr>
<td>Median time to cardiac response (days)</td>
<td>81 (range: 46-167)</td>
<td>115</td>
</tr>
<tr>
<td>Median reduction in NT-proBNP</td>
<td>74%</td>
<td>50%</td>
</tr>
</tbody>
</table>

8011 Poster Discussion Session; Displayed in Poster Session (Board #337), Mon, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:45 PM

Outcomes of patients with light chain amyloidosis who had autologous stem cell transplantation with three or more organs involved. First Author: Abdullah Al Saleh, Mayo Clinic Rochester, Rochester, MN

Background: Literature suggests that three or more organ involvement is a contraindication for autologous stem cell transplant (ASCT) in light chain amyloidosis (AL). Most centers limit transplantation to patients who have no more than two organs significantly involved. We retrospectively reviewed all patients with AL Amyloidosis involving three or more organs and who had ASCT between 1996-2015 at Mayo clinic, Rochester, Minnesota. Results: Seventy five patients underwent ASCT with three or more organs involved. Median age at diagnosis was 54 years and 67% were males. The heart was involved in 95%, followed by kidneys (84%). Thirty eight patients (51%) had no induction treatment prior to ASCT. Full dose melphalan (200mg/m2) was given in 45%, and the remaining received a reduced dose (140 mg/m2). Overall response rate (hematological) was 75%. The median progression-free (PFS) and overall survival (OS) were 16.3 and 68.9 months, respectively. The 100-day mortality was 16% and overall forty four patients (59%) died during the follow up period. The most common causes of death were cardiovascular events (32%) and progressive amyloidosis (25%). On multivariable analysis, predictors for PFS were Mayo stage III-IV (HR 3.3, P = 0.0012) and hematological response (=VGPR, RR 0.4, P = 0.012). An NT-proBNP level of \(>2000 \text{pg/ml}\) was an independent predictor for shorter PFS (HR 2.6, P = 0.013). Predictors for OS included any hematological response (RR 0.1, P < 0.0001) and Mayo stage III-IV (RR 7, P < 0.00001). When looking at the NT-proBNP, a level \(\geq 2000\) was prognostic (RR 5.5, P = 0.001). Number of organs involved (3 vs. 4-5) was not significant in either PFS or OS. Conclusions: Our cohort demonstrates that even if a patient has multiple organ involvement, mortality is the main driver for the poor outcome in patients who have three or more organs involved. Using selection criteria defined for safe transplantation in cardiac amyloidosis should result in low therapy-related mortality independent of the number of organs involved. The concept of considering patients with three organs involved ineligible for stem cell transplantation should be abandoned.

8012 Poster Discussion Session; Displayed in Poster Session (Board #338), Mon, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:45 PM

Safety and tolerability of BION-1301 in adults with relapsed or refractory multiple myeloma. First Author: William Bensinger, Fred Hutchinson Cancer Research Center, Seattle, WA

Background: BION-1301 (BION) is first in class humanized monoclonal antibody directed against a proliferation-inducing ligand (APRIL) for treatment of relapsed/refractory (R/R) multiple myeloma (MM). APRIL secreted by cells in the bone marrow microenvironment drives MM cell proliferation. BION is a humanized anti-APRIL monoclonal antibody (mAb) that reports its own therapeutic activity via an intracellular transmembrane activator and CAML interactor (TACI) on human MM cells to drive their proliferation and survival. In patients (pts) with MM, serum APRIL levels are elevated and are correlated with promotion of malignancy, chemoresistance and immune- evasion. We conclude the activity of BION in R/R MM is the result of BION monotherapy in R/R MM pts. Methods: Adults with MM, progression after \(\geq 3\) systemic therapies, and ECOG 0-1 were enrolled in this phase 1/2, open-label study. The phase 1 study is evaluating 6 cohorts with increasing BION doses of 50, 150, 450, 900, 1350 and 4500 mg administered Q2W intravenously (cohort 6 - 1350 mg dose given QW and Q2W). Response was assessed by investigators Q4W. Serum was analyzed for BION, anti-drug antibodies (ADA), and soluble unbound “free APRIL” (FAPRIL) and evaluated by PK-PD modeling. Results: As of 7 Dec 2018, 15 pts were enrolled in 4 cohorts at doses between 50-1350 mg given Q2W. 5/15 (33%) had ECOG 0 and pts received median of 6 prior systemic therapies (range 4-17). Related treatment emergent adverse events (TEAE) were reported in 8/15 (36%); most common related TEAE included anemia (n=3), arthralgia (n=2), and dysgeusia (n=2). 1 subject receiving 4th dose of BION experienced grade 3 wheezing looking at the NT-ProBNP, a level \(\geq 2000\) was prognostic (RR 2.6, P = 0.013). Predictors for OS included any hematological response (=VGPR, RR 0.4, P = 0.012). An NT-proBNP level of \(>2000 \text{pg/ml}\) was an independent predictor for shorter PFS (HR 2.6, P = 0.013). Predictors for OS included any hematological response (RR 0.1, P < 0.0001) and Mayo stage III-IV (RR 7, P < 0.00001). When looking at the NT-proBNP, a level \(\geq 2000\) was prognostic (RR 5.5, P = 0.001). Number of organs involved (3 vs. 4-5) was not significant in either PFS or OS. Conclusions: Of 14/15 evaluable for response, no objective response was observed and 5/14 (36%) had stable disease. Median time on treatment was 2 months (range: 0.9-4.9) and median of 3 doses of BION (range: 2-11) were administrated. BION exposure increased dose proportionally from 50-1350 mg, and half-life (t1/2) and clearance (CL) did not differ significantly (median t1/2 = 9.0 days: 3.9-20, median CL = 0.52 L/day (range: 0.32-0.72)). Levels of FAPRIL in serum and BM decreased with increasing BION doses. By 450 mg, 95% target engagement (TG) was achieved among neutralizing BMI:0.7 to 1.5. Pts received 49 doses. Results: Of 14/15 evaluable for response, no objective response was observed and 5/14 (36%) had stable disease. Median time on treatment was 2 months (range: 0.9-4.9) and median of 3 doses of BION (range: 2-11) were administrated. BION exposure increased dose proportionally from 50-1350 mg, and half-life (t1/2) and clearance (CL) did not differ significantly (median t1/2 = 9.0 days: 3.9-20, median CL = 0.52 L/day (range: 0.32-0.72)). Levels of FAPRIL in serum and BM decreased with increasing BION doses. By 450 mg, 95% target engagement (TG) was achieved among neutralizing BMI:0.7 to 1.5. Pts received 49 doses. Conclusions: BION at doses 50-1350 mg given Q2W was well-tolerated and dose-dependently reduces serum levels of FAPRIL. To date, objective responses have not been observed. The study is ongoing with pts exposed to higher and/or more frequent doses with the objective of achieving accelerated and sustained APRIL TG. Clinical trial information: NCT03340883.
Background: Previous studies indicate patients with relapsed/refractory multiple myeloma (RRMM) who receive high-dose BCMA-targeting CAR-T cells may achieve better remission but have worse adverse events. Moreover, once the disease progresses again, the influence of CAR-T cells is not effective. To solve this dilemma, we have developed a novel BCMA-targeting CAR-T (CT103A) with a lentiviral vector containing a CAR structure with a fully human anti-BCMA antibody fragment. The Phase 1b/2 trial was a non-randomized, open-label, dose escalation phase 1b/2a trial conducted at Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

Methods: CHCTR1800018137 is a single-center and single-arm trial of CT103A in patients with RRMM. The primary objectives are to characterize the safety and tolerability in patients with RR MM. The secondary objectives include evaluation of anti-myeloma activity, cytokines, CAR T-cell persistence, and pharmacokinetics. Between September 7, 2018, and January 21, 2019, nine patients (including 3 patients having relapsed after being given a murine BCMA CAR-T) received CT103A in 3+3 dose-escalation trial (dose levels at 1, 3 x 10^6/kg after a conditioning chemotherapy regimen of cyclophosphamide and fludarabine. All Patients had received a median of 4 prior lines (range 3 - 5) of MM therapy. Results: At the time of the February 4, 2019 data analysis, the overall response rate was 100% (Table), and all patients had a rapid response within 14 days, with 67% (2/3) reaching CR/CRi at the lowest dose. The pharmacokinetics of CT103A were assessed by a digital polymerase chain reaction. Robust expansions were seen even at the lowest dosage level. In addition, CmAX and AUCO-28 reached levels comparable to reported CD19 CAR-T. In the first two dose levels of the grade of cytokine release syndrome (CRS) was assessed. In the 6 x 10^6/kg dose group, DLT had been observed in one patient. Conclusions: Data from this early-stage clinical study showed the unparalleled safety and efficacy of CT103A. Major AE were transient, manageable, and reversible, three patients who relapsed the murine CAR-T were treated with CT103A, two patients achieved CRi, and one patient achieved VGPR. 100% ORR and a rapid response within 2 weeks, suggests CT103A could be developed as a competitive therapeutic approach to patients with RRMM. Treatment Response (Case 1 and 7, patients who relapsed the murine BCMA CAR-T). Clinical trial information: CHCTR1800018137.

Outcomes of patients with t(11;14) multiple myeloma: An International Myeloma Working Group (IMWG) multicenter study. First Author: Brian G. Dune, Cedars-Sinai Comprehensive Cancer Center, Los Angeles, CA

Background: Multiple myeloma (MM) is a heterogeneous disease with varying survival outcomes depending on the presence of certain genetic abnormalities. Common abnormalities include translocations involving chromosome 14, 13, and 17; amplifications or deletions of chromosomes 1, 13, and 17; t(11;14), occurring in approx. 15% of patients (pts) with MM, is considered a standard risk abnormality, but recent data suggest that the prognosis may be inferior to what had been expected. This is of particular relevance as new therapeutic options such as the BCL-2 inhibitor venetoclax have been shown to be effective in these pts.

Methods: This was a multicenter study designed and conducted by the IMWG, to identify the outcomes of pts with t(11;14) using a retrospective cohort of pts. Pts with MM diagnosed between 2005 and 2015 with t(11;14) identified on FISH performed within six months (mos) of diagnosis, and with treatment details available and if alive, a minimum of 12 mos of follow up, were enrolled. Results: The current analysis includes 848 pts with a median age of 64.4 years; 60.0% are male. The median follow-up from diagnosis for the entire cohort was 45.7 mos; 84.7% of the pts were alive at the last follow up. ISS stage distribution included: Stage I (35.3%), Stage II (38.9%) and Stage III (25.8%). The distribution of FISH abnormalities included: del 13q (14.5%), 1q amp (12.1%), del 17p or monosomy 17 (6.1%). Pts received initial therapy with different regimens: IMiD-24.3%, PI-41.0%, both-20.8% and 13.8% had no novel agent. The drug classes by line of therapy are shown in the Table. An early stem cell transplant (SCT) was offered in patients with R/R MM. The secondary objectives include evaluation of anti-myeloma activity, cytokines, CAR T-cell persistence, and pharmacokinetics. Between September 7, 2018, and January 21, 2019, nine patients (including 3 patients having relapsed after being given a murine BCMA CAR-T) received CT103A in 3+3 dose-escalation trial (doses at 1, 3 x 10^6/kg after a conditioning chemotherapy regimen of cyclophosphamide and fludarabine. All Patients had received a median of 4 prior lines (range 3 - 5) of MM therapy. Results: At the time of the February 4, 2019 data analysis, the overall response rate was 100% (Table), and all patients had a rapid response within 14 days, with 67% (2/3) reaching CR/CRi at the lowest dose. The pharmacokinetics of CT103A were assessed by a digital polymerase chain reaction. Robust expansions were seen even at the lowest dosage level. In addition, CmAX and AUCO-28 reached levels comparable to reported CD19 CAR-T. In the first two dose levels of the grade of cytokine release syndrome (CRS) was assessed. In the 6 x 10^6/kg dose group, DLT had been observed in one patient. Conclusions: Data from this early-stage clinical study showed the unparalleled safety and efficacy of CT103A. Major AE were transient, manageable, and reversible, three patients who relapsed the murine CAR-T were treated with CT103A, two patients achieved CRi, and one patient achieved VGPR. 100% ORR and a rapid response within 2 weeks, suggests CT103A could be developed as a competitive therapeutic approach to patients with RRMM. Treatment Response (Case 1 and 7, patients who relapsed the murine BCMA CAR-T). Clinical trial information: CHCTR1800018137.

Regimen type | Line 1 | Line 2 | Line 3 |
---|---|---|---|
IMiD | 139 (24.3%) | 139 (37.9%) | 134 (44.5%) |
PI | 144 (25.9%) | 86 (25.8%) | 86 (25.8%) |
IMiD and PI | 119 (20.8%) | 48 (13.0%) | 16 (5.7%) |
Other | 38 (6.8%) | 30 (8.6%) | 27 (11.0%) |
Number of pts | 571 | 369 | 279

First Author: Paul G. Richardson, Jerome Lipper Myeloma Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: TCR-MM is defined as being refractory to immunomodulatory agents, proteasome inhibitors, and anti-CD38 mAbs, representing an urgent unmet medical need with a median OS of 3-6 months (Pick M et al, Eur J Haem 2018; Gandhi U et al, ASH 2018). Sd has shown a 26.2% overall response rate (ORR) in 122 patients (pts) with TCR-MM in the Phase 2b STORM study (Chari A et al, ASH 2018). Here, we evaluate the OS of pts in the STORM study with Sd and in pts with t(4:14) in patients with MM whose first therapy after their MM reached TCR status was Sd and in pts in the FHAD who received ≥ 1 therapy after their MM reached TCR status. The index date for this evaluation was the start date of treatment after their MM reached TCR status. A Cox proportional hazards regression model was performed to assess the survival impact of Sd. In STORM, ORR was assessed by an Independent Review Committee. Based on limbic extension, IDO, PD1-L2, and PD1-L1, the pts in this study were identified. In the FHAD pts had a higher frequency of high-risk MM, a longer time since diagnosis of MM, and higher baseline hemoglobin and platelet values. Among the 122 pts in STORM, 64 received Sd as their first therapy after their MM became TCR, and ORR was 32.8%. Among the 69 pts from FHAD, 37 received ≥ 1 therapy after their MM became TCR. Median OS (N = 64) was 10.4 months for pts receiving Sd in STORM and 5.2 months (N = 37) for pts not receiving Sd in FHAD (HR = 0.49, p = 0.0241). Conclusions: The prognosis of TCR-MM in the real-world population appears very poor within the limits of this analysis. Pts not receiving Sd as their first therapy after their MM becomes TCR is significantly better than those not receiving Sd, suggesting that Sd may be associated with an OS benefit in pts with TCR-MM. Clinical trial information: NCT02336815.
Efficacy of daratumumab (DARA) + bortezomib/halobazine/dexamethasone (D-VTd) in transplant-eligible newly diagnosed multiple myeloma (TE NDMM) based on minimal residual disease (MRD) status: Analysis of the CASSIOPEIA trial. First Author: Herve Avez-Leoise, Unite de Genomique du Myelome, IUTC Oncopole, Toulouse, France

Background: In TE NDMM patients (pts), the CD8 monoclonal antibody DARA significantly reduced the risk of progression/death and improved stringent CR, ≥CR, and MRD-negative rates when added to VTD in the phase 3 CASSIOPEIA study. MRD status and its association with progression-free survival (PFS) was evaluated in TE NDMM pts receiving D-VTd vs VTD as pre-transplant induction/ post-transplant consolidation in Part 1 of CASSIOPEIA. Methods: In Part 1, TE NDMM pts were randomized 1:1 to 4 cycles of pre-ASCT induction and 2 cycles of post-ASCT consolidation with DARA + VTD or VTD. Landmark analyses of MRD were performed on bone marrow aspirates after induction by multiparametric flow cytometry (FC; ≥0.5% sensitivity threshold) and after consolidation (at Day 100 post ASCT) by MFC (10^5) and next-generation sequencing (NGS; 10^5) for all pts, regardless of response. Results: A cohort of 1083 pts was randomized (D-VTd, n = 543; VTD, n = 542). Post-induction and post-consolidation MRD-negative rates were significantly higher for D-VTd vs VTD (Table). Post-consolidation MRD-negative rates (MFC) were consistent across pt subgroups, including ISS stage III or high-risk cytogenetics. Multivariate analyses accounting for treatment arm and MRD negativity (MFC) showed a PFS benefit in pts reaching MRD negativity (HR, 0.48; 95% CI, 0.30-0.78; P = 0.0028). Analysis of MRD based on response (per IMWG criteria) will be presented.

Conclusions: Adding DARA to VTD induction and consolidation deepened responses, as demonstrated by significant increases in MRD-negative rates. MRD negativity was associated with a PFS benefit regardless of treatment strategy. However, deepened responses with D-VTd led to improved outcomes, with MRD negativity associated with prolonged PFS, versus VTD in pts with TE NDMM. Clinical trial information: NCT02541383.

### Table: MRD-negative Rates

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Post-transduction CR</th>
<th>CR</th>
<th>≥CR</th>
<th>MRD-negative</th>
<th>P *</th>
<th>P **</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-VTd</td>
<td>54.6</td>
<td>29.1</td>
<td>&lt;0.0001</td>
<td>23.6 (14.1, 37.3)</td>
<td>0.0028</td>
<td></td>
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<tr>
<td>VTD</td>
<td>36.7</td>
<td>24.3</td>
<td>(0.06)</td>
<td>17.0 (7.4, 35.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGS, 10^5</td>
<td>39.1</td>
<td>22.8</td>
<td>(0.06)</td>
<td>15.8 (7.1, 34.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = MFC evaluable populations.

8019 Poster Discussion Session; Displayed in Poster Session (Board #345), Mon, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:45 PM

Ixabozumab, lenalidomide, and dexamethasone for patients with POEMS syndrome. First Author: Angela Dispenzieri, Mayo Clinic, Rochester, MN

Background: POEMS syndrome is a rare paraneoplastic syndrome caused by an underlying plasma cell disorder. Most of the information regarding treatment has been gleaned from retrospective data. The combination of a proteasome inhibitor, an IκB kinase inhibitor and dexamethasone was shown to be effective in POEMS syndrome.

Methods: We designed a pilot using a 28-day oral regimen of ixazomib (4 mg days 1, 8, 15), lenalidomide (25 mg days 1-21), and dexamethasone (20 mg each 3 cycles) for patients (pts) who had relapsed or refractory disease. In Group A (n = 8) and Group B (n = 3) there were two groups (intended enrollment 15 per gp): Gp A, 13 cycles for 4 to Gp A and 9 to Gp B. 11 pts were analyzed (2 dropped out before receiving any therapy). Data were frozen as of 1/21/2019. Results: Median age was 55; 73% were male. So far, overall 64% met prior endpoint of VEGF CR (Table). The median follow-up of survivors is 12.4 mo (6, 24). 1 pt came off study for non-refractory disease and died thereafter. 38% of patients had grade 3-4 hematologic AE; 72% had grade 3-4 neurologic AE. These included: rash, respiratory infection and hypotension in 1 pt; and anemia, neutropenia and thrombocytopenia in 1 each. 4 pts had no objective worsening of their neuropathy. Conclusions: These preliminary results suggest that ixa-Len-Dex is an effective and tolerable regimen for patients with POEMS syndrome. Clinical trial information: NCT02921993.

### Table: Response after 3 cycles

<table>
<thead>
<tr>
<th>Response after 3 cycles</th>
<th>N</th>
<th>CR</th>
<th>Impr</th>
<th>Stable</th>
<th>Prog</th>
<th>N</th>
<th>CR</th>
<th>Impr</th>
<th>Stable</th>
<th>Prog</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF</td>
<td>8</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CR</td>
<td>8</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<tr>
<td>PT</td>
<td>8</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<tr>
<td>NIS</td>
<td>8</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
| CR, complete response; Impr, improvement as protocol; prog, progression; NIS, neuropathy impairment score; baseline (BL) = not measurable in this domain at baseline (BL) = non-measurable disease at BL

8020 Poster Discussion Session; Displayed in Poster Session (Board #346), Mon, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:45 PM

Serum BCMA levels to predict outcomes for patients with MGUS and smoldering multiple myeloma (SMM). First Author: Angela Dispenzieri, Mayo Clinic, Rochester, MN

Background: BCMA (B-cell maturation antigen) is a TNF receptor family member found on normal and malignant B-cells, including multiple myeloma (MM). It plays a role in proliferation and antiapoptotic pathways. Levels of serum (s)BCMA and BCMA levels in patients (pts) with plasma cell disorders (PCD) and increased BCMA levels are associated with each stage of disease: healthy donor<s; BCMA < SMM < active untreated MM. The purpose of this study was to test whether sBCMA levels predict progression of MGUS or SMM to MM. Methods: There were 3 cohorts in this retrospective study: MGUS progressing to MM (n=42); MGUS not progressing to MM (n=19); SMM progressing to MM (n=32). sBCMA levels were measured using an ELISA-based assay with a polyclonal anti-BCMA antibody from R&D Systems (Minneapolis, MN). The Kruskal-Wallis analysis was used to assess differences. The relationships between sBCMA and time to progression and overall survival were also assessed using Cox proportional hazard models. Results: The highest values of sBCMA were seen among pts with more advanced PCD (Table). The lowest baseline levels were seen in pts with MGUS who did not progress; the change of sBCMA over time was lowest in the MGUS non-progressors. ROC analysis identified a cutoff of 74.4 ng/mL (p<0.001) to predict progression. sBCMA levels above this cut-point was associated with a risk ratio of progression of 5.8 (95%CI 3.2, 11.3) for all comers, a risk ratio of death for all comers of 2.5 (95%CI 1.5, 4.2), and a risk ratio of death for MGUS pts of 3.3 (95%CI 1.9, 5.7). Conclusions: Serum BCMA levels were predictive of diagnosis, progression and death among pts with MGUS or SMM. Limitations of the current study are that only a minority of pts had baseline bone marrow exams or serum FLCs to place sBCMA risk in the context of other previously described risk factors. Serum FLC is now being determined on all patients.
**8021**

**Poster Session (Board #347), Mon, 8:00 AM-11:00 AM**

**Phase 1 study of elotuzumab in combination with autologous stem cell transplantation and lenalidomide maintenance for multiple myeloma. First Author: Karen Goorin, Mayo Clinic, Scottsdale, Arizona, AZ.**

**Background:** Elotuzumab is a humanized monoclonal antibody directed against SLAMF7 that is approved for use in relapsed myeloma. We initiated a single-center, open label, phase 1 trial based on the hypothesis that the addition of elotuzumab and autologous peripheral blood mononuclear cell (PBMC) reconstitution to standard-of-care autologous hematopoietic stem cell transplantation (auto-SCT) and lenalidomide maintenance for consolidation therapy in myeloma patients will be safe and feasible. Methods: This is a Phase 1b, open-label, trial investigating elotuzumab and autologous PBMC reconstitution with auto-SCT consolidation therapy and lenalidomide maintenance. The primary objective of this study is to assess the safety and tolerability of elotuzumab and autologous PBMC reconstitution in the setting of auto-SCT and lenalidomide maintenance. The secondary objectives are to assess myeloma disease status and progression-free survival (PFS) after one year of treatment. Subjects must be eligible for auto-SCT, and meet inclusion/exclusion criteria. Fifteen patients participated in this study. The treatment plan is: In addition to PBSC harvest, subjects undergo steady-state leukopheresis for PBMC collection. Subjects receive standard melphalan (day -1) and autologous stem cell rescue (day 0). Autologous PBMC are reinfused on day +3 and cycle 1 of elotuzumab 20 mg/kg IV is given on day +4. Subjects receive elotuzumab every 28 days up to cycle 12.

Lenalidomide maintenance at 10 mg orally daily begins with cycle 4 of elotuzumab. The evaluable population constitutes all subjects who received at least four of the first five planned doses of elotuzumab.

**Results:** 15 subjects have been enrolled in the study. All of these subjects are included in the safety population, having received at least 1 dose of elotuzumab. Nineteen of 15 subjects have completed 4 of the first 5 planned elotuzumab infusions. IgG- and IgA-containing anti-elotuzumab antibodies (AEs) were attributed to PBMC reconstitution. **Conclusions:** The combination of elotuzumab and PBMC reconstitution with standard auto-SCT and lenalidomide maintenance for consolidation therapy appears to be safe and feasible. The trial is ongoing and has completed accrual. The clinical results will be updated for presentation.

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**8023**

**Poster Session (Board #349), Mon, 8:00 AM-11:00 AM**

**Effect of iFISH defined 1q21 amplification/gain in multiple myeloma patients treated on total therapy protocols. First Author: Maurizio Zangari, UAMS Myeloma Center, Little Rock, AR.**

**Background:** The amplification of the proximal 1q21 region has been reported by interphase FISH (iFISH) in about 40% of newly diagnosed patients, and in 70% of MM patients at relapse. We hereby report the prognostic value of 1q21 amplification/gain by iFISH at enrollment in subjects treated on total therapy (TT) 4, 5, and 6 protocols.

**Methods:** TT4 protocol enrolled newly diagnosed patients with LR disease as defined GEP 70 model < 0.66. TT5 was designed for newly diagnosed patients with HR MM. TT6 enrolled previously treated patients with both HR and LR disease. iFISH was performed on bone marrow samples obtained at the time of study enrollment. FISH probes were generated from specific BAC DNA clone for C651B gene locus (1q21) gene locus. MM cells were identified post hybridization using isotype specific antibody conjugated with 7-amin-4-methylcoumarin-3-acetic acid (AMCA) to stain Ig-Kappa or Ig-Lambda light chain in cytoplasm (clg) of MM cells. The iFISH signals in 100 of MM cells were recorded. A 20% cutoff point was used for detection of significant abnormalities i.e. gain of 1q21 (≥ 3 copies).

**Results:** 607 patients were included in this analysis. With a median age of 61 years, 39% had high risk and 88% low risk disease. 1q21 abnormalities were present in 55% of patients at enrollment. 591 patients (97%) received at least one HDT ASCT. The analysis included 382 TT4 patients with a median PFS of 7.2 years and OS not yet reached. 75 patients enrolled on TT5 protocol experienced median PFS of 2.2 years and median OS of 5.6 years. 150 TT6 enrolled patients experienced median PFS of 4.1 years and median OS of 7.5 years. Statistically significant difference in PFS (p < 0.0001) and OS (p < 0.0001) was observed between 1q21 defined groups (figure 1). No differences in survival were observed based on the 1q21 copy number > 3. **Conclusions:** This retrospective analysis clearly showed that 1q21 amplification/gain detected by interphase FISH in different stages of disease can identify patients with significant shorter progressive free and overall survival even if exposed to total therapy regimens. Clinical trial information: NCT00734877, NCT00869232.

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**8202**

**Poster Session (Board #348), Mon, 8:00 AM-11:00 AM**

**Pharmacokinetics, pharmacodynamics, safety, and tolerability of BION-1301 in adults with relapsed or refractory multiple myeloma. First Author: Jeroen Elassaiss-Schaap, Aduro Biotech, Berkeley, CA.**

**Background:** APRIL (a proliferation-inducing ligand) levels are elevated in the serum of patients diagnosed with multiple myeloma (MM) and is correlated to promotion of malignancy, chemo- and immune-resistance. BION-1301 (BION) is a recombinant, humanized monoclonal antibody against APRIL. We report on the initial pharmacokinematic/pharmacodynamic (PK-PD) profile, safety, and tolerability of BION in adults with relapsed or refractory MM.

**Methods:** Adults with relapsed/refractory MM disease progression after ≥ 3 systemic therapies were recruited for the study. BION was administered every 14 days through intravenous infusion. This ongoing Phase 1/2, open-label, multicenter study is evaluating 6 cohorts with increasing BION dose levels of 50, 150, 450, 1350, and 2700 mg adm- inistrations at 2-week intervals (cohort 6 - 1350 mg dose given QW and Q2W). Serum was analyzed for BION, anti-drug antibodies (ADA), and free APRIL (iAPRIL) at baseline and upon treatment, and evaluated by PK-PD modeling.

**Results:** As of 7Dec2018 reporting through the first 4 cohorts, 15 patients were enrolled in the study (N = 3-4 per cohort). BION has been well-tolerated to date. While exposure increased dose-proportionally from 50 to 1350 mg, half-life and clearance did not significantly differ between 50 and 1350 mg. APRIL serum levels decreased with increasing BION doses. To date no DLT was observed. Non- neutralizing ADA were detected in 1 of the 15 patients. BION transiently reduced iAPRIL levels starting at a dose of 50 mg. A prolonged reduction was seen at higher doses, and at 450 mg, reduction was maintained in 2 patients on treatment for 6 cycles (5.5 months). The area under the normalized iAPRIL curve (Days 1-15) decreased 5-fold from 50 to 1350 mg. Data fit well in an exploratory PK-PD model, with kinetic binding of BION and iAPRIL according to in vitro parameters, and peripheral compartments for both entities. While at 450 mg, 95% target engagement of APRIL was achieved and peak exposure levels were reached at 1350 mg this 95% TG was maintained throughout the dosing interval of 3 doses.

**Conclusions:** BION dose-dependently inhibits serum levels of iAPRIL to 50 to 1350 mg dose levels. Exposure was approximately dose-linear over the dose range evaluated, with a low incidence of ADA. A favorable safety profile supports continued dose escalation and more frequent dosing regimens based on PK-PD modeling. The study is ongoing with subjects exposed to higher and/or more frequent doses anticipated to result in accelerated and sustained APRIL TG. Clinical trial information: NCT03340883.
8025 Poster Session (Board #351), Mon, 8:00 AM-11:00 AM
A health-related quality-of-life (HRQoL) analysis of pomalidomide + low-dose dexamethasone + daratumumab in relapsed refractory multiple myeloma (RRMM) after lenalidomide treatment. First Author: Donna Ellen Reece, Princess Margaret Hospital, Toronto, ON, Canada

Background: Treatment (Tx) of RRMM is complex and requires evaluation of disease and patient (pt) factors to maximize efficacy and minimize toxicity. HRQoL has become an important aspect of MM Tx, as survival has improved with therapeutic advances. Results of the ongoing phase 2 MM-014 trial (NCT01946477) have demonstrated that pomalidomide (POM) + low-dose dexamethasone (DARA) is safe and effective in RRMM pts after first- or second-line lenalidomide (LEN)-based Tx failure. Here we report the impact of this regimen on HRQoL. Methods: RRMM pts with 1 to 2 prior Tx lines, LEN-based Tx as their most recent regimen, and progressive disease during or after their last Tx line received POM + LoDEX + DARA in 28-day cycles (MM-014 cohort B). HRQoL, an exploratory endpoint of interest B, was assessed via EuroQol’s EQ-5D. Results: As of October 15, 2018, 108 pts were evaluable for HRQoL. Baseline characteristics were similar to those of the IIT population (N = 112). EQ-5D completion rates for each cycle (1-6) were ≥ 88%. Mean change from baseline in the EQ-5D index and VAS health score was stable through 6 Tx cycles. At cycle 6, 28.8% and 39.0% of pts achieved minimum clinically important improvement in the EQ-5D index (≥ 0.1) and VAS health score (≥ 6), respectively. EQ-5D index values were stable, with a trend toward improvement in usual activities, pain/discomfort, and anxiety/depression (Table). Conclusions: In RRMM pts with early-line LEN Tx failure, HRQoL was maintained and/or trended toward improvement in all but 1 DARA arm, despite the combination of 3 drugs with distinct toxicities. These findings further support the earlier use of POM-based Tx in RRMM immediately after LEN failure. Clinical trial information: NCT01946477.

Change in EQ-5D at Cycle 6 (n = 80).

<table>
<thead>
<tr>
<th>EQ-5D From Baseline to Cycle 6, %</th>
<th>Mobility</th>
<th>Self-care</th>
<th>Usual Activities</th>
<th>Pain/Discomfort</th>
<th>Anxiety/Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete resolution</td>
<td>5.0</td>
<td>3.6</td>
<td>15.0</td>
<td>23.8</td>
<td>11.3</td>
</tr>
<tr>
<td>Partial resolution</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
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<td>1.5</td>
</tr>
<tr>
<td>Stable</td>
<td>83.8</td>
<td>93.8</td>
<td>71.3</td>
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</tr>
<tr>
<td>Remain in worst state</td>
<td>0.0</td>
<td>1.3</td>
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</tr>
<tr>
<td>Partial deterioration</td>
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<td>1.3</td>
<td>10.0</td>
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</tr>
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<td>Complete deterioration</td>
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<td>2.5</td>
<td>3.8</td>
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</table>

8026 Poster Session (Board #352), Mon, 8:00 AM-11:00 AM
Minimal residual disease clinical monitoring and depth of response in multiple myeloma. First Author: Joaquin Martinez-Lopez, Hospital 12 de Octubre, IBSAL, Madrid, Spain

Background: MRD assessment is a known surrogate marker for survival in multiple myeloma (MM). Most data come from patients enrolled in clinical trials. We present a single institution’s experience assessing MRD in patients receiving frontline therapy and therapy for relapsed disease. We describe the impact of depth, duration, and direction of response on prognosis. Methods: 181 MM patients at University of California, San Francisco (UCSF) from 2007 to 2016. 172 were newly diagnosed and 55 in ≥2nd line. MRD was assessed in patients achieving VGR or better by IMWG criteria. MRD assessment was performed by NGS (Adaptive Biotechnologies, Seattle, WA). PFS curves were plotted by the Kaplan-Meier method, and the log-rank test was used to evaluate statistical significance. Results: 398 MRD samples were analyzed. MRD was available at 3 time points for 59 patients and 2 time points for 36 patients. Median follow up was 26.0. Overall, 66 of 181 patients (36%) achieved MRD- (< 10⁻⁶) on one or more samples. In the newly diagnosed group, 43 of 126 (34%), achieved MRD- at least once. These patients had a prolonged PFS versus patients who were persistently MRD+ (HR 3.14 [95% CI, 0.51–18.7], p = 0.006). Of the 55 patients who received therapy for relapsed disease, 21 achieved MRD- (38%) and PFS was also prolonged versus patients who remained MRD+ (>53m vs 23m, p = 0.03). We analyzed the effects of depth of response, Patients who were MRD- or who were MRD+, at a very low level (between 10⁻⁷ and 10⁻⁹), had a better prognosis then those with higher disease burdens (p = 0.001). Finally we analyzed the effect of repeated MRD monitoring on PFS. Three categories were identified in newly diagnosed patients: (A) patients with ≤ 3 MRD- samples, (B) patients with continuously declining detectable clones, and (C) patients with a stable number of clones. Groups A and B had a more prolonged PFS than group C (HR 3.14 vs 31m, p = 0.001). Conclusion: In our single site, real-world setting has the same predictive power as that seen in clinical trials. MRD dynamics can accurately predict disease evolution and drive clinical decision-making. This study lends support to the concept of MRD-driven decision-making and helps validate the relevance of MRD.

8027 Poster Session (Board #353), Mon, 8:00 AM-11:00 AM
Safety and efficacy of once-weekly carfilzomib (K) dosing in frail patients (pts): A subgroup analysis from the phase 3 A.R.R.O.W. study. First Author: Maria-Victoria Mateos, University Hospital of Salamanca/IBSAL, Salamanca, Spain

Background: A.R.R.O.W. demonstrated superior progression-free survival (PFS) with once-weekly K (70 mg/m²)-dexamethasone (Kd70) vs twice-weekly K (27 mg/m²)-dexamethasone (Kd27) in relapsed and refractory multiple myeloma (RRMM). PFS in regard to frailty status, a distinct subgroup of RRMM, was not explored for relapsed or refractory MM (1–3 prior therapy lines). For a comprehensive fitness measure, frailty scales were developed incorporating age, comorbidities, and functional status. (Palumbo Blood 2015; Facon Blood 2015). Here we assessed post hoc pt outcomes by frailty status. Methods: PFS and safety were assessed by treatment arm and a frailty algorithm incorporating age, medical history-derived Charlson Comorbidity Index, and ECOG performance status; pts with frailty scores of 0, 1, or >2 were classified as fit, intermediate (int), or frail, respectively. PFS was assessed with the Kaplan-Meier method. Safety was assessed in pts who received ≥1 treatment dose. Results: Pt distribution by frailty status was generally balanced between arms (Table). Once-weekly Kd70 vs twice-weekly Kd27 resulted in median PFS for fit, int, and frail pts of 15.7, 15.5, and 7.7 mos (HR 0.53 [95% CI, 0.33–0.86]). 11.1 vs 7.7 mos (HR 0.53 [95% CI, 0.55–0.93], and 10.3 vs 6.6 mos (HR 0.76 [95% CI, 0.49–0.91], respectively. Rates of grade ≥3 treatment-emergent adverse events (TEAEs) of interest were similar between treatment arms across frailty subgroups (Table). In the once-weekly Kd70 subgroups, there was no grade ≥3 peripheral neuropathy (PN), grade ≥3 cardiac failure rates were <4%. Conclusions: Once-weekly Kd70 resulted in PFS benefits vs twice-weekly Kd27 with a favorable benefit-risk profile regardless of frailty score as defined. These results support once-weekly Kd70 as a treatment option for both fit and frail RRMM pts. Clinical trial information: NCT02412878.

8028 Poster Session (Board #354), Mon, 8:00 AM-11:00 AM
Carfilzomib (K) in relapsed and refractory multiple myeloma (RRMM): Frailty subgroups (NR analysis). First Author: Maria-Victoria Mateos, University Hospital of Salamanca/IBSAL, Salamanca, Spain

Background: K-based regimens improved progression-free survival (PFS) and overall survival (OS) in RRMM patients (pts) in ASPIRE (K [27 mg/m²]-lenalidomide-dexamethasone [KRD] vs Rd) and ENDEAVOR (K [56 mg/m²]-dexamethasone [Kd56] vs bortezomib-dexamethasone [Vd]), regardless of age. Frailty scores have been developed based on age, comorbidities, and functional status (Palumbo Blood 2015; Facon Blood 2015). Here we assessed post hoc pt outcomes by frailty status. Methods: PFS, OS, and safety were assessed by treatment arm and frailty score (based on age, medical history-derived Charlson Comorbidity Index, and ECOG performance status); frailty scores: 0 = fit, 1 = intermediate (int), and ≥2 = frail. Results: Pt frailty status was balanced between treatment arms in ASPIRE and ENDEAVOR. Median PFS and OS were longer with K-based regimens vs controls in ASPIRE and ENDEAVOR across frailty subgroups (Table). Rates of treatment-emergent adverse events are summarized in the Table. Conclusions: Kd56 and KRd consistently improved outcomes vs Vd and Rd, respectively, in all frailty subgroups as defined by the algorithm above. These findings support the favorable benefit-risk profile of KRd and Kd56 regardless of frailty score. Clinical trial information: NCT01080391 and NCT01568866.

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Conclusions: Prolonged treatments have significantly improved survival in newly diagnosed multiple myeloma (NDMM). Lenalidomide (IMiDs), is currently approved in this indication, but remains a daily treatment, although oral, and may favor side effects in the long run. Furthermore, the use of a proteasome inhibitor (PI) is warranted in certain type of MM, such as high-risk. Carfilzomib, a second generation PI, has proved active combined with an acceptable safety profile but its added benefit when given continuously is unknown. We thought to study maintenance Carfilzomib for elderly NDMM (eNDMM).

Methods: The IFM 2012-03 multicenter phase I KMP (Carfilzomib, Melphalan, Prednisone) weekly study for eNDMM (>65 years old) determined the maximum tolerated dose of weekly Carfilzomib at 70mg/m². We focus herein on the second part of the study with IV Carfilzomib monotherapy given at 36mg/m² for 13 cycles maintenance on an every 2 weeks schedule.

Results: Thirty eNDMM were recruited in IFM 2012-03. Median age is 75, with 56% R-ISS 2 or 3 and 11% high-risk cytogenetic. With K weekly from 36 to 70mg/m², OS is reported at 93.3%, including 46.7% cCR; median PFS is 35.8 months and median OS was 77 months (73%) patients started K maintenance and 16 (73%) completed it. Four patients progressed and 2 stopped for AEs (renal amylosis, sensory neuropathy) during that maintenance. At maintenance completion, 50% were aCR. From the start of maintenance, in landmark analysis, median PFS is 28.1 months and the estimated 36-month OS is 72%

Conclusions: Carfilzomib monotherapy can be used safely in maintenance for 1 year in eNDMM, including for patients above 75 years. K maintenance may lead to deep response rate, certainly a more relevant prognostic factor for prolonged survival. Therefore, Carfilzomib maintenance, characterized with a simple administration modality, might be considered as an alternative to Lenalidomide and integrate the armamentarium of prolonged therapy in eNDMM. Clinical trial information: NCT02302495.

Background: Our prior studies identified the prognostic significance of ≥400 cPCs/150,000 analyzed events quantified by MFC in NDMM. We evaluated if a similar quantification of cPCs using MFC can add prognostic value to the current R-ISS classification of NDMM pts. Methods: We evaluated all NDMM pts seen at the Mayo Clinic, Rochester from 2009-2017 who had their peripheral blood samples evaluated by 6-color MFC prior to therapy. The cPCs detected were reported as the number of clonal events/150,000 collected total events. Survival analysis was performed by the Kaplan-Meier method and differences assessed using the log rank test.

Results: This cohort consisted of 566 consecutive pts with NDMM with a median age of 66 years (27-95). The distribution of the R-ISS classification of this cohort is as follows: Stage I- 128 (23%) pts, Stage II- 369 (65%) pts and Stage III- 69 (12%) pts. The median number of cPCs was 59 (0-46,412)/150,000 events. The median time-to-next-treatment (TTNT) and overall survival (OS) for pts with >400 cPCs (n = 140, 25%) was 19 months and 46 months compared with 34 months and 77 months for those with <400 cPCs respectively (n = 426, 75%) (p = 0.001 for both). The median TTNT and OS for pts based on their R-ISS classification as well as with and without the presence of ≥400 cPCs by MFC was as follows in the following Table.

Conclusions: Quantifying >400 cPCs/150,000 analyzed events by MFC can potentially upstage the R-ISS classification of a subset of NDMM pts with stage I and II disease and identify those pts with a worse than expected survival outcome.
Multimorbidity patterns and their association with survival in a large national cohort of older veterans with multiple myeloma. First Author: Nathaniel Fillmore, VA Boston Healthcare System, Boston, MA

Background: The majority of older adults carry two or more chronic conditions (multimorbidity). Although comorbidity in multiple myeloma (MM) has often been described with comorbidity counts, the impact of multimorbidity clusters has yet to be investigated. Methods: In a national cohort of 7815 patients aged >60 years diagnosed with and treated for MM in Veterans Affairs Healthcare System, we extracted 53 chronic conditions from claims in the 3 years preceding diagnosis using the Centric of Medicine and Medical Services-defined chronic and disabling conditions. We performed latent class analysis to identify patterns of multimorbidity that coexisted with MM at diagnosis. We then assessed whether these multimorbidity patterns were associated with survival in 5992 non-transplanted patients initially treated with either doublet or triplet chemotherapy regimens, adjusted for MM stage, sociodemographic factors, and prognostic lab values. Results: Mean follow up time was 3.1 years (SD, 2.6). We identified 6 multimorbidity clusters at the time of MM diagnosis: minimal disease (1302 patients, 16.7%), cardiovascular disease (2011, 25.7%), diabetes and complications (1820, 23.3%), psychiatric and substance use disorder (1931, 19.9%), chronic renal disease (759, 9.7%), and multisystem impairment (992, 12.7%). In patients initially treated with doublet or triplet chemotherapy, survival varied across multimorbidity patterns (p < 0.001); patients with minimal disease had the best survival (median survival [MS] = 4.5 years, 5-year survival = 47.5%), and patients with multisystem impairment had the worst (MS = 2.4 years, 5-year survival = 24.3%). After adjustment for covariates, patients with clusters of chronic lung disease (HR = 1.40 [1.22-1.60]), psychiatric and substance use (HR = 1.57 [1.37-1.79]), and multisystem impairment (HR = 1.71 [1.50-1.94]) had higher hazards of death than patients with minimal disease. Conclusions: We found higher-import and lower-import multimorbidity clusters among older veterans with newly-diagnosed MM treated with chemotherapy. Unique combinations of chronic diseases may interact with MM itself to drive differences in mortality.

Hematologic Malignancies—Plasma Cell Dyscrasias

Multimorbidity patterns and their association with survival in a large national cohort of older veterans with multiple myeloma. First Author: Nathaniel Fillmore, VA Boston Healthcare System, Boston, MA

Impact of age on efficacy and safety of daratumumab in combination with lenalidomide and dexamethasone (D-Rd) in patients with transplant-ineligible newly-diagnosed multiple myeloma (NDMM): MAIA. First Author: Saad Zafar Usmani, Levine Cancer Institute/Atrium Health, Charlotte, NC

Background: D-Rd significantly reduced the risk of progression/death by 44% in transplant-ineligible NDMM pts vs Rd in the phase 3 MAIA study. To examine the impact of age on efficacy/safety of D-Rd vs Rd in this population, a subgroup analysis was conducted in pts <75 and >75y of age. Methods: Transplant-ineligible NDMM pts were randomized 1:1 to Rd or D-Rd; stratification was based on age (<75 vs >75y). ISS (I, II, III), and region (North America vs Other). Pts received 28-day cycles of either R 25 or 10 mg (based on renal function) PO QD on Days 1-21 and either D 10 or 5 mg (based on age or BMI) PO QD until progression. In the D-Rd arm, pts received daratumumab 16 mg/kg IV QW for Cycles 1-2, Q2W for Cycles 3-6, and Q4W thereafter until progression. FFS is the primary endpoint. Results: Among 737 randomized pts (D-Rd, n=388; Rd, n=369), 321 (44%) were <75 y of age. For D-Rd vs Rd, relative median dose intensity for R was 79% vs 93% for <75 y subgroup and 66% vs 89% for >75 y subgroup, respectively. After median follow-up of 28 mo, significant PFS benefit of D-Rd vs Rd was maintained in both <75 and >75 y subgroups (Table). Deeper responses and MRD-negative rate (10^{-5} threshold) were higher in D-Rd vs Rd in both subgroups (Table). Most common grade 3/4 TEAEs in <75 y pts were neutropenia (60% vs 41%), lymphopenia (19% vs 12%), anemia (16% vs 22%), pneumonia (15% vs 10%), leukopenia (12% vs 8%), and thrombocytopenia (8% vs 11%). Fewer pts receiving D-Rd vs Rd discontinued treatment due to TEAEs (<75 y: 5% vs 12%; >75 y: 10% vs 21%). Conclusions: D-Rd pts received less Rd vs Rd group regardless of age. Efficacy of D-Rd in <75 and >75 y pts was consistent with the ITT population, and D-Rd demonstrated acceptable tolerability regardless of age. Together with the phase 3 ALCYONE study, these findings confirm clinical benefit of daratumumab plus standard-of-care in transplant-ineligible NDMM pts ≥75 y of age. Clinical trial information: NCT02252172.

Hematologic Malignancies—Plasma Cell Dyscrasias

Implications and outcomes of MRD-negative multiple myeloma patients with immunofixation positivity. First Author: Marcella Taschukows, Mayo Clinic, Rochester, MN

Background: Minimal residual disease (MRD) assessment in multiple myeloma (MM) has improved our ability to assess disease activity, resulting in more advanced prognostication. While MRD assessment remains confined to the bone marrow (BM) plasma cell population, serum studies including immunofixation (IFE) are required to complete response evaluation. The significance of those who are MRD_{neg} yet have detectable monoclonal protein through IFE remains unclear. Methods: We retrospectively studied 256 MM patients who had MRD_{neg} assessment via the Euroflow multiparametric flow cytometry on the BM with concomitant serum IFE testing. Patients who were MRD_{neg} were included in the study. Outcomes included probability of disease progression (PD) at 1 year. The Cox-proportional hazards model was used to compare probability of PD among different groups. Time to progression (TTP) was calculated as the difference from date of MFC analysis to PD in months. Results: Among the entire cohort, 178 (70%) patients were MRD_{neg} and median follow-up from MRD assessment was 6.3 months. Among these patients, 74 (42%) had a positive IFE at the time of MRD analysis. Within the MRD_{neg}/IFE_{pos} group, 31 (42%) patients remained MRD_{neg} after a median follow up of 5.5 mo from initial MRD/IFE testing while 34 patients eventually became IFE_{neg} after a median of 2.8 mo with no subsequent IFE available in 9 patients. The 1 year probability of PD in the MRD_{neg}/IFE_{pos} group was 20% compared to 41% in the MRD_{neg}/IFE_{neg} group (P < 0.01, Wilcoxon test). When comparing subsequent IFE status in MRD_{neg} patients were MRD_{neg} at 1 year, MRD_{neg} patients had a trend towards shorter TTP compared to patients who later became IFE_{neg}. Conclusions: Persistent monoclonal protein in the face of MRD negativity predicts for a shorter TTP. This likely reflects persistent disease that was not sampled on the BM aspirate in many of these patients compared to those who were IFE_{neg} at diagnosis and thus became MRD_{neg} at a trend towards longer TTP owing to the prolonged half-life and therefore clearance of M protein. This supports the current strategy of assessing for MRD at the time of suspected complete response to reduce the chance of positive MRD tests and thus avoidance of multiple BM exams.

Plasma cell-free DNA chromosomal instability score as early predictor to monitor tumor burden in response to antitumor therapy in multiple myeloma patients. First Author: Juan Du, Department of Hematology, Myeloma & Lymphoma Center, Shanghai Chang Zheng Hospital, Shanghai, China

Background: Multiple myeloma (MM) is a plasma cell malignancy characterized by chromosomal instabilities (CIN). Here we investigate the potential of cell-free DNA CIN as an non-invasive biomarker to predict early response for MM treatments. Methods: In this prospective study, we recruited 11 relapsed/refractory (RRMM) and 19 newly diagnosed (NDMM) patients at Changsheng Hospital. Plasma samples were collected after finished two cycles or one month (RRMM) of therapy, with matched ones before the current regimen. cfDNA was extracted, followed by CIN analyses using a customized bioinformetics workflow, ultrasensitive chromosomal aneuploidy detector (UCAD). Criteria for response and progression were according to the IMWG (Duret BG et al. 2006). Results: 7 (23%) patients (5 RRMM and 2 NDMM) showed high cfDNA CIN regard as strong positive after two cycles of treatment. Plasma cfDNA CIN profiling found complex clonal evolution compared two cycles to baseline. Multiple genomic regions, including chr7, 17p (TP53), 12q and 3p, were involved in clonal evolution. The degree of cfDNA CIN correlated with myeloma stage and overall survival. Remarkably, of the 5 heavily treated RRMM patients and 1 primary refractory newly diagnosed patient, 3 died within 60 days after the last time of cfDNA detection. Nine patients (30%) of patients showed positive cfDNA CIN after two cycles of treatment, which response rate was 11% (n=1) with SD, 33% (n=3) with PR, and 56% with CR, respectively. Fourteen patients with 5 RRMM and 9 NDMM were detected marginal or negative cfDNA CIN after two cycle of treatment, which response rate was 11% (n=1) with SD, 33% (n=3) with PR, and 56% with CR, respectively. Subsequently, these three heavily treated RRMM patients have chance to enroll the chimeric antigen receptor T-Cell immunotherapy (CAR-T) therapy (enrolled NCT03093168). Surprisingly, all of them benefit from the CAR-T therapy to improve responses dramatically, meanwhile, the dynamic of total cfDNA concentration in patients correlated with tumor burden progression and response. We provide evidence that cfDNA level correlates with tumor burden to negative. Meanwhile, the dynamics of total cfDNA concentration in patients correlated with tumor burden progression and response. We provide evidence that cfDNA level correlates with tumor burden to negative. Therefore, serial plasma cfDNA analysis is a robust and sensitive tool for monitoring response to therapy.
**Background:** Nowadays, therapy for relapsed or refractory multiple myeloma (rMM) usually consists of multi-targeted combination regimens for achieving complete remission. In this context, resistance resembles a therapeutic challenge that may be overcome by novel biomodulatory therapies communnicating with reprogramming dysregulated cellular and intercellular homeostasis in neoplasia. Methods: The present, prospective phase II, one-arm, one-stage multi-center, open label trial, following phase I, focused on reprogramming myeloma and adjacent stroma cells in order to control rMM beyond >2nd line treatment and following lenalidomide resistance in prior line. Adults with rMM were eligible for receiving continuously, oral, daily, dexamethasone 1mg, pioglitazone 45mg, low-dose treosulfan as metronomic chemotherapy (250mg bid) and lenalidomide 15mg, respectively, until disease progression. Results: Thirty-nine patients (mean time since diagnosis, 5.7 years; 66.7% with age >60 years) had received a median of 5.5 (range 2 to 10) prior treatments. 89.5% of the patients were refractory to last therapy (all IMiD resistant), and 48.7% had received autologous stem-cell transplants. The overall response rate (CR, VGPR) was 17.9%. Eighteen patients (46.2%) had partial response or better; ten patients (25%) had stable disease; 5% had progressive disease. The disease control rate (DCR) was 71.8%. Time-to-progression was not significantly different between IMiD refractory patients and patients progressing following prior IMI therapy or between high-risk versus non-high-risk cytogenetics. The median progression-free survival (PFS) and overall survival was 5.6 months (95% confidence interval (CI), 3.8 to 8.5) and 17.6 months (95% CI, 14.9 to 39.2), respectively. The major AE (NCI-CTCAE grade) with grade (≥3) was based on the year of diagnosis; group 1-2004-07 (n=831), group 2-2008-12 (n=1161), and group 3-2013-17 (n=1457). Survival of the groups were estimated using Kaplan-Meier method, and compared using log rank test.

**Results:** The median age was 64 years (22 to 96); 60% were male and 40% were female. 14% were >75 years, 33% were aged 65-75 and 53% were ≤65 years. The median overall survival for the whole cohort was 5.7 years (95%; 5.4, 6.3). The median OS for the groups 1, 2 and 3 were 39.6, 67.4% and 67.4%, respectively. The 3-yr OS for groups 1, 2 and 3 were 85%, and 75%, respectively. While patients experienced improvements in OS over time, improvement in group 3 was most prominent for those >75 years. In patients ≤65 years, the 4-yr OS for groups 1, 2 and 3 were 57, 71, and 79% respectively. In patients 65-75 years of age, the 4-yr OS for groups 1, 2 and 3 were 48, 70, and 75% respectively. In patients >75 years, the 4-yr OS for groups 1, 2 and 3 were 24, 35, and 56% respectively. While patients with high-risk disease did not see as much benefit in the earlier period, substantial progress was seen in the last group. The 3-yr OS for patients with high-risk cytogenetics were 52, 55, and 73% for groups 1, 2 and 3 compared to 67, 75, and 85% for standard-risk cytogenetics respectively. 2067 patients were involved, according to the International Staging System and the median OS for stages 1 and 2 were 6.5, 4.6 and 2.4 in group 1; 9.2, 6.6 and 3.5 in group 2 and NR for any of the stages in group 3. Conclusions: The results confirm continued improvement in survival of newly diagnosed multiple myeloma patients, including elderly and high-risk MM.

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Austrian RWE 3-4th line

zomib 20/56 mg/m² was administered on days 1, 8, 15, Lenalidomide 25mg/27mg/m² and limited to 18 months exposure. We have reported already that International phase 3 study. However, K was used on a twice a week basis at one combination (KRd) has led to approval in early RRMM based on ASPIRE Triplet-based Carfilzomib (K), Lenalidomide and Dexamethasone (Rd).

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A phase I trial of ruxolitinib, lenalidomide, and methylprednisolone for patients with relapsed/refractory multiple myeloma (MM). In this study, we aimed to evaluate the safety, clinical benefit rate (CBR) and overall response rate (ORR) of this regimen in patients with relapsed/refractory MM.

Methods: A traditional 3+3 dose escalation design was used to enroll subjects in four cohorts with planned total enrollment to be 49 pts. The endpoint was time to progression assessed by Kaplan-Meier method.

Results: 119 were male, 130 were female. Most (n=179, 72%) were diagnosed at age 50-69 years, with a prevalence of 0.38 (0.28, 0.53) per year; approximately 50% are diagnosed in the setting of immune-related disorder.

Conclusions: These results suggest that T cell redirection with simultaneous checkpoint inhibition in the synapse is highly potent while minimizing off-tumor toxicity, therefore, has high therapeutic potential for patients with relapsed MM.

Hematologic Malignancies—Plasma Cell Dyscrasia

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Phase I trial of a novel DNA vaccine in patients (pts) with smoldering Waldenstrom macroglobulinemia (sWM).

**Background:** Idiotype determinants of the surface immunoglobulin (ig) associated with a given pt's B-cell lymphoma are unique to that tumor, and thus are a tumor-specific marker. This study aims to use an idiotype DNA vaccine to lengthen the smoldering phase of WM without inducing cross-resistance to available therapies. Administered vaccine recombinant plasmid DNA encoding a fusion protein, consisting of autologous lymphoma scFv (specific idiotype) and human CCL20 (macrophage inflammatory protein-3 alpha - MIP-3a) chemokine. Targeted delivery of this fusion protein to APCs, and subsequent processing and presentation, is hypothesized to break tolerance and generate an immune response against the idiotype, eradicate circulating antigen-expressing B-cell lymphoma cells. Methods: sWM received i.d. vaccinations of pt-specific DNA vaccine at 4-week (wk) intervals (wks 0, 4, and 8). Two dose levels (500μg; 2500μg) were evaluated in a 3+3 design. Primary objective: to evaluate the vaccine's safety and identity it's MTD. Secondary objectives: 1) to assess immunogenicity of the vaccine 2) to determine time to symptomatic WM. Results: Between 1/2016-1/2019, 9 pts (7 men) were treated (500 mg): n = 3; 2500μg: n = 6. Median age at enrollment was 67 yrs (range 56-78); median time from diagnosis to 1st vaccination was 26.5 mos (8.8-120.9). MYD88 L265P + (6 pts). CXCR4 WHIM + (1 pt). With median follow up of 26.5 months (range: 8-36.4), all pts remain alive. Seven have stable disease; 2 progressed to symptomatic WM (8 mos. (1pt) and 26 mos. (1pt) from 1st vaccination). All pts completed planned therapy. No DLTs or Grade 4 AEs occurred. Ten mos. after the 3rd vaccination, 1 pt had a grade 3 pleural effusion and leukopenia with an increase in rheumatoid factor (23.1 IU/mL [normal range 0.0-15.9]) and ANA titer of 1: 100; all resolved within 2 mos. Grade 1 AE's were: anemia (5), leukopenia (2), fatigue (1), leukocytopenia (1), and co-morbidities unrelated to treatment. 9 (64%) achieved an objective response (8 PR, and 1 VGPR) and no patient has progressed to MM. Non-Cancer adverse events included 3 grade 1 GI events, 2 grade 3 lung infection, 1 grade 2 acute kidney injury, and 1 had grade 1 fatigue that was possibly related to treatment. Results of immunogenicity assays are underway, and will inform whether tumor specific immune responses are induced. Additional follow up is required to determine time to symptomatic WM. Clinical trial information: NCT01209871.

**Conclusion:** Idiotype (scFv-CCL20) DNA vaccine therapy appears to be safe in pts with sWM. Evaluation of immune response to this therapy, and its impact on clinical response, is ongoing.

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**ECOG-ACRIN EAA172: Phase 1/2 study of daratumumab, bortezomib, dexmachemase (DVd) with or without venetoclax in relapsed/refractory multiple myeloma (RRMM) with assessment for t(11;14) status.**

**Background:** The most common translocation in multiple myeloma (MM) is t(11;14)(q13;q2) present in approximately 20% of cases. MM cells with t(11;14) usually have a favorable high BCL-2 level and inferior outcomes compared to standard risk myeloma cells. BCL-2, a potent, selective, orally available small-molecule BCL-2 inhibitor that induces cell death in MM cell lines and primary samples. VEN has single agent activity in relapsed/refractory MM (RRMM) with an acceptable safety profile, especially in t(11;14) MM; however, non-t(11;14) MM patients may benefit from single agent VEN and VEN incorporation in multi-agent RRMM regimens. Dexchemase (d) promotes Bcl-2 decrease in MM resulting in sensitivity to VEN and this combination with bortezomib (Vd-VEN) has an acceptable safety profile with high response rates in heavily treated MM patients. Combination therapy with daratumumab and bortezomib (DVd) has become a standard of care in heavily pretreated MM patients. Our hypotheses are that the addition of VEN will improve upon this standard and be most effective in the t(11;14) positive subset. Methods: Eligibility criteria include RRMM with measurable disease, not bortezomib refractory, platelet count $>100K. t(11;14)$ patients were treated with at least 1 prior line of therapy who have undergone autologous stem cell transplantation and are transplant ineligible. After a Ph1 study to determine the recommended phase 2 VEN dose, patients are randomized to DVd +/- VEN (stratified by prior lines of therapy and R-ISS). The primary Ph2 objectives are to compare 8-cycle minimal residual disease (MRD) negative rate and to inform the role of t(11;14) as a biomarker. The Ph2 design proposed by Freidlin et al. follows a decision algorithm as outlined in the table below. Simulations were run to establish an optimal sample size given various parameters including biomarker prevalence and power to make appropriate decisions for a Ph3 design. Target Ph2 accrual is 120 patients with a 1/3 positive:2/3 negative t(11;14) split. Clinical trial information: NCT03701321.
SGNBCMA-001: A phase 1 study of SEA BCMA, a non-fucosylated monoclonal antibody targeting BCMA, a plasma cell-specific protein that is expressed on MM cells of most patients. Based on preclinical data, SEA-BCMA displays enhanced antibody-dependent cellular cytotoxicity through increased FcγRIII binding, antibody-dependent cellular phagocytosis, and blocking of BCMA-mediated pro-survival and proliferative signaling. SEA-BCMA is active at 0.03 mg/kg in xenograft models and does not cause adverse effects in preclinical models, supporting clinical investigation for MM. **Methods:** This is a phase 1, open-label, multicenter, dose-escalation study to evaluate the safety, tolerability, and preliminary activity of SEA-BCMA in adult patients with relapsed/refractory multiple myeloma (MM). Enrollment began in November 2018 for adults aged ≥18 years with histologically confirmed MM, Eastern Cooperative Oncology Group performance status of ≤1, and no other therapeutic options available. Prior therapies must include a PI, an IMiD, and an anti-CD38 antibody. Prior receipt of BCMA-targeting agents is prohibited. BCMA-expressing myeloma will be stratified into 10 groups for study entry but will be tested retrospectively. Dose-escalation is being conducted in ~25 subjects using the modified toxicity probability interval method. During dose-expansion, ~40 subjects will be treated at the maximum tolerated or optimal dose. Responses are assessed per the 2016 International Myeloma Working Group criteria. Biomarker and pharmacokinetic evaluations will be performed on peripheral blood and bone marrow. **Clinical trial information:** NCT03582033.

DARA + VRd (D-VRd) demonstrated efficacy and tolerability in the safety run-in cohort of the ongoing phase 2 Griffin study that included transplant-eligible NDMM pts. To determine whether D-VRd demonstrates efficacy and tolerability in NDMM pts for whom transplant is not intended as initial therapy the phase 3 CEpheus study will evaluate the efficacy and safety of D-VRd vs VRd alone in this pt population. **Methods:** This is an ongoing multicenter, open-label, randomized phase 3 study of D-VRd vs VRd alone in pts with NDMM for whom transplant is not planned as initial therapy: A multicenter, randomized, phase III study (CEpheus). **First Author:** Sonja Zweegman, Department of Hematology, Amsterdam UMC, Amsterdam, Netherlands

Background: DARA is a human, anti-CD38 IgGκ monoclonal antibody that significantly reduced the risk of progression/death with a manageable safety profile across several phase 3 studies in relapsed/refractory MM and NDMM. DARA + VRd (D-VRd) demonstrated efficacy and tolerability in the safety run-in cohort of the ongoing phase 2 Griffin study that included transplant-eligible NDMM pts. To determine whether D-VRd demonstrates efficacy and tolerability in NDMM pts for whom transplant is not intended as initial therapy, the phase 3 CEpheus study will evaluate the efficacy and safety of D-VRd vs VRd alone in this pt population. **Methods:** This is an ongoing multicenter, open-label, randomized phase 3 study of D-VRd vs VRd alone in pts with NDMM for whom transplant is not intended as initial therapy. Approximately 360 pts will be stratified by ISS stage and age/transplant eligibility (age ≥70 years and refusal to transplant, or age ≥70 years and will be randomized in a 1:1 ratio. All pts will receive 8 cycles of VRd (V: 1.3 mg/m² SC Days 1, 4, 8, 11; R: 25 mg PO Days 1-14; d: 40 mg PO Days 1-4, 9-12) for 24 weeks of maintenance until PD; upon loss of CR or MRD-negative status, pts will restart DARA treatment. All pts will receive preinfusion medications. The primary endpoint is progression-free survival (PFS). Secondary endpoints include MRD-negative rate, overall response rate, PFS on next line of therapy, overall survival, time to and duration of response, health-related quality of life, pharmacokinetics, immunogenicity, stem cell yield after mobilization, time to engraftment post-ASCT, and safety. **Clinical trial information:** NCT03710603.

Background: The role of adjuvant chemotherapy for pathological stage I non-small cell lung cancer (NSCLC) is controversial. The purpose of this study was to investigate the effect of adjuvant chemotherapy for pathological stage I NSCLC with high-risk factors for recurrence. Methods: Prospectively collected data from 1,278 patients with pathological stage I (8th edition) NSCLC undergoing lobectomy were retrospectively analyzed. High-risk factors for recurrence were determined by multivariable Cox proportional hazards model for recurrence-free survival (RFS), RFS, overall survival (OS), and cancer-specific survival (CSS) were compared between patients who received adjuvant chemotherapy and those who did not. Results: In multivariable analysis, age ($\geq$70; hazard ratio (HR), 2.14), invasive component size ($>2$ cm; HR, 1.60), visceral pleural invasion (HR, 1.81), lymphatic permeation (HR, 1.67), and vascular invasion (HR, 2.78) were identified as independent factors for RFS. In patients with high-risk factors for recurrence such as invasive component size of $>2$ cm, visceral pleural invasion, lymphatic permeation, or vascular invasion (high-risk group; n = 641), RFS was significantly different between patients who received adjuvant chemotherapy (n = 222; 5-y RFS, 81.4%) and those who did not (n = 418; 5-y RFS, 73.8%; P = 0.023). OS and CSS were also significantly better in patients who received adjuvant chemotherapy (5-y OS, 92.7%; 5-y CSS, 95.0%) than in those who did not (5-y OS, 81.7%; P < 0.0001; 5-y CSS, 89.5%; P = 0.012). In patients without any high-risk factors for recurrence (low-risk group; n = 637), RFS was not significantly different between patients who received adjuvant chemotherapy (n = 83; 5-y RFS, 98.1%) and those who did not (n = 554; 5-y RFS, 95.7%; P = 0.30). OS and CSS were also not significantly different between patients who received adjuvant chemotherapy (5-y OS, 98.0%; 5-y CSS, 100.0%) and those who did not (5-y OS, 95.9; 5-y CSS, 99.4%; P = 0.52). Conclusions: Adjuvant chemotherapy may improve survival in patients with pathological stage I NSCLC who have high-risk factors for recurrence such as invasive component size of $>2$ cm, visceral pleural invasion, lymphatic permeation, or vascular invasion.
8504 Oral Abstract Session, Sat, 1:15 PM-4:15 PM
Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): Clinical and correlative results from the NEOSTAR study. First Author: Cassandra, The University of Texas MD Anderson Cancer Center, Houston, TX
Background: Neoadjuvant immune checkpoint inhibitors (ICIs) induce major pathologic response (MPR) rates of 20 to 45% in resected NSCLCs. We report the results of NEOSTAR - a phase 2 trial of neoadjuvant N or NI for NSCLCs.
Methods:Pts with stage I-IIIA (single N2) resectable NSCLC (ACC 7th), PS 0-1, were randomized to N (3 mg/kg IV, D1, 15, 29) or NI (1 mg/kg IV, D1) followed by surgery (n = 444). Primary endpoint was MPR, with MPRTM hypothesized to be higher than MPR to induction chemotherapy historical controls. Tumor immune infiltrates and pre- and post-ICI tumor PD-L1 were assessed by flow cytometry & IHC. Wilcoxon rank sum test & Fisher’s exact test were used for comparisons. Results:44 pts were randomized, 23 N, 21 NI: mean age 66, 64% males, 18% never smokers, 59% adenocarcinomas, stages: IA 8 (18%), IB 15 (34%), IIA 7 (16%) IIB 5 (11%), IIIA 9 (20%). Only 3 pts received < 3 doses due to TRAEs (7%), 34 pts had surgery post ICIs (7 not resected [7/44], 17, [2 N, 5 NI, 3 pending]). There were 10 MPRs in 41 pts overall (24, 4, 6 NI), of which 6 were path CRs (15%, 2 [N], 4 [NI, 21%]. Among 34 resected pts, MPR rate was 29% (N 20%, NI, 45%). Median % of viable tumor was lower post NI vs N (20% vs 65%, p = .097). ORR (RECIST v1.1) was 22% (8 PRs [5 N, 3 NI], 1 CR [NI]); 15% of pts had PD (3 N, 3 NI). The proportion of CR+PR in MPR+ was higher than in MPR- (60% vs 2 %), p < .001). Surgical complications included 2 bronchopleural fistulas (BPFs) in N & 8 air leaks (5 N, 3 NI), 25% invasive cancer in MPR- due to BPF post steroid-treated pneumonitis (G5, N), G3 pneumonia, hypoxia, hypermagnesemia (1 each, all N), G3 diarrhea (1 NI). CD3+ & CD103+ tissue resident memory CD8+ TILs were higher in NI- vs N-treated tumors (CD3+ 81.2% vs 54.4%, p = .028; CD8+ 56.2% vs 38.3%, p = .069). Median pre-treatment tumor PD-L1 was higher in responders (MPR+ vs CR+PR vs non-responders [80% vs 1%, p = .024), and the % of viable tumor was lower in tumors with PD-L1 > 1% vs PD-L1 ≤ 1% (median 20% vs 80%, p = .046).
Conclusions: A 24% MPR rate to neoadjuvant ICIs was observed. NI induced a higher % of non-viable tumor and of tissue resident memory TILs vs N. Antitumor activity was associated with higher pre-treatment PD-L1 levels. Clinical trial information: NCT03158129.

8505 Oral Abstract Session, Sat, 1:15 PM-4:15 PM
Effect of trilaciclib, a CDK 4/6 inhibitor, on myelosuppression in patients with previously treated extensive-stage small cell lung cancer receiving topotecan. First Author: Yang, H, Florida Cancer Specialists and Research Institute, Fort Myers, FL
Background: Multi-lineage myelosuppression is an acute toxicity of cytotoxic chemotherapy leading to hematologic adverse events and dose reductions and delays. Current therapies are lineage specific and administered after chemotherapy damage. Trilaciclib (T), a highly selective, reversible CDK4/6 inhibitor, is designed to preserve hematopoietic stem and progenitor cells and prolong the systemic function during chemotherapy (myelopreservation).
Methods: In this blinded, placebo-controlled, multicenter Phase 2 study, patients with previously treated ES-SCLC were randomized to T (240 mg/m2) + 0.75 mg/m2 topotecan, T (240 mg/m2) + 1.5 mg/m2 topotecan, or placebo (P) + 1.5 mg/m2 topotecan IV on days 1-5 of 21-day cycles. Patients had access to standard supportive care, except in cycle 1 where prophylactic growth factors were not allowed. Eligible patients had adequate organ function, measurable disease, ECOG PS 0-2, and disease progression during or after prior 1st/2nd-line chemotherapy. Objectives included safety, tolerability, measures of myelosuppression and tumor efficacy.
Results: 91 patients were randomized: 30 patients received T + 0.75 mg/m2 topotecan, 32 patients received T + 1.5 mg/m2 topotecan and 28 patients received P + 1.5 mg/m2 topotecan. In patients receiving 1.5 mg/m2 topotecan, there was no difference in TRAE 3/4 rates (3 N, 3 NI). The proportion of CR+PR in MPR+ was higher than in MPR- (6 [60%] vs 0 [0%]), and duration in cycle 1 [2 days (T) vs 8 days (P), p < .0001] of severe neutropenia. T-treated patients had fewer HBOC transfusions on/after week 5, GCSF administrations, and all-cause dose reductions. Chemotherapy efficacy was comparable in both arms (P and T) treated with 1.5 mg/m2 topotecan (29% of risk reduction in 0.5 years vs 9% of risk reduction in 0.5 years, HR = 0.83). OS data is immature.
Conclusions: T combined with topotecan mitigated chemotherapy-induced myelosuppression and improved tolerability of topotecan vs P. Results suggest the addition of T to cytotoxic chemotherapy for the treatment of ES-SCLC is clinically beneficial. Clinical trial information: NCT02514447.

8506 Oral Abstract Session, Sat, 1:15 PM-4:15 PM
Efficacy and safety profile of lurbinectedin in second-line SCLC patients: Results of a phase II single-agent trial. First Author: Luis Gainza, Hospital Universitario 12 de Octubre, CiberOnc, Universidad Complutense and CNIO, Madrid, Spain
Background: Lurbinectedin (L) is a novel anticancer drug that inhibits activated transcription and induces DNA double-strand breaks, leading to apoptosis. Methods: A multicenter phase 2 basket trial assessed the efficacy and safety of L in several cancer types, including small cell lung cancer (SCLC). Primary end point of the confirmed overall response rate (ORR) by RECIST v1.1, to the SCLC cohort, a target ORR of ≥30% was set. One-hundred and five patients (pts) with ECOG PS 0-2 who had received one prior chemotherapy line were treated with L 3.2 mg/m2 as a 1-hour i.v. infusion on Day 1 q3wk. Results: Median age was 60 years (range, 40-83), 60% were male, ECOG PS 0/1/2 (32%/62%/6%), liver metastasis 41%, history of CNS involvement 3.8%, prior platinum 100%, median chemotheraphy-free interval (CTFI): 3.5 (0-16.1) months, prior IO: 3.8%. No treatment-related deaths were reported. Multi-lineage myelosuppression is an acute toxicity of cytotoxic chemotherapy. The acceptable and manageable safety profile is also associated to a convenient treatment administration (Day 1 q3wk). As a second-line treatment in SCLC emerges as a new promising drug for this unmet clinical need. Clinical trial information: NCT02454972.

8507 Poster Discussion Session; Displayed in Poster Session (Board #263), Sun, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sun, 11:15 AM-12:45 PM
Randomized Phase II study of adjuvant afatinib for three months versus three months in patients with resected stage I-II EGFR mutant NSCLC. First Author: Jamie E. Chaft, Thoracic Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY
Background: EGFR tyrosine kinase inhibitors are superior to chemotherapy in patients with advanced EGFR+ lung cancers. In the adjuvant setting, erlotinib for two years modestly improves recurrence free survival (RFS) compared to historical controls. The optimal duration of adjuvant TKI is unknown. Methods: Patients with completely resected Stage I-II NSCLC with a sensitizing EGFR mutation were enrolled after standard adjuvant therapy. Pts were randomly assigned to 3 months (3m) or 2 years (2y) of afatinib. The primary study endpoint. The RFS curves show a durable and clinically relevant 2 years after standard adjuvant therapy. Results: Patients without toxicity after 28 days were allowed to escalate to 40 mg daily. Patients were imaged with CT every 6 months for 3 years and then annually or as clinically indicated. RFS was measured from the date of randomization. The primary study endpoint was recurrence rate at 2 years. 60 randomized patients would provide 82.5% power to detect a 26% difference in 2-year recurrence rate. Results: Patient characteristics are in the Table. The study was terminated for slow accrual after 46 of the planned 60 patients. Planned treatment was completed by 92% (22/24) pts in the 3m arm and 41% (9/22) of pt in the 2y arm. 22 patients required ≥1 dose modification due to toxicity including expected expected DLT and skin AEs. With a median follow-up of ≥38 months there were 10 recurrences and 3 deaths in the 3m arm and there were 5 recurrences (2 on treatment) and 2 deaths in the 2y arm. Median RFS has not been reached in either arm, but recurrence-free survival was more common in the 3m arm at every landmark. 2y-recurrence rates were 29% for 3m and 15% for 2y. Conclusions: Recurrences at 2 years were 14% less common with 2y versus 3m of adjuvant afatinib. This difference did not meet the primary study end point. The study’s curves show a durable and clinically meaningful separation with substantial follow-up. Failure to meet significance was likely influenced by under-accrual and early drug discontinuation on the 2y arm. In the era of TKIs with improved tolerance, duration of adjuvant therapy remains an important question. Clinical trial information: NCT01746251.
8508 Poster Discussion Session; Displayed in Poster Session (Board #264), Sun, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sun, 11:15 AM-12:45 PM
The role of EGFR inhibitors as adjuvant therapy for EGFR mutation positive non-small cell lung cancer. First Author: Peng Xie, Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Jinan, China
Background: Cisplatin-based chemotherapy as adjuvant therapy for resected NSCLC has reached its plateau, and was limited by high risk of recurrence and significant toxicities. The clinical value of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in resected non-small cell lung cancer (NSCLC) harboring EGFR mutation remains uncertain. In the current study, we performed a meta-analysis to evaluate the role of EGFR inhibitors as adjuvant therapy for targeted patients. Methods: Studies were identified via an electronic search on Pubmed, EMBASE, ISI Web of Science, ScienceDirect, SpringerLink, The Cochrane library and so on. Pooled odds ratio (OR) for disease-free and overall survival (OS) were calculated for meta-analysis. Registration number: PROSPERO (CRD42018093144). Results: There were 11 trials (1,152 resected NSCLC patients with EGFR sensitive mutations) in this meta-analysis. Results showed that adjuvant treatment with EGFR-TKIs can prolong DFS and overall survival (OS) compared with chemotherapy in patients with completely resected EGFR-mutant NSCLC (DFS: OR, 0.58; 95% CI, 0.49-0.80, P = 0.004; heterogeneity I²= 37%, P = 0.1). Results of predefined subgroup analyses in this meta-analysis suggested a greater DFS with EGFR-TKIs mono compared with chemotherapy, whereas the OS benefit failed to show a similar difference between the two arms (p > 0.2). We also find that patients with documented EGFR mutation and who received adjuvant chemotherapy was associated with significantly longer DFS as well as OS than chemotherapy mono in patients with completely resected EGFR-mutant NSCLC (DFS: OR, 0.48; 95% CI, 0.34-0.68, P < 0.00001; heterogeneity I²= 15%, P = 0.29; OS: OR, 0.50; 95% CI, 0.31-0.78; P = 0.003; heterogeneity I²= 57%, P = 0.40). When we included less aggressive EGFR TKIs (CI 95% 71-95%), and 24 (71%) of them had a complete pathologic response (CR) (CI 95% 54-87%). Downstaging was seen in 90% (CI 95% 81-100%) of cases. By RECIST, 29 pts (71%) (CI 95% 56-85%) had partial response and 3 (7%) CI 95% 0-16% complete response. Conclusions: This is the first meta-analytic study to CT-IO in the neoadjuvant setting in stage II. Neoadjuvant CT-IO with niraparib in resectable II NSCLC yields a high complete pathologic response rate that has never been seen previously and unsuspected by RECIST criteria. Preliminary correlative analyses in blood samples are included in a separate abstract. EudraCT Number: 2016-003732-20. Clinical trial information: NCT 03081689.

8510 Poster Discussion Session; Displayed in Poster Session (Board #266), Sun, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sun, 11:15 AM-12:45 PM
Velparip (Vel) in combination with chemoradiotherapy (CRT) of carboplatin/paclitaxel (CP) plus radiation in patients (pts) with stage III non-small cell lung cancer (NSCLC) (M14-360/AFT-07). First Author: David E. Kozono, Dana-Farber Cancer Institute, Boston, MA
Background: CRT is standard treatment (Tx) for pts with unresectable stage III NSCLC. Vel, a potent oral PARP1/2 inhibitor, interferes with repair of chemotherapy-induced DNA damage and shows favorable efficacy vs placebo when added to CP in stage IV NSCLC. The reported phase 1 trial assessed the safety and efficacy of Vel + CP-based CRT in Tx of stage III NSCLC (NCT02412371). Methods: Eligible pts (n=18) (unresectable stage III NSCLC, no prior NSCLC therapy) received Vel + CRT of weekly C area under the curve (AUC) 2 + 45 mg/m² weekly + 60 Gy (2 Gy/day) RT over 6-9 weeks (wk). Vel was dose escalated from 60 mg twice daily (BID) to 240 mg BID followed by Vel 120 mg BID added to consolidation therapy (CON) once every 3 wk of AUC 6 + P 200 mg/m² for 2 cycles (cohort 1–5). Cohort 6 received Vel 240 mg BID + CRT followed by Vel 240 mg BID + CON. Samples for pharmacokinetic (PK) analysis were collected on wk 4 day –3. The primary endpoint was to establish the recommended phase 2 dose (RP2D) of Vel + CRT+Vel+CON. Results: As of Sep 2018, 48 pts enrolled into cohorts 1–6 at Vel 60 mg/120 mg (n = 7), 80 mg/120 mg (n = 9), 120 mg/120 mg (n = 7), 200 mg/120 mg (n = 8), 240 mg/120 mg (n = 12), and 240 mg/240 mg (n = 5) added to CRT+CON; median age 65 yr (range 48–81). Vel PK was dose proportional: 39 (81.3%) pts completed therapy, Grade ≥3 Tx-emergent adverse events (AEs) were reported in 37 (77.1%) pts; anemia and febrile neutropenia (10.4% each) were the most common. Serious AEs were observed in 19 (39.6%) pts. Dose-limiting toxicities occurred at 200 mg/120 mg (n = 1; fatigue, anemia, and pneumonitis), 300 mg/120 mg (n = 1; insomnia), and 240 mg 240 mg (n = 2; febrile neutropenia, neutropenia, thrombocytopenia, esophagitis, suprapubic pain, sepsis); Vel 240 mg BID + CRT+Vel 120 mg CON was chosen as the maximum tolerated dose/RP2D. Of 41 pts evaluable for tumor assessment, 26 (63.4%) had a confirmed response. Interim median progression-free survival (PFS) in stage III NSCLC is not reached; median overall survival is 9.7 months (95% CI 2.4–14.0). DLTs were not observed in any of the cohorts (C1 to C5). Grade ≥3 immune-related adverse events (irAEs) occurred in 4 patients (18%). irAEs included: Grade 5 (bilateral pneumonitis, Grade 3 (2 pneumonitis, 1, 1, respectively (6 total)); Grade 4 hyperglycemia (1); Grade 3 intestinal nitis (1); Grade 2 thyroiditis (4); Grade 2 myositis (1); Grade 1-2 transaminits (3). Median PFS for patients who received ≥2 doses (n=18) of pembrolizumab was 20.3 mo. Conclusions: Combined treatment with PD-L1 and CRT for stage III NSCLC was well tolerated with per protocol PFS at 24 months (7/16 pts) and 1-year PFS rate of 56%, particularly in Stage III NSCLC. Based on these encouraging results, further prospective study of PD-L1 and CRT for Stage III NSCLC is warranted. Clinical trial information: NCT02621398.

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Phase II trial combining atezolizumab concurrently with chemoradiation therapy in locally advanced non-small cell lung cancer. First Author: Steven H. Lin, Markey Cancer Center, Houston, TX

Background: Consolidation durvalumab after chemoradiation (CRT) is the new standard of care in locally advanced NSCLC (LA-NSCLC). We hypothesized that adding immunotherapeutic agents to CRT (CRT+IO) would increase loco-regional control without significant additive toxicity. To test this concept, we conducted a phase II trial called DETERRED combining atezolizumab (atezo) with cCRT followed by consolidation full dose carboplatin/paclitaxel (CP) with atezo (CP-atezo) for 2 cycles and maintenance atezo (CP-atezo) for 1 year. The primary endpoint was safety and feasibility. Methods: This study enrolled patients (pts) between February 2016 - April 2018 and was done in two parts: In Part 1 (N=10), conventionally fractionated CRT (60-66 Gy in 33-34 fractions combined with weekly low dose CP) was followed by CP-atezo then maintenance atezo. Part 2 was CRT (N=30) with atezo followed by CP-atezo then maintenance atezo. Atezo was given at 1200 mg IV q3 weeks. Severe adverse events (SAEs) >= grade 3 were defined by CTCAE v5.0. Evaluable pts received at least one dose of atezo. PD-L1 staining utilizes the DAKO 22C3 platform. Kaplan Meier were analyzed for progression free survival (PFS) and overall survival (OS), and chi-square test for PD-L1 levels on any recurrence, with significance set at <0.05. Results: In Part 1, atezo related SAEs were seen in 4 pts (40%) (2 grade 3 arthralgia, 1 grade 3 dyspnea and 1 grade 5 TE fistula). Grade 2 radiation pneumonitis (RP) was seen in 1 pt. In Part 2, seven (23%) pts had atezo related SAEs (diabetes mellitus [DM], grade 3 hyperglycemia [4], fatigue [1], and heart failure [1]). N=5 (17%) and 1 grade 3, which led to atezo discontinuation. In Part 1, with an overall median follow up (fu) time of 22.5 months and 27.4 months for survivors, the 1-yr PFS was 50%, and OS is 79%. In Part 2, with a median fu time of 11.8 months and 13.9 months for survivors, the 1-yr PFS was 51% and OS was 79%. Baseline CD8+ TBI/SU biopsy PD-L1 status was evaluable for 34 pts. There were no significant differences in cancer recurrence for PD-L1 <=1% (7/16=44%) vs >=1% (8/18=44%), or for the PD-L1 cutoff of <50% (11/26=42%) vs >=50% (2/8=25%). Conclusions: Concurrent atezo with CRT followed by CP-atezo and maintenance atezo is safe without increased toxicities compared to CRT alone followed by CP-atezo and maintenance atezo. Updated efficacy results from DETERRED will be presented. Ultimately, the combination benefits of immunotherapy with CRT followed by consolidation chemo-immunotherapy will need to be compared to the PACIFIC regimen in a larger randomized trial. Clinical trial information: NCT02525757.

Biomarker driven phase II umbrella trial study of AZD1775, AZD2041, AZD2811 monotherapy in relapsed small cell lung cancer. First Author: Sehhoon Park, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: Recent progress in genomic profiling of small cell lung cancer (SCLC) has resulted in 3 illustrated that a high proportion of SCLC harbor mutations in cell cycle-related genes and RICTOR amplification. With the recent introduction of cell-cycle altering small molecules, AZD1775 (VEE1 inhibitor), AZD2811 (aurora kinase B inhibitor) and mTOR/PI3K inhibitor (AZD2041), biomarker-driven umbrella study is being conducted in relapsed SCLC. Its methods and purposes are to include patients with multiple monotherapy arms in resistant SCLC who has failed prior platinum-based chemotherapy and known genomic profile from pre-designed screening study of SUKSES-S (Small cell lung cancer Umbrella Korea Study EUSS, NCT02688894). Patients with MVA family amplification or co-alteration in CDKN2A and RICTOR, among patients was ALK-TKIs (N=7) or N1 (n = 24) showed no objective response rate and stable disease was observed in 3 patients (42.9%) and 6 patients (25.0%), respectively. The median progression-free survival (PFS) was 12.8 months (95% confidence interval [CI] 11.8-23.0) and 9.6 months (95% CI 7.9-23.7) for the sensitive and resistant stratum, respectively. SUKSES-S (n = 4) showed no objective response as well as no stable disease with PFS of 12.5 months (95%CI 0.98-NA). SUKSES-N3 (n = 15) showed no objective response with 5 stable disease (33.3%) and PFS of 1.61 months (95%CI 1.18-NA). For the safety, adverse events (AES) generally observed were as follows: SAEs: N=0 (0%), P=1 (3.2%), D=2 (6.9%), 75.0%, N3 =9 (60%). Notably, neutropenia (grade=3) was frequently observed (n = 8, 53.3%) in AZD2811 arm including a case of septic shock. 

Conclusions: SUKSES is the first biomarker-driven umbrella study with the largest cohort of genomic profiling in pre-selected in resistant SCLC patients (n = 275). However, it does not support further development of the current regimens of AZD1775, AZD2811, AZD2041. Altered administration schedule or combination regimen is under development. Clinical trial information: NCT02593019, NCT03791015, NCT03366675.

8513 Poster Discussion Session; Displayed in Poster Session (Board #269), Sun, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sun, 11:15 AM-12:45 PM

Phase II trial of carfilzomib and inrotecan in relapsed small cell lung cancer (NCT01941316). First Author: Susanne M. Arnold, Markey Cancer Center, University of Kentucky, Lexington, KY

Background: Relapsed small cell lung cancer (SCLC) is incurable with limited therapeutic options. This phase II study evaluated efficacy and tolerability of carfilzomib + inrotecan in SCLC pts who progressed after prior platinum-based therapy, based on expected synergy of proteasome inhibitor carfilzomib and topoisomerase I inhibitor inrotecan. Methods: Patients with SCLC pts who progressed after one platinum-containing regimen (no maintenance therapy allowed) for recurrent/metastatic disease were eligible. Pts were stratified by response to platinum-based therapy: sensitive (progressive disease [PD] > 90 days after chemo) versus refractory (PD 30 to 90 days after chemo). Pts were treated with up to 6 cycles of carfilzomib (20 mg/m2 D1, 2, 8, 9, 15, 16 q28D) and inrotecan (125 mg/m2 D1, 8, 15 q28D), imaging was performed every 2 cycles. The primary efficacy endpoint was 6-month overall survival (OS). Results: 62 pts enrolled and were evaluable for efficacy and adverse events. The 6-month OS was 59% in the platinum sensitive stratum and 54% in the platinum refractory stratum. Overall response rate: sensitive stratum 21.6% (1.6% CR + 16.4% PR) and refractory stratum 12.5% (all PR). Disease control (SD+PR+CR) was 68% in platinum sensitive and 56% in refractory patients. Progression free survival and OS were 3.6 months (95% CI 2.6 - 4.6) and 6.9 months (95% CI 4.3 - 12.3) in the sensitive stratum, and 3.3 months (95% CI 1.6 - 7.4) and 9.0 months (95% CI 5.9 - 13.2) in the refractory stratum. Twenty-nine pts (47%) experienced at least one grade 3 adverse event. Adverse events were: Cytopenia (4), Dyspnea (1), and endocrine disorders (3) in Arm A; diarrhea (3) and nausea/vomiting (2) in Arm B. Grade 4 toxicities: decreased neutrophils, leukocytes, and lymphocytes, diarreha, vomiting, sepsis, hypokalemia, hypocalcemia, and dehydration. There were three treatment related deaths: myocardial infarction (possible), lung infection (possible), sepsis (probable). Therefore, this combination is not recommended for subsequent progression on immunotherapy (IO) or in subjects who cannot receive IO, and should be further explored in a randomized phase III trial. Clinical trial information: NCT01941316.
Ph1/2 study of Rova-T in combination with nivolumab (Nivo) ± ipilimumab (Ipi) for patients (pts) with 2L+ extensive-stage (ED) SCLC. First Author: Jyoti Malhotra, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Background: Rovaplituzumab tesirine (Rova-T™) is an antibody-drug conjugate targeting DLL3, a notch ligand expressed in SCLC but not normal tissue. Nivo ± Ipi has activity in 2L+ SCLC. Preliminary data suggest Rova-T may result in immunogenic cell death, complementing effects of Nivo ± Ipi. Methods: Eligibility: DLL3 expression (DLT phase only), progression after ≥1 line of therapy including a platinum-based regimen; ECOG 0-1; no prior immunotherapy. All pts received 0.3 mg/kg Rova-T IV on Days 1 and 2 every 21-day cycle. Cohort 1 (C1) received two 3-wk cycles of 1 mg/kg Nivo beginning on wk 4. Cohort 2 (C2) received four 3-wk cycles of 1 mg/kg Nivo and 1 mg/kg Ipi beginning on wk 4. Both cohorts then received 480 mg Nivo q4wks until PD. Primary objective: safety. Secondary: antitumor activity by RECISTv1.1, OS, Exploratory: PK. Results: As of Sep 7, 2018, 30 pts were dosed in C1 and 12 in C2. SST were DLL3 high (≥75% DLL3 expression). 2B (67%) completed 2 planned cycles of Rova-T. 4 pts (1 in C1, 3 in C2) experienced DLTs including rash (3), pneumonitis (1) and colitis (1). C1 completed recruitment, and C2 enrollment was stopped after DLT evaluation phase. Preliminary PK showed Nivo ± Ipi had no substantial effect on Rova-T exposure. Clinical trial information: NCT03026166. Conclusions: Despite activity in 2L+ ED-SCLC, Rova-T with Nivo/Ipi is not appropriate due to DLTs. Rova-T/Nivo demonstrated some durable responses; however, the safety data suggest that optimization of dose and schedule is warranted. NCT03026166.
AUC was 0.77, 95% CI (0.64-0.88). with tumor size of 1-2 cm, the sensitivity and specificity were 92% and 80%.

Furthermore, we analyzed the sensitivity and specificity of the same three-gene panel for lung cancer diagnosis using the best individual gene was used to identify patients with high risk of lung cancer development.

Author: Myung-Ju Ahn, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

References:

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8525 Poster Session (Board #281), Sun, 8:00 AM-11:00 AM

Oncologic outcomes of segmentectomy versus lobectomy for radiologically aggressive small-sized lung cancer. First Author: Atsushi Kamigaichi, Department of Thoracic Surgery, Hirosima University, Hiroshima, Japan

Background: Despite increasing evidence of favorable outcomes after segmentectomy for indolent lung cancer, such as ground glass opacity-dominant tumors, the adaptation of segmentectomy for radiologically aggressive lung cancer remains controversial. We attempted to elucidate oncologic outcomes after segmentectomy for radiologically aggressive lung cancer.

Methods: Data from a multicenter database of 1353 patients with completely resected clinical Stage IA1–IA2 lung cancer at three institutions were retrospectively analyzed to identify radiologically aggressive lung cancer and compare outcomes of segmentectomy versus lobectomy in patients with radiologically aggressive lung cancer using propensity score matching.

Results: Multivariable analysis showed that consolidation to maximum tumor (CT) ratio on preoperative high-resolution computed tomography was predictive of recurrence-free survival (RFS). The criteria for radiologically aggressive lung cancer were determined as CT ratio $\geq 0.8$ or SUVmax $\geq 2.5$, for which 522 patients were identified. RFS and overall survival (OS) were significantly worse in patients with aggressive lung cancer (5-year RFS, 83.3%; 5-year OS, 89.4%) than in those without the same (5-year RFS, 97.0%; P < 0.0001; 5-year OS, 97.3%; P = 0.0001). Among patients with aggressive lung cancer, no significant difference in RFS and OS was found between those undergoing lobectomy ($n = 392$) (5-year RFS, 81.3%; 5-year OS, 88.3%) and segmentectomy ($n = 130$) (5-year RFS, 90.0%; P = 0.03; 5-year OS, 92.3%; P = 0.76). Among the 111 pairs propensity matched for age, sex, smoking history, solid tumor size, CT ratio, SUVmax, tumor location, clinical stage, andhistology, similar RFS and OS were found between those undergoing lobectomy (5-year RFS, 85.5%; 5-year OS, 88.3%) and segmentectomy (5-year RFS, 99.1%; P = 0.92; 5-year OS, 94.5%). Conclusions: For radiologically aggressive small-sized lung cancer, oncologic outcomes of segmentectomy were equivalent to those of lobectomy.

8527 Poster Session (Board #283), Sun, 8:00 AM-11:00 AM

Randomized phase II trial of uracil/tegafur and cisplatin versus pemetrexed and cisplatin with concurrent thoracic radiotherapy for locally advanced unresectable stage III non-squamous non-small-cell lung cancer: JNLCG001. First Author: Kana Watanabe, Department of Respiratory Medicine, Miyagi Cancer Center, Natori, Japan

Background: It is unknown which regimen is the best in concurrent chemoradiotherapy (CRT) of locally advanced non-squamous non-small cell lung cancer (NSCLC). Our previous randomized phase II study, JNLCG0601, showed that chemoradiotherapy with uracil/tegafur (UFT) and cisplatin achieved promising efficacy with acceptable toxicities. In this trial, this regimen was compared to a regimen with pemetrexed and cisplatin for stage III non-squamous NSCLC.

Methods: Patients with inoperable stage III non-squamous NSCLC were randomized to UFT 400 mg/m$^2$ on days 1–14 and 29–42, and cisplatin 80 mg/m$^2$ on days 8 and 36 (UP), or pemetrexed 500 mg/m$^2$ and cisplatin 75 mg/m$^2$ on days 1, 22, and 43 (PP). Involved-field radiotherapy (IFRT) was administered from day 1 to a total dose of 66 Gy radiotherapy in 33 fractions. Consolidation chemotherapy after CRT was not planned for this study. The primary endpoint was 2-year overall survival (OS), with expected rates of 55% and a lower limit of 35% (alpha 0.05, beta 0.2). Secondary endpoints were the objective response rate (ORR), progression-free survival (PFS), OS, and toxicity profile.

Results: From November 2010 to June 2017, 86 patients were enrolled from 11 institutions. Of the 85 eligible patients, the rate of 2-year OS was 78.6% (95% CI: 62.8–88.3%) in the UP arm and 85.5% (95% CI: 70.5–93.2%) in the PP arm. The ORR was 76.7% in the UP arm and 81.0% in the PP arm. With a median follow-up of 54 months, median PFS and OS were 12.3 and 64.2 months in the UP arm, and 22.6 months and not reached in the PP arm, respectively. Grade 3/4 febrile neutropenia was more frequent in the UP arm than in the PP arm (14.0%, 2.0%, respectively). Grade 3/4 pneumonitis occurred in 7.0% and 4.8% of patients in UP and PP arms, respectively. Conclusions: Both regimens with IFRT achieved the expected 2-year survival rate. UP had more favorable results than UP in terms of OS and PFS. We selected the PP arm for the next step.
**8528 Poster Session (Board #284), Sun, 8:00 AM-11:00 AM**

Identifying actionable somatic mutations in lung cancer using cell-free DNA from bronchial washing fluid. 
First Author: Xin Zhang, Zhongshan Hospital Fudan University, Shanghai, China

**Background:** Bronchial washing is the most common technique for sampling the components of the alveolar space. Here, we evaluated the potential use of bronchial washing fluid (BWF) in liquid biopsy in lung cancer. **Methods:** This study enrolled 65 lung cancer patients. BWF (separated supernatant and precipitate) samples, peripheral blood lymphocytes (PBL) and formalin-fixed paraffin-embedded tissues were obtained and subjected to next-generation sequencing using a 1021-gen panel. **Results:** Mutations were identified in 58 (89.2%) of BWF precipitate (BWFp) samples and 64 (98.5%) of BWF supernatant (BWFs) samples, comparing with 61 (93.8%) of tumor tissues. In total, 461 somatic mutations were identified in tissues, of which 331 (71.8%) were detected in matched BWFp and BWFs samples. In 61 of the 65 patients, BWF samples identified actionable variants.

**Conclusions:** In summary, liquid biopsy using BWF showed high potential to identify actionable mutations and to calculate TMB grade of cases while being patient-friendly and minimally invasive. The combined results of three types of samples showed that, 49.2% of patients carrying actionable variants and 24.6% of patients with TMB-H, which suggested more patients benefit from targeted therapy or immunotherapy.

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**8530 Poster Session (Board #286), Sun, 8:00 AM-11:00 AM**

Alteration in tumor immune microenvironment after chemo-radiotherapy for locally advanced non-small cell lung cancer. 
First Author: Kazukiyo Kato, Department of Thoracic Surgery, University of Occupational and Environmental Health, Kitakyushu, Japan

**Background:** The consolidation treatment with durvalumab, an anti-PD-L1 antibody, after concurrent chemo-radiotherapy (CCRT) has become a new standard of care for locally advanced non-small cell lung cancer (LA-NSCLC). The rationale of the addition of anti-PD-L1 antibody is based on preclinical evidence suggesting that chemotherapy and radiotherapy may up-regulate PD-L1 expression on tumor cells. However, there has been no clinical evidence showing up-regulation of PD-L1 expression after CCRT. **Methods:** LA-NSCLC patients with paired sufficient histologic specimens for immune-histochemical analysis of tumoral PD-L1 expression (tumor proportion score, TPS) and stromal CD8-positive tumor-infiltrating lymphocyte density (CD8D-density) before and after pre-operative treatment were eligible in this study. Twenty-three patients who underwent CCRT were reviewed in comparison with 18 patients who underwent chemotherapy.

**Results:** PD-L1 expression was significantly enhanced after CCRT (median TPS, 48 from 1; P<0.01), but not after chemotherapy (median TPS, 7.5 from 1; P=0.62). No significant correlation between baseline TPS and TPS after CCRT (P=0.119). Stromal CD8D-density was significantly increased after CCRT (median, 39 from 11; P<0.01) and after chemotherapy (median, 23 from 12; P<0.01). No significant correlation between baseline TPS and TPS after CCRT (P=0.378). Among CCRT cases, stromal CD8D-density after treatment was significantly higher in cases with higher pathologic response to CCRT (median, 55 versus 27; P=0.01), and higher stromal CD8D-density was a significant factor to predict a favorable survival after surgery (P=0.03 for recurrence-free survival; P=0.02 for overall survival). **Conclusions:** PD-L1 expression was significantly upregulated after CCRT regardless of baseline PD-L1 status, which may provide a pathologic rationale for the use of anti-PD-L1 agent after CCRT to improve the prognosis. Stromal CD8D-density also increased after CCRT, which was correlated with pathologic response to CCRT and provided a significant prognostic impact.

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**8531 Poster Session (Board #287), Sun, 8:00 AM-11:00 AM**

Efficacy and safety of neoadjuvant PD-1 blockade with sintilimab in resectable squamous non-small cell lung cancer. 
First Author: Kazukiyo Kato, Department of Thoracic Surgery, University of Occupational and Environmental Health, Kitakyushu, Japan

**Background:** NSCLC patients who have potentially resectable disease often subsequently relapse after surgery. New therapy that prevents relapse after surgery is desperately needed. In this study, we tested the efficacy and safety of neoadjuvant sintilimab, an anti-PD-1 antibody, for patients with resectable squamous NSCLC in China. **Methods:** All patients who had treatment-naive resectable sqNSCLC (stage IB-IIIA) that was confirmed by histopathology. Patients received two cycles of sintilimab (200 mg IV) on Day 1 and 22. Surgery was performed between Day 29-43. An enhanced PET/CT was obtained at baseline and seven days prior to surgery. Preliminary analysis of safety profile and efficacy was planned after at least 20 patients had received treatment. **Results:** As of Jan 28, 2019, 22 patients (20 males and 2 females) with sqNSCLC received two doses of sintilimab followed by radical resection. The median age was 61.5 yr (range, 48 to 70). Six (27.3%) and four (18.2%) patients experienced neoadjuvant treatment emergent adverse events (TEAEs) and neoadjuvant treatment-related AEs (TRAES), respectively. Most of the TEAEs and TRAEs were grade 1 or 2. Three patients achieved radiological partial response: an ORR of 13.6% based on RECIST 1.1. Ten patients (45.5%) achieved a major pathologic response (MPR, ≥30% decrease of SUV), including four (18.2%) who had complete pathologic response (no viable tumor cell). There was a direct correlation between pathological response and decrease in the standardized uptake values (SUV) in the primary tumor. Among nine patients with >30% decrease of SUV, eight had MPR, compared with no MRP response in the 11 patients with ≤30% decrease of SUV. **Conclusions:** Neoadjuvant sintilimab for sqNSCLC patients was tolerable and the 45.5% MRP rate is encouraging. A decrease in SUV may be predictive of pathologic response and may improve survival in sqNSCLC. Clinical trial information: ChiCTR-OIC-17013726.
Background: Neoadjuvant immune checkpoint inhibitors (ICIs) are being explored in resectable non-small cell lung cancer (NSCLC). Here, we studied the composition and changes in the T cell repertoire in a cohort of NSCLC patients (n = 44) treated with neoadjuvant nivolumab (N) alone or in combination with ipilimumab (NI) following surgery (NEOSTAR trial).

Methods: Sequencing of the variable CDR3β chain of the T cell receptor (TCR) involved in antigen binding was performed in pre-treatment and surgical tumors, matched adjacent uninvolved lung specimens, as well as paired longitudinal blood at baseline, prior to each dose of therapy, prior to surgery, and within 8 weeks post-surgery. T cell repertoire density, diversity, and clonality (reactivity) were evaluated in addition to tumor PD-L1 expression pre- and post-neoadjuvant treatment. Results: Median T cell diversity in the blood post-therapy was 3.3-fold higher in Ni- compared to N- treated patients (40.993 [Ni], n = 3) vs 12.177 [N, n = 4] unique TCR rearrangements, n.s., but median T cell clonality (0.093 [N, n = 4] vs 0.026 [Ni, n = 3], n.s.) was 3.8-fold higher in the tumor post-therapy in patients receiving Ni than in those receiving N (0.076 [Ni, n = 7] vs 0.020 [N, n = 5], n.s.). Interestingly, diversity in the blood at baseline and the tumor post-therapy were positively correlated (r = 0.71; r = 0.82, respectively) and negatively correlated with a lower % of viable tumor at time of surgery in both treatment arms (N = 71, r = -0.77; p = 0.04).

Conclusions: Our study is the first to assess the TCR repertoire in NSCLC patients treated with combination neoadjuvant ICIs. These findings highlight potential mechanistic differences compared to N alone. Neoadjuvant Ni is associated with higher clonality in tumors and lower clonality in blood post-therapy, suggesting increased T cell trafficking into the tumor. Finally, lower pre-treatment clonality in the periphery was correlated with higher % viable tumor post-neoadjuvant ICIs. Clinical trial information: NCT03158129.

8535 Poster Session (Board #291), Sun, 8:00 AM-11:00 AM
Neutrophil-to-lymphocyte ratio and subsequent recurrence of non-small cell lung cancer patients in remission. First Author: Abigail Sy Chan, Sinai Hospital of Baltimore, Department of Internal Medicine, Baltimore, MD.

Background: Baseline neutrophil-lymphocyte ratio (NLR), a surrogate marker for systemic inflammation and immunosuppression, is a well-established prognostic marker in non-small cell lung cancer (NSCLC). This study tests if interim NLR is prognostic in NSCLC patients in remission.

Methods: This single-center, retrospective cohort study analyzed 131 NSCLC patients treated from 2010-2015 who achieved complete remission. Patient data included demographics, histologic subtypes, stage, and treatment type. NLR was calculated at baseline and from the first available blood sample during remission. Kaplan-Meier estimates of overall survival (OS) and time to recurrence were compared using the log-rank test for trend. Multivariable analysis was conducted using the Cox proportional hazards model. Results: Of 131 cases, 63 had subsequently recurred at the last follow up. Mean age was 64 ± 10 years. Histology: adenocarcinoma (60%), squamous cell (33%), and unspecified (7%). Ninety percent were smokers. Thirty-five percent had stage I, 24% had stage II, and 41% had stage III disease. Treatment modalities varied from surgery (28%), chemotherapy (2%), or radiation therapy (10%) alone, or combination (50%). The time from end of neoadjuvant, median (range), to the interim NLR was 9.2 months (2.2, 66.7). The baseline and interim median NLR were 2.6 (0.6, 34.0) and 3.1 (0.5, 20.5), respectively. The median follow-up duration was 44 months (5.9, 101). For the univariate analysis interim NLR was binned into tertiles. In multivariable analysis remission NLR remained strongly prognostic for OS (P<0.001 as distinct patient’s age (IP<0.002), but the race, sex, and baseline NLR. Conclusions: Our study found that interim NLR, obtained in remission, was strongly prognostic for OS and recurrence. The results may indicate that even subclinical disease promotes immunosuppression or alternatively that immunosuppression increases recurrence risk. NLR during remission may be a useful addition to NSCLC patients at risk of recurrence and may thus be of value in surveillance of lung cancer survivors.

Interim NLR with progression-free survival and overall survival.
Interim NLR 2-y overall survival ≥ 1 SEE (%) 2-y progression-free ≥ 1 SEE (%) <2 97.4 ± 2.5 78.9 ± 6.6 2-4.08 84.7 ± 5.7 55.0 ± 7.9 >4.08 58.8 ± 8.3 50.5 ± 9.0

P for trend 0.0004 0.032

8536 Poster Session (Board #292), Sun, 8:00 AM-11:00 AM
Interim safety analysis of consolidation nivolumab and ipilimumab versus nivolumab alone following neoadjuvant pembro for unresectable stage IIIA/IIIB NSCLC: Big Ten Cancer Research Consortium LUN 16-081. First Author: Melissa Yan, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN.

Background: Consolidation PD-1 inhibition after chemoradiation (chemoRT) for unresectable stage IIIA/IIIB NSCLC improves overall survival. The efficacy and safety of combining a CTLA-4 inhibitor with a PD-1 inhibitor in this setting are unknown but may further improve efficacy in high-risk patient populations.

Methods: In this randomized, multi-center, phase II study, 105 pts with unresectable stage IIIA/IIIB NSCLC will receive chemoRT, then randomize 1:1 to either nivolumab 480mg IV q4 wks (nivo) or nivolumab 3mg/kg IV q2 wks + ipilimumab 1mg/kg IV q6 wks (nivo/ipo), for up to 24 wks. In this interim analysis, we assess the safety of the first 20 patients treated.

Results: From 9/2017 to 11/2018, 20 patients were accrued. Characteristics of those treated on the nivo arm (n = 10) were: median age 62 years, stage IIIA/B 7/3; non-squamous/squamous 7/3; and the nivo/ipo arm (n = 10): median age 61 years; stage IIIA/B 6/4; non-squamous/squamous 7/3. Most toxicities were grade 1 or 2 and the most frequently noted grade 2 AEs included fatigue (25%), pneumonia (25%), extremity pain (20%). Adverse events reported in the Nivo only arm included 81 total events with only 4 grade 3 events and a single grade 4 thromboembolic event. The Nivo/ipo arm reported 101 total AEs, with only grade 3 events and a single grade 4 toxicity (amylose elevation). With respect to immune-related adverse events (irAEs), in the nivo arm there were two cases of grade 2 pneumonitis and no grade 3/4 events. In the nivo/ipo arm, there was one grade 2 pneumonitis, three grade 3 irAEs (pneumonitis, colitis, pancreatitis), and one asymptomatic grade 4 amylose elevation. No treatment-related deaths were observed in either arm.

Conclusions: There were no unexpected safety signals in the first 20 patients treated on BIG10CRC LUN 16-081. The incidence of grade 3 or higher irAEs was higher in the nivo/ipo arm, as expected, but this was manageable with the use of established guidelines. The study currently remains open to accrual (32 of 105 have been randomized as of 2/8/19). Clinical trial information: NCT03285321.
Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers

8536 Poster Session (Board #292), Sun, 8:00 AM-11:00 AM
10-year patient journey of stage III non-small cell lung cancer patients: A single-center, observational, retrospective study in Korea real-time automatically updated with nGS in bedside cloud (UNIVERSE - ROOT study). First Author: Keunchil Park, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: The current standard of care (SoC) for locally advanced stage III NSCLC is concurrent chemoradiotherapy (CCRT) but the outcomes are poor and unsatisfactory. The purpose of this study is to analyze the clinical features of patients with locally advanced lung cancer and to explore the possible treatment strategies for future treatment strategy. Methods: This study through big data analysis retrospectively collected de-identified patient data from clinical data warehouse (CDW) using an unique algorithm with Standard Query Language (SQL). This new algorithm was developed by the close interactive collaboration between senior data scientists and medical oncologists. These algorithms include clinical natural language processing (NLP) systems that generate structured information from unstructured free text and structured data capture (SDC). We performed pre-processing work and data quality management (DQM) operation using over 700 clinical variables from 23,735 patients with NSCLC. Through data extraction, transformation and validation, we have developed a systematic and optimized program for lung cancer cohorts, including clinical features and molecular study and outcomes. It is also automatically updated every 24 hours in real time. Results: In the past 10 years, 23,735 patients were diagnosed with NSCLC and complete clinical data were available in 22,718 patients (95.7%). Out of these, 12,718 patients were diagnosed with stage III NSCLC. Among them, 2,676 patients (64.7%) received any type(s) of anti-cancer treatments or regular follow up at our institute. Of these 2,676 patients, 1,275 (47.6%) received curative surgery (+/- neo- and/or adjuvant chemotherapy); 685 (25.6%) patients definitive CCRT; 220 (8.2%) patients palliative chemotherapy. Conclusions: This study using the institutional big data analysis system in Korea showed the current standard of care (SoC) for locally advanced stage III NSCLC is not so ideal for off-the-shelf vaccine development. (2) HLA-A*1101 is the most frequent allele shared by 3% of the patients with stage III NSCLC. Two neoantigens were derived from patients younger than 55 years (P = 0.010). Additionally, carcinomas with better differentiation had lower expression of BAFFR in CAFs (P = 0.005). Further studies related to BAFFR expression in NSCLC patients will be beneficial for patients suffering from common cancers, like lung cancer. The present findings suggest that the expression of BAFFR in CAFs may be a useful biomarker with prognostic and predictive value, representing possibly an unknown biological relation, which merits further investigation.

8537 Poster Session (Board #293), Sun, 8:00 AM-11:00 AM
Association of BAFFR expression in CAFs with overall survival and response to platinum-based chemotherapy in NSCLC. First Author: Fotinos-Ioannis D. Dimtrakopoulos, Clinical and Molecular Oncology Laboratory, Medical School, University of Patras, Patras, Greece

Background: B-cell activating factor receptor (BAFFR) is a surface receptor, which leads to activation of the Nuclear Factor-kappaB (NF-κB) alternative pathway, a pathway with an important role in non-small cell lung cancer (NSCLC). In addition, cancer associated fibroblasts (CAFs) are major players of the tumor microenvironment promoting NSCLC. The aim of this study was to investigate the role of BAFFR expression in CAFs with response to first-line chemotheraphy. Methods: Immunohistochemical analysis of BAFFR expression on CAFs was performed on tumor and tumor-adjacent formalin fixed and paraffin embedded tissue samples from 124 operated patients with NSCLC. Patients were under follow-up for at least 60 months, while response to chemotherapy was evaluated in patients who relapsed during this period. Results: BAFFR expression, which was noted exclusively in the cytoplasm of CAFs, was associated with OS only in patients with no infiltration of regional lymph nodes. Higher expression levels of BAFFR in CAFs were related to shorter OS (P = 0.027 and P = 0.040, respectively). This finding persisted after multivariate analysis with age, gender, histological subtype, histological differentiation and disease stage as coefficients (P = 0.009; HR, 2.734; 95% CI, 1.283-5.828). In addition, response to first line chemotherapy was associated with BAFFR expression in CAFs (P = 0.026). Patients with chemotherapy induced lower BAFFR levels. Furthermore, BAFFR expression in CAFs was associated with patients’ age. In particular, older patients had higher expression of BAFFR compared to patients younger than 55 years (P = 0.010). Additionally, carcinomas with better differentiation had lower expression of BAFFR in CAFs (P = 0.005). Further studies related to BAFFR expression in NSCLC patients will be beneficial for patients suffering from common cancers, like lung cancer. The present findings suggest that the expression of BAFFR in CAFs may be a useful biomarker with prognostic and predictive value, representing possibly an unknown biological relation, which merits further investigation.

8538 Poster Session (Board #294), Sun, 8:00 AM-11:00 AM
EGFR L858R mutation as a possible target for individual-independent immunotherapy Chinese group, and . First Author: Yu Wang, Department (Thoracic Surgery, Nanjing Medical University Affiliated Cancer Hospital, Jiangsu Key Laboratory of Molecular and Translational Cancer Research, Cancer Institute of Jiangsu Province, Nanjing, China

Background: Neoantigens arise from tumor-specific mutations and potentially provoke immune responses. General vaccines targeting these peptides could be beneficial for patients suffering from common cancers, like lung cancer. Therefore, a retrospective analysis was performed on 799 non-small cell lung cancer (NSCLC) tissues from clinical outcomes. Each sample was collected from a unique patient, from whom peripheral blood or normal tissue was also obtained as control. Methods: Sequencing data were generated and pre-analyzed according to our in-house procedures. HLA typing was done using Optype V1.0 (required sequences were captured by 1021-gene panel) and neoantigens were predicted by netMHCpan v4.0 based on typed HLA alleles and curTed non-frameshIft somatic mutations with frequency >5%, which were called in pre-analysis. A neoantigen is considered mutant-specific if IC50 mut is < 500 nM and IC50 wild is > 500 nM, and especially, it is considered a strong-binder if IC50 mut is < 50 nM. Results: HLA typing returned 141 unique alleles, with the top 3 by carrier frequency being A*1101 (39%), C*0102 (33%) and A*2402 (28%). A further investigation into HLA alleles, mutations and neoantigens revealed two mutations on EGFR, L858R (CAFs (P = 0.025). Patients who progressed had lower BAFFR levels. Furthermore, BAFFR expression in CAFs was associated with patients’ age. In particular, older patients had higher expression of BAFFR compared to patients younger than 55 years (P = 0.010). Additionally, carcinomas with better differentiation had lower expression of BAFFR in CAFs (P = 0.005). Further studies related to BAFFR expression in NSCLC patients will be beneficial for patients suffering from common cancers, like lung cancer. The present findings suggest that the expression of BAFFR in CAFs may be a useful biomarker with prognostic and predictive value, representing possibly an unknown biological relation, which merits further investigation.

8539 Poster Session (Board #295), Sun, 8:00 AM-11:00 AM
The spatiotemporal evolution of early-stage non-small-cell lung cancer. First Authors: Siwei Wang, Department (Thoracic Surgery, Nanjing Medical University Affiliated Cancer Hospital, Jiangsu Key Laboratory of Molecular and Translational Cancer Research, Cancer Institute of Jiangsu Province, Nanjing, China

Background: Lung cancer is a genetically heterogeneous disease. The genomic basis of tumorigenesis and cancer cell spread, as well as intratumor heterogeneity (ITH) and subclonal evolutionary patterns might correlate with patients’ clinical outcomes. In this prospective study, we aimed to investigate such associations through comprehensive spatiotemporal genomic profiling in early-stage non-small cell lung cancers (NSCLCs). Methods: We performed deep targeted sequencing (GeneseeqPrime, 425 genes) of 503 primary tumor regions and 141 metastatic lymph node tumors from surgery and 378 longitudinal plasma biopsies (pre- and post-operation) across 128 Stage I-III NSCLC patients. ITH and phylogenetic tree for each patient were analyzed and correlated with clinical outcomes. Results: Spatial ITH varied among patients and was associated with clinical phenotypes. Geographical stratification of clonal structure, with localized confinement of subclones, was linked with slower tumor progression. In contrast, early expansion of subclones to multiregions was associated with rapid tumor growth and lymph node metastases. EGFR and TP53 mutations were nearly always clonal, whereas subclonal mutations in PI3K, WNT and TGF-beta pathway that occurred later in evolution were found in more than 50% of the patients. By tracking these phylogenetic events, we identified five evolutionary subtypes with distinct clinical outcomes, including a rare subtype characterized by independent origin of multiple EGFR driver mutations. ctDNA profiling could capture the spatial ITH to a certain extent with additional unique signatures. Further longitudinal and phylogenetic ctDNA analyses indicated early detection of relapse and adjuvant chemotherapy resistance. Conclusions: ITH is a key factor associated with clinical outcomes of early-stage NSCLC patients, which show diverse evolutionary subtypes underpinning the disease progression such as lymph metastasis and relapse. ctDNA sequencing can be used to capture spatial ITH, predict recurrence and track drug resistance.
8540 Poster Session (Board #296), Sun, 8:00 AM-11:00 AM
Comprehensive genomic profiling in Chinese patients with lung squamous cell carcinoma. First Author: Zeping Lian, Rui Kang Hospital Affiliated to Guangxi University of Chinese Medicine, Nanning, China

Background: Lung squamous cell carcinoma (LUSC) is a major histological subtype of non-small cell lung cancer (NSCLC) and accounts for 30% of NSCLC. Previous studies had revealed the genomic characterization of LUSC in Western patients (pts). However, the comprehensive genomic features of LUSC in Chinese pts have not been well understood. Methods: Deep sequencing targeting 450 cancer genes was performed on FFPE and matching blood samples collected from 311 LUSC pts. Genomic alterations (GAs) including single nucleotide variations, short and long insertions and deletions, copy number variations, and gene rearrangements were analyzed. Tumor mutational burden (TMB) was measured by an algorithm developed in-house. Results: The median age of LUSC pts was 63 years old (range 57-85.5), of which 88% were male. The most frequently mutated genes were TP53 (28%), PIK3CA (54%), CDKN2A (23%), CDK2 (26%), MDM2 (25%), LGH11 (23%), KMT2D (19%), PRKCI (19%), NF2EL2 (18%) and MAP3K13 (17%). Interestingly, the mutation rates of PIK3CA (p = 1.93e-05) and CDKN2 (p = 2.4e-05) were significantly higher than that in TCGA cohort. Genomic alterations in eight druggable genes recommended by the NCCN guideline occurred in 32% of pts, and alterations to PI3K/mTOR signaling pathway related genes occurred in 52% of pts. One patient with PIK3CA amplification achieved stable disease for eight months after everolimus treatment. Moreover, variants in the homologous recombination (HR) pathway were identified in 17% of pts. The median TMB of LUSC pts was 10.8 Muts/MB (range 6-14.5 Muts/MB) which was higher than Western populations (PMID: 28420421). The 1st Quartile (TMB-L), median and 3rd Quartile (TMB-H) TMB value was 6.9, 10.8 and 14.5 Muts/MB respectively. Comparing with the TMB-L group, frequencies of CDK2NA (39% vs 19%, p = 0.005), LRP1B (45% vs 8%, p < 0.001) and KMT2D (28% vs 8%, p = 0.002) were higher in TMB-H group. Conclusions: In summary, we characterized the genomic alteration profile of Chinese LUSC pts. Consistent with previous reports, high mutation rates of TP53, PIK3CA and CDKN2A are the most important genomic features of LUSC. However, the proportion of PIK3CA and CDKN2A mutations in Chinese LUSC pts is higher than that of Western populations. In addition, we also found targetable pathways (including PI3K/mTOR) along with gene related variations and high TMB in many pts, providing potential targeted therapy and immunotherapy options for LUSC pts.

8542 Poster Session (Board #298), Sun, 8:00 AM-11:00 AM
Retrospective study of capecitabine and temozolomide in advanced lung neuroendocrine neoplasms. First Author: Raymeh E. Al-Toubah, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: Patients with advanced lung neuroendocrine neoplasms (NE) have few treatment options. Capecitabine and temozolomide (CAPTEM) was selected IIIb non-small cell lung cancer (NSCLC): Molecular analysis of the ESPATUE randomized phase III trial. First Author: SayedMohammad Hasheminasab, Clinical Cooperation Unit Translational Radiation Oncology, German Cancer Consortium (DKTK) Center Heidelberg, German Cancer Research Center (DKFZ), Germany, Heidelberg, Germany

Methods: Among 104 pts enrolled in the ESPATUE randomization phase III trial, 85 were included in the final analysis. The median age of enrolled pts was 67 years (range 39-80) and 70% were male. The majority (90%) of pts presented with stage III disease. Patients received induction chemotherapy with cisplatin and paclitaxel followed by concurrent RCHT with 45 Gy (1.5 Gy twice daily) and cisplatin/vedotin according to the ESPATUE protocol. Tumor tissue was sampled from tumor enriched areas marked by pathologists at diagnosis (biopsies, n = 23) and post RCHT during surgical resection (n = 22, ESPATUE-Arm B) corresponding to 16 paired samples (PS). Transcriptome analysis (n = 45, 16PS), methylation analysis (n = 35, 12PS), deep whole exome sequencing (WES) including copy number variation (CNV) analysis by low-pass whole genome sequencing (WGS, n = 34, 13PS) were performed. Similarity plots of the transcripts identified 37 putative clusters of tumor evolution under RCHT. Cluster 1 was highly enriched for STS (5 out of 7 Pat.) compared to cluster 3 enriched for LTS (4 out of 6), p < 0.02. 146 transcripts were differentially expressed as the function of RCHT (FDR <0.05). Among them, 61 genes were upregulated and enriched for ECM and tissue remodeling (COL6A3/4, COL1A1, LAMA2, PAI1, MMP2, p53 signaling [p21, GAD045B] and stress response (FOSB, EGR1) pathways, p < 0.01. 39 downregulated genes were enriched for genes attributed to cell cycle- and DDR signaling (FANCI, SLX1A) p < 0.05. Seven inversely regulated genes were found with SLIT3 and TBX5 being among upregulated and hypomethylated genes. WES analysis revealed patterns of tumor evolution with a range of clonal diversity. In 5/13 pairs the clonal composition remained unchanged after RCHT. Approximately 500 post RCHT exclusive mutations were found. Conclusions: Clonal, transcriptional and methylation dynamic of tumor evolution towards RCHT selection pressure is unrelated in patients with locally advanced NSCLC. This multi-scale dynamic approach provides novel means for development of biomarker and therapeutic targets. Clinical trial information: ESPATUE.
8544 Poster Session (Board #300), Sun, 8:00 AM-11:00 AM

Immune landscape of the tumor microenvironment to predict prognosis and DNA mutations in patients with lung adenocarcinoma. First Author: Sunyoung S. Lee, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: The tumor microenvironment (TME) influences prognosis and response to therapy. The correlation between immune profiles in the TME and cancer DNA mutations is not well established. Methods: Clinical outcomes data, mRNA-seq, and DNA mutation of 480 patients (pts) with lung adenocarcinoma (LAD) were obtained from TCGA. Pts were clustered into 4 groups using unsupervised machine learning, based on mRNA expression of genes related to antigen presentation (AP) and cytokolytic activity (CA): group (G) 1 with high AP and CA (52 pts); G2, high AP, low CA (82); G3, low AP, high CA (66); G4, low AP and CA (280). Analysis of the immune landscape was performed using mRNA-seq of 191 genes enriched in cellular and structural elements of TME. DNA mutations were analyzed using the R package ggpubr and correlated in G1-G4. Results: Pts in G1 have high expression of genes related to immune activation (IA) and decreased expression of immune suppression (IS) and have the best prognosis. Pts in G2 have intermediate prognosis with decreased IA genes and intermediate expression of genes related to IS and immune checkpoints. Pts in G3 have the worst prognosis with high expression of genes related to immune checkpoints, desmoplasia, T cell co-inhibition, and IS. They also have low CD39 expression implying low cancer antigen-driven T cells. Pts in G4 have intermediate prognosis with highly depressed IA genes. Out of 70,199 non-synonymous mutations, the top 50 mutated genes in each pt group were identified: 36, 26, 31, and 17 DNA mutations were only found in G1, G2, G3, and G4 (refer to presentation). EGFR mutation was only found in G2; KRAS in G2/4; TP53 in G2/3/4. Conclusions: Our correlation analysis of mRNA-seq and DNA mutation shows that the immune landscape of TME can predict DNA mutations and prognosis. It further demonstrates a close correlation between TME and clinical stage and disease prognosis, which might appear to have valuable prognostic potential in the clinical setting with now widely available genomic testing.

8545 Poster Session (Board #301), Sun, 8:00 AM-11:00 AM

Benefit of combining local treatment and systemic therapy for stage IV NSCLC: Results from the National Cancer Database. First Author: Meaghan Daily, Division of Thoracic Surgery, Yale University School of Medicine, New Haven, CT

Background: To determine the potential benefit of combining local and systemic therapy in stage IV non-small cell lung cancer (NSCLC). Methods: Data from stage IV NSCLC patients receiving systemic therapy alone, surgical resection and systemic therapy, or external beam radiation therapy/thermal ablation (EBRT/TA) and systemic therapy were acquired from the 2010-2015 National Cancer Database (NCDB). EBRT and TA patients were combined to enhance the power of this study. Overall survival (OS) was evaluated via multivariable proportional hazards models. Comparison was made between EBRT/TA and systemic therapy alone utilizing 1:1 propensity matching analysis. A multivariable logistic regression model was used to determine variables predictive of lung cancer treatment. Significant variables (p < 0.05) were used to calculate the propensity score, and patients receiving EBRT/TA and systemic therapy were 1:1 matched using a greedy (nearest-neighbor) approach. Results: 46,964 patients from the NCDB database fulfilled inclusion criteria (surgical resection n = 1,235; EBRT/TA n = 12,456; systemic therapy alone n = 33,273.) Treatment differed across patient demographics and disease characteristics, with limited matched numbers and patients with stage IV NSCLC being under-represented in EBRT/TA. EBRT/TA treatment demonstrated superior survival compared to systemic therapy alone after accounting for confounders via propensity matching (HR = 0.95, 95% CI: 0.93-0.98, p = 0.002). Interaction analyses indicated heterogeneous effectiveness of EBRT/TA according to patient demographics and cancer factors: the survival benefit of EBRT/TA over systemic therapy alone was especially pronounced in stage IV squamous cell carcinoma patients with metastatic involvement of bone (HR 0.92, 95% CI: 0.85 to 0.98, p < 0.001) compared to systemic therapy alone; OS rates at 1-year = 50.9% vs. 42.4%; 2-years = 26.5% vs. 19.8%; 3-years = 17.2% vs. 10.1%.

Conclusions: Stage IV NSCLC patients who received EBRT/TA or surgical resection in addition to systemic therapy demonstrated prolonged survival. EBRT/TA in combination with systemic therapy should be preferred in selected patients that are ineligible for surgical candidates.

8546 Poster Session (Board #302), Sun, 8:00 AM-11:00 AM

Lung cancer diagnosed by an incidental lung nodule program or lung cancer screening. First Author: Matthew Smeltzer, University of Memphis, School of Public Health, Memphis, TN

Background: Early detection reduces lung cancer (LC) mortality. We prospectively evaluated LC patients diagnosed through Lung Cancer Screening (LCS) or an Incidental Lung Nodule Program (ILNP) (‘early detection’ programs) compared to routinely diagnosed LC patients in a multidisciplinary program (MDP). Methods: We compare demographics, tumor characteristics, and survival between the three groups diagnosed within the same healthcare system from 2015-2018. The ILNP prospectively tracks patients with suspicious lung lesions on routinely-performed studies flagged by radiologists using a standard macro text. LCS used Medicare eligibility criteria. Results were compared with MDP using Pearson’s chi-square test and Wilcoxon rank sum test. Results: 70/69/67 years (p = 0.0083); African Americans were under-represented in LCS (25%/11%/32%, p = 0.0104). LCS had the highest proportion with commercial insurance (46%/54%/31%, p = 0.0013), while MDP had 926 LC cases not detected by LCS or ILNP. Mean age at diagnosis for ILNP/LCS/MDP was 70/69/67 years (p = 0.0083), and diagnoses were RDX in 35 pts (40%), MXRA5 in 20 pts (23%), BAP1 in 13 pts (16%) and 18 pts (21%) and CD8 in 19 pts (46%) with PFS > 6 months for 40 pts (49%), 6 months for 41 pts (51%). Results: 187 functional somatic mutations were identified. Genomic alterations/patient were 1 gene in 29 pts (33%), 3 genes in 18 pts (21%) and ≥ 5 genes in 2 pts (2%). The most frequent somatic mutations were RDX in 35 pts (40%), MXRA5 in 20 pts (23%), BAP1 in 13 pts (15%) and ACTG1 in 9 pts (11%). When patients were collated by stage, the most frequent mutations were: MXRA5 in 16 pts in stage III (29%), BAP1 in 5 pts in stage IV (19%) and RDX in 16 pts in stage IV (62%). The percentage of somatic mutations in patients with FFS as first-line chemotherapy for ≥ 6 and > 6 months was 2.2 and 1.6 (p = 0.032), respectively. The most frequent mutations/patient in stage IV were BAP1 (HR 10.15, 95% CI: 2.0 to 51.8), with FFS > 6, RDX in 19 pts (46%) with FFS > 6 and MXRA5 in 11 pts (27%) with FFS > 6. Conclusions: This preliminary data suggests a possible role that a genetic signature may play in distinguishing MPM with different clinical-pathological features. The results are expected to be clarified further in the second step of the study, which is ongoing. Clinical trial information: 2016-0113-36.
8548 Poster Session (Board #304), Sun, 8:00 AM-11:00 AM
Outcome of neo-adjuvant chemotherapy in 225 surgical candidates with malignant pleural mesothelioma.

First Author: Nobuyuki Kondo, Department of Thoracic Surgery, Hyogo College of Medicine, Nishinomiya, Japan

Background: Since surgery for malignant pleural mesothelioma (MPM) is cytoreductive, effective chemotherapy is a prerequisite for surgery. In this context, we give neo-adjuvant chemotherapy (NAC) to all surgical candidates. Methods: Hyogo College of Medicine MPM Surgery Program mandates all surgical candidates to receive NAC, and only patients with stable disease (SD) or better response proceeds to surgery. The program comprised NAC followed by extrapleural pneumonectomy (EPP) and hemithoracic radiation until CR, and NAC followed by pleurectomy/decortication (PD) and postoperative chemotherapy thereafter. Eligibility criteria are histologically confirmed non-sarcomatoid MPM, clinically resectable stage (T1-3N0-1M0), performance status 0–1, and no major comorbidity. Results: From December 2006 to December 2018, 225 patients were enrolled. Of 225, 24 patients (10.7%, Group A) did not proceed to surgery because of progressive disease (n=23) or serious adverse events (n=2). Of the remaining 201 patients with partial response (n=38, 16.9%) or stable disease (n=163, 72.4%), 19 refused surgery (Group B), 16 received exploratory thoracotomy (Group C), and 165 completed surgery (Group D, EPPS, PD07P). Twofold surgery rate: 1.1% (n=2) and 2.8% (n=5), and surgical morbidity (≥ grade 3) was 26.0% (n=47). Median survival time and survival rates of each group were shown in the table. Briefly, 2-yr survival competed among Group B, C and D, whereas 5-yr survival rapidly dropped in Group B and C. Conclusions: Approximately 90% of MPM patients with surgical intent succeded in treatment either of PD or PD07P after effective chemotherapy with acceptable surgical mortality and morbidity. Comparison of patients who refused or accepted surgery suggested that surgery contributed to long-term survival.

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8549 Poster Session (Board #305), Sun, 8:00 AM-11:00 AM
Phase 2 study of tremelimumab plus durvalumab for previously-treated malignant pleural mesothelioma (MPM).

First Author: Deepthi Venkatraman, Dana-Farber Cancer Institute, Cambridge, MA

Background: Treatment options are limited for patients (pts) with MPM who experience disease progression after first-line pemetrexed-based chemotherapy. This study was designed to explore the activity of combined CTLA-4 + PD-L1 immune checkpoint inhibition using tremelimumab plus durvalumab in previously-treated MPM. Methods: We conducted a phase 2 study of tremelimumab 75 mg plus durvalumab 1500 mg administered intravenously every 4 weeks for four cycles followed by durvalumab maintenance every 4 weeks. Eligible pts had previously received pemetrexed-based platinum doublet chemotherapy and had measurable disease using modified RECIST criteria for mesothelioma. The primary endpoint was overall response rate (ORR) and secondary endpoints were progression-free survival (PFS), overall survival (OS), and duration of response (DoR) as well as safety and tolerability of this combination. A Simon two-stage design was employed to enroll up to 40 patients if 4 or more responses were observed among the first 19 study patients. Pre-treatment, on-treatment, and optional post-progression biopsies underwent flow-cytometric immunoprofiling for correlative studies. Results: Among 19 pts enrolled in this study, the best objective response was a confirmed partial response in one patient (5%), stable disease in 9 pts (47%), progressive disease in 8 pts (42%), and not evaluable in one patient. At a median follow-up of 7.1 months, the median PFS was 2.8 months (95% CI 2.04-5.72), and the median OS was 7.6 months (95% CI 5.2-10.0 not reached). Of 17 PD-L1 evaluable cases, 10 (59%) were PD-L1 negative, and 7 (41%) had a PD-L1 tumor proportion score ≥ 1%. Treatment was generally well-tolerated and there were no treatment-related serious adverse events. Flow cytometric immunologic changes over the course of treatment associated with disease control will be presented. Conclusions: Tremelimumab + durvalumab was well-tolerated in unselected pts with previously-treated MPM. This study did not meet its primary endpoint. Additional strategies are necessary to develop novel immunotherapeutics and biomarkers of response in MPM. Clinical trial information: NCT03075527.

8551 Poster Session (Board #307), Sun, 8:00 AM-11:00 AM
Radiological response patterns in the phase 2 STELLAR trial of TTFIELDS with chemotherapy for first-line treatment of malignant pleural mesothelioma (MPM). First Author: Federica Grosso, SS Antonio e Biagio Hospital, Department of Oncology, Alessandria, Italy

Background: Tumor Treating Fields (TTFields) are an anti-mitotic, regional treatment modality, utilizing low intensity alternating electric fields delivered non-invasively to the tumor using a portable, medical device. TTFields have significantly extended survival of patients with glioblastoma. In vitro, human MPM cells were highly susceptible to TTFields. In the STELLAR study, patients with unresectable MPM treated with first line chemotherapy in combination with TTFields had a significantly higher median overall survival compared to historical controls (18.2 vs. 12.1 months). We report on analysis of radiological data from STELLAR patients whose tumors responded while receiving the combined therapy. Methods: The STELLAR trial accrued 80 patients with unresectable, previously untreated mesothelioma. Patients were treated with continuous 150 kHz TTFields (>18/day) in combination with pemetrexed and cisplatin or carboplatin (at standard dosing). Inclusion criteria included ECOG PS of 0-1, pathologically proven mesothelioma and at least one measurable lesion according to modified RECIST criteria. Patients were followed for q3w (CT scan q6w) until disease progression. Radiological assessments were done at each study site. Results: Partial responses (PRs) were seen in 40.3% of evaluable patients and clinical benefit (PR+SD) was seen in 97.2% of these patients. The median time between treatment start and PR was 1.8 months (range: 1.4-4.4 months). All patients presenting with PR during the STELLAR study had continuous reduction in the total sum of lesion diameters, suggesting no initial/pseudo-progression. 83% of the patients who responded to the combined therapy finally had disease progression within a median response duration of 5.7 months (range: 1.4-13.7 months), per Kaplan-Meier Estimator. One patient did not progress for more than 27 months. Conclusions: The STELLAR study met its primary endpoint of significant survival extension for previously untreated mesothelioma patients. Response rates were similar to the ones reported for the current standard of care treatment, but lasted longer with the addition of TTFields. Clinical trial information: NCT02397928.

8552 Poster Session (Board #308), Sun, 8:00 AM-11:00 AM
Association of BAP1 alterations with malignant pleural mesothelioma treated with trimodality therapy.

First Author: Margerie Glass Zauderer, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Trimodality therapy with pleurectomy/decortication, cytotoxic chemotherapy, and adjuvant pleural intensity modulated radiation therapy (IMPRINT) is an emerging standard of care for locally advanced epithelioid mesothelioma (Rimner, Zauderer et al. JCO 2016). Some patients, however, progress rapidly and we therefore sought to identify potential predictive markers of response to this treatment. Given the putative role of BAP1 in DNA damage repair, we hypothesized that alteration in BAP1 would be associated with improved local control after radiation therapy. Methods: We identified patients previously treated at our institution with IMPRINT to a median dose of 4680Gy in 26 fractions. Targeted next generation sequencing was performed with MSK-IMPACT on archival tissue samples. Chart review was undertaken for clinicopathologic features and outcome data. Results: MSK-IMPACT testing was successfully performed on 58 patients who completed IMPRINT. The majority were male with a median age of 70 years. Ninety-seven percent had epithelioid subtype while 3% were biphasic with predominantly epithelioid histology. Median overall survival was 30.2 months with a median follow-up of 45.3 months, consistent with prior reports. Somatic BAP1 mutations were identified in 34% of the specimens. Those with BAP1 mutant tumors had a median time to local failure of 22.4 months (IQI 10.9 – 36.9 months) while those with BAP1 wild type tumors only had a median of 12.1 months (IQI 8.7-15.85 months) to local failure (p = 0.057). We identified a trend towards improved overall survival among those with BAP1 altered tumors compared to those with BAP1 wild type (HR = 0.61, p = 0.14). Conclusions: BAP1 alteration may be associated with improved duration of local control and improved overall survival after IMPRINT therapy. Further analysis and validation in a large data set is needed and a platform for identifying and validating predictive biomarkers should be included in the planned NRG randomized trials of IMPRINT.
Efficacy and safety of apatinib in extensive stage small cell lung cancer patients failed from two or more lines of chemotherapy. First Author: Yutao Liu, MD, National Cancer Center/Guangzhou Hospital, China Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Information on the optimal therapy beyond the second-line treatment of small cell lung cancer (SCLC) is very limited and controversial. Inhibiting the components of the VEGF signaling pathway is an attractive treatment option for SCLC patients. Apatinib, a selective inhibitor of VEGF receptor-2 (VEGFR-2)-tyrosine kinase, has been proven to be safe and effective for the treatment of breast cancer and gastric cancer. In this Apatinib for SCLC (Apatinib in Extensive Stage SCLC) clinical study, we aim to evaluate the efficacy and safety of single-agent apatinib as treatment of extensive-stage (ES) SCLC patients after failure from at least two prior chemotherapy regimens.

Methods: Twenty-two ES-SCLC patients treated with single-agent apatinib after failure from at least two prior chemotherapy regimens in our institution between November 2016 to August 2018 were enrolled in the clinical study. Apatinib mesylate was orally administered at a dose of 500 mg once daily on a 28-day cycle until evaluation of disease progression (PD) or the occurrence of unacceptable toxicity. Dosage reduction to either 425 mg or 250 mg once daily were permitted based on the evaluation of toxicities. The primary endpoint was progression-free survival (PFS). The secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR) and adverse events (AE). Results: The median age was 56 years, ranging from 36 to 70 years. A majority (63.6%, 14/22) received apatinib as third-line treatment, while 22.7% (5/22) and 13.6% (3/22) received it as fourth or fifth-line treatment, respectively. Disease control was achieved by 3 (13.6%) patients and stable disease exhibited by 18 (81.8%) patients. The median PFS and OS were 5.4 and 10.0 months, respectively. Apatinib demonstrated a manageable toxicity profile, with grade I-III secondary adverse events were only observed in 3 (13.6%) patients with either hypertension (1 patient) or hypertension and proteinuria as the most common AE. Grade III adverse events were achieved by 1 (4.5%) patient and 1 (4.5%) patient who experienced proteinuria (2 patients). Except for these 3 patients, all the other patients experienced grade I-II adverse events. No grade IV and VAE were observed among the patients. Multivariate analysis revealed secondary hypertension as an independent predictor of OS (p = 0.047). Conclusions: Apatinib is safe and effective in managing ES-SCLC patients and can be considered as a treatment option after failure from at least two prior chemotherapy regimens. Secondary hypertension can be a potential prognostic factor for apatinib treatment in extensive-stage small cell lung cancer.

Clinical trial information: NCT02995187.
8557 Poster Session (Board #313), Sun, 8:00 AM-11:00 AM

First Author: Satoshi Oizumi, National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan

Background: The clinical impact of PD-L1 expression and oncoenic gene status in patients with small cell lung cancer (SCLC) is not well characterized. We initiated this immuno-onoecnom biomarker study as part of nationwide genomic screening by LC-SCRUM-Japan (LC-SCRUM-IBIS).

Methods: Tumor samples from lung cancer patients enrolled in LC-SCRUM-IBIS were primarily subjected to targeted next-generation sequencing (NGS) with Oncomine™ Comprehensive Assay. The PD-L1 expression was also analyzed by 4 immuno-onoecnom (IHC) assays for 22C3, 28-8, SP263 and SP142. At this analysis, 22C3, 28-8, and SP263 were assessed in tumor cells (TC) as positive in > 1%, and SP142 in both TC and tumor-infiltrating immune cells (IC) as positive in > 1% TC/IC, as previously reported. The association of PD-L1 expres- tion, oncoenic gene status and clinical outcome was investigated in SCLC patients. Results: Between Feb 2017 and May 2018, 1017 lung cancer patients were enrolled in LC-SCRUM-IBIS. Among them, 933 patients had adequate tumor samples including 101 SCLC and 832 non-small cell lung cancer. Of 101 SCLC patients, the results of PD-L1 expression by 4 IHC assays were 18% in 22C3, 17% in 28-8, 11% in SP263 and 8% in SP142, respectively. Targeted NGS showed that 8 patients had at least one targetable oncoenic alterations, including 3 PIK3CA and 1 KRAS as mutations and 3 PTEN and 1 TSC2 as inactivating mutations. PD-L1 expression by 22C3 was associated with good performance status (P = 0.05) and the presence of oncoenic alterations (P = 0.004). PD-L1 status was not associated with response to cytotoxic chemotherapy and progression-free survival and overall survival in first-line treatment of SCLC patients.

Conclusions: The frequency of PD-L1 expression in SCLC patients was relatively lower compared with that reported in other solid cancers. PD-L1 status by TC in 22C3 appears to be not correlated with clinical outcomes for cytotoxic chemotherapy of SCLC patients. Further investigation is needed to explore a predictive biomarker for immune checkpoint inhibitors. Updated results will be presented at the meeting.

8558 Poster Session (Board #314), Sun, 8:00 AM-11:00 AM

Impact of large-scale nationwide genomic screening project for small cell lung cancer (LC-SCRUM-Japan). First Author: Hitoshi Akamatsu, Wakayama Medical University Hospital, Wakayama, Japan

Background: SCLC rapidly recurs after first-line platinum therapy, and while several agents are approved in the relapsed/refractory setting, there is no approved agent or existing standard of care for third-line in Japan. Rova-pituzumab tesirine (Rova-T™) is an antibody-drug conjugate targeting Delta-like 3 protein (DLL3), an atypical Notch ligand that is highly expressed in SCLC but not in normal tissue. This was the first study to evaluate the safety, PK, and preliminary anti-tumor activity of Rova-T in Japanese pts.

Methods: This was an open-label Phase 1, 3+3 dose-escalation study of Rova-T in Japanese pts with advanced recurrent SCLC (NCT03086239). Eligibility: progressive disease after ≥2 prior systemic regimens incl. ≥1 platinum-based regimen; ECOG 0-1. Pts received 0.2 or 0.3 mg/kg Rova-T IV on Day 1 of a 6-week cycle for 2 cycles. Objective was to evaluate safety, tolerability, PK, and preliminary efficacy and expression of DLL3. Antitumor activity was measured by RECISTv1.1, and DOR, PFS, OS were evaluated. Results: 29 pts were treated with Rova-T (6 at 0.2mg/kg, 23 at 0.3 mg/kg). Median age 68 yrs; 76% male; 64% DLL3 high (≥75% expression); 86% DLL3 positive (>25%). 20 pts (69%) had received ≥3 prior lines of therapy. Similar PK and AEs were seen compared to previous studies in non-Japanese pts. The most frequently reported drug-related AEs were platelet count decreased, pleural effusion, oedema peripheral, and aspartate aminotransferase increased, the majority Grade 1/2. No DLT occurred, and both dose levels were accepted. Three pts previously treated with ≥3 prior lines of therapy had confirmed partial response (10% of all pts; 17% of DLL3 high pts). For partial response by investigator (10% of all pts; 17% of DLL3 high pts). For pts (69%) had received ≥3 prior lines of therapy. Similar PK and AEs were accepted.

Conclusions: Rova-T demonstrated a manageable safety profile with promising preliminary efficacy in Japanese SCLC pts, in particular pts with DLL3 high expression. These data support further exploration of Rova-T treatment in Japanese pts with SCLC in global Phase 3 studies. Clinical trial information: NCT03086239.

8559 Poster Session (Board #315), Sun, 8:00 AM-11:00 AM

Impact of large-scale nationwide genomic screening project for small cell lung cancer (LC-SCRUM-Japan). First Author: Kei-En Nishimura, Department of Internal Medicine, Division of Respiratory Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

Background: A variety of genetic analyses have been performed in small cell lung cancer (SCLC), however the clinical relevance of them remains unclear. We prospectively analyzed clinical samples of small-cell lung cancer using a nationwide genomic screening project (LC-SCRUM-Japan).

Methods: Submitted tumor samples were subjected to a next-generation sequencing (NGS) system, Oncomine™ Comprehensive Assay, enabling the simultaneous analysis of 143 (ver.1) or 161 (ver.3) cancer-related genes. From July 2015 to January 2019, 707 SCLC patients had been enrolled. The median age was 68 years. 77% were male and 94% were smokers. Among 588 samples completed between 2003 and 2016. The endpoints included brain metastases, oncogenic gene status and clinical outcome was investigated in SCLC patients. The frequency of PD-L1 expression in SCLC patients was relatively lower compared with that reported in other solid cancers. PD-L1 status by TC in 22C3 appears to be not correlated with clinical outcomes for cytotoxic chemotherapy of SCLC patients. Further investigation is needed to explore a predictive biomarker for immune checkpoint inhibitors. Updated results will be presented at the meeting.

8560 Poster Session (Board #316), Sun, 8:00 AM-11:00 AM

Thoracic twice-daily radiotherapy and brain metastasis in patients with small cell lung cancer. First Author: Hao-Wen Zheng, Department of Radiation Oncology, Shandong Cancer Hospital Affiliated to Shandong University, Jinan, China

Background: Although thoracic twice-daily radiotherapy (TDRT) is one of standards of care for small cell lung cancer, its impact on brain metastases remains unknown. This study aimed to compare TDRT with once-daily radiotherapy (ODRT) for the brain metastases rate after prophylactic cranial irradiation in patients with small cell lung cancer. Methods: Consecutive patients received TDRT (45Gy/30f) or ODRT(50-66Gy/25-33f), chemotherapy and prophylactic cranial irradiation were retrieved from eight hospitals’ databases between 2003 and 2016. The endpoints included brain metastases, progression-free survival and overall survival. Brain metastases rate was evaluated using competing risk analysis. A 1:1 propensity score matching approach was used to control confounding between these two groups. Con founding covariates included eight demographic variables and eight treatment related covariates. Results: Of the 778 eligible patients with median age of 55-year (IQR, 48-61), 204 (26.2%) were female. At a median follow-up time of 23.6 months (IQR, 14.2-38.2), 131 (16.8%) experienced brain metastases. The rates in TDRT were significantly higher than ODRT (3-year, 26.0% vs. 16.9%; HR = 1.55, 95%CI 1.06-2.26, P = 0.03). Of the 338 matched patients (169 in ODRT vs. 169 in TDRT), 60 (17.8%) experienced brain metastases with 3-year rate of 14.9% in ODRT vs 26.0% in TDRT (HR = 1.71, 95%CI 1.02-2.88, P = 0.04). Progression-free survival was similar in both the whole cohort and the matched one. Overall survival in ODRT tended to be significantly longer after matching (median, 47.2 months in ODRT vs. 30.8 months in TDRT); HR = 1.41, 95%CI 1.05-2.71, P = 0.03). Conclusions: Patients with small cell lung cancer who were treated with thoracic TDRT appeared to have higher risk of brain metastases than those with ODRT, which strongly supports the need for further prospective randomized clinical trials, especially in China or other parts of Asia.
RESILIENT: Study of irinotecan liposome injection (nal-IRI) in patients with small cell lung cancer—Preliminary findings from part 1 dose-defining phase.

First Author: Luis G. Paz-Ares, Hospital Universitario 12 de Octubre, CiberOnc, Universidad Complutense and CNIO, Madrid, Spain

Background: Nal-IRI is investigated as monotherapy in patients with SCLC who progressed on or after platinum regimen. The RESILIENT study is a Part 1 study of a Phase 2/3 trial to assess safety, tolerability, and efficacy of Irinotecan Liposome Injection in patients with SCLC. Methods: Nal-IRI is evaluated in patients ≥18 yrs with advanced SCLC with an ECOG performance status ≤1 and adequate organ function; prior exposure to immunotherapy is allowed. Safety and tolerability at dose levels of 85 mg/m² and 70 mg/m² are the primary endpoints, with assessment of exploratory efficacy signal. Results: At 24 Dec 2018 safety cutoff 12 patients in Part 1 received ≥1 dose of nal-IRI (Cohort 1 [C-1] at 85 mg/m² dose n=4; Cohort 2 [C-2] at 70 mg/m² dose n=8; median age 60.0 yrs; range 49–73 yrs). Three patients experienced ≥1 DLT (Cohort 1 n=3/4; Cohort 2 n=0). Most frequent treatment-emergent adverse events (TEAE) were gastrointestinal (GI) disorders (any grade); diarrhea (91.7%), nausea (58.3%), vomiting (41.7%), decreased appetite (58%), abdominal pain (33%) manageable by antidiarrheal regimen and antiemetics; as well as fatigue (50%) and asthenia (37.5%). Overall, lung Cancer toxicity was neutropenia (any grade) at 16.7% and anemia (any grade) at 16.7%. At 11 Dec 2018 efficacy cutoff the best objective response was partial response (PR) at 33.3% in 4/12 patients (C-1 n=1/4; C-2 n=2/8), median time to response was 6 wks. Overall disease control rate (DCR) was 58.3%; progressive disease (PD) was observed in 2 patients (16.7%), and patients were non-evaluable (25%). Conclusions: Initial assessment suggests that nal-IRI at 70 mg/m² dose given bi-weekly is well-tolerated and has promising antitumor activity in patients with SCLC who progressed on or after platinum regimen. Part 1 dose expansion is ongoing. Clinical trial information: NCT03088813.
8566  Poster Session (Board #322), Sun, 8:00 AM-11:00 AM Clinical application of circulating cell-free DNA for monitoring the biological course of thymic epithelial tumors. First Author: Margaret Ottaviano, Oncology Unit, Department of Clinical Medicine and Surgery, University Federico II of Naples, Italy Background: Thymic epithelial tumors (TETs) are rare thoracic malignancies. Widely recognized as different histopathological entities, thymoma (T) and thymic carcinoma (TC), show a different biological behavior with a higher tendency to hematogenous dissemination for TC and thoric recurrence for T, sharing, however, a poor prognosis when characterized by high tumor burden. Up to date, there are no specific biomarkers for the monitoring of pre-therapy status of TET and outcome of these rare tumors. Analysis of circulating cell-free DNA (cfDNA) has potential applications throughout the natural course of cancer development, diagnosis and treatment, never the less several studies have suggested that cfDNA levels closely parallel overall tumor burden. For the first time the detection and the correlation of cfDNA levels with tumor burden and histological subtype of TET has been carried on in this monocentric study. Methods: Starting from July 2018, serum samples from 19 patients with TET, 4 with completely resected TET (rTET) and 15 with advanced (aTET), were prospectively obtained before the initiation of therapy. Serum samples from 15 healthy donors were used as control. Five ml of blood was collected and processed within one hour or less, followed by centrifugation at 3000g for 10 minutes and storage at -80°C. The serum samples were processed for QiAamp MinElute cell-free DNA mini kit extraction (Qiagen). cfDNA quantification was assessed using Qubit Fluorometric Quantitation (Thermo Fisher Scientific). Clinical, and histo-pathological features of TET were reported. Results: cfDNA level of 10.8 ng/ml (0.083-0.868) was registered. A median cfDNA of 0.512 ng/ml (0.178-1.42) resulted for the rTET, including the value of 0.178 for the resected TC. A median cfDNA of 2.53 ng/ml (1.20-6.11) resulted for the aTET, with respectively a median of 2.845 ng/ml (1.35-2.24) and of 1.5 ng/ml (1.1-2.17) for T and TC, respectively. The highest registered cfDNA level (6.11 ng/ml) and thymic carcinoma (5.24 ng/ml) correlates with the highest tumor burden. Conclusions: To the best of our knowledge, this is the first study to explore and quantification of cfDNA in TET. Higher baseline levels than the control group and the rTET group have been registered for both advanced T and TC. High levels of cfDNA may be associated with high tumor burden despite the histological subtype. We envision that further valuable information will be obtained with mutational analysis.

8568  Poster Session (Board #324), Sun, 8:00 AM-11:00 AM The risk of second primary malignancy in patients with localized thymoma: A U.S. Surveillance, Epidemiology and End Results study. First Author: Dipesh Uprety, Gunderson Health System, La Crosse, WI Background: Thymoma is a rare neoplasm of anterior mediastinum. Patients often have an indolent disease. The prognosis of limited stage disease is excellent with a 10-year survival rate of 70 to 80%. Data regarding the risk of second primary malignancy in thymoma survivors are limited in recent years. In this study, we aimed to determine the risk of second primary malignancies (SPM) in patients with limited stage disease. The database of Surveillance, Epidemiology and End Results (SEER)-13 registry was used to identify adult patients (≥18 years) with limited stage thymoma. We calculated the risk of SPM, developing ≥6 months after an index thymoma diagnosis, using Multiple Primary Standardized Incidence Ratio and an Absolute Excess Risk (AER) between 2004 and 2010. Statistical significance was defined as p < 0.05. Results: The database identified a cohort of 1,544 patients with limited stage thymoma with a median follow-up duration of 107 months (11-281 months). A total of 176 (11.39%) patients developed SPMs with a median latency of 62.5 months (range 6-272 months). Median age at diagnosis of SPM was 69 years (range 25-96 years). Overall, SPM occurred at an observed to expected (O/E) ratio of 1.53 (95% CI 1.32-1.76), p < 0.001 with an AER of 60.52 per 10,000 patient-years at risk. The risk was not significant for lymphoma (Hodgkin and non-Hodgkin), chronic leukemia, lymphohyalgeal, digestive tract and hepatobiliary cancer as SPM. Conclusions: The risk for SPMs is significantly increased in patients with thymoma compared to general population. Given the long-term risk of SPM, patient should be followed closely with judicious use of appropriate cancer screening.

8567  Poster Session (Board #323), Sun, 8:00 AM-11:00 AM Anti-EGFR target therapy in advanced thymic epithelial tumors. First Author: Mario Giuliano, Department of Clinical Medicine and Surgery, Oncology Unit, University of Naples, Federico II, Naples, Italy Background: Thymic epithelial tumors (TETs), show a high rate of EGFR immunohistochemistry (IHC) positivity, however, the prognostic and predictive role of EGFR has not yet been well defined, and contradictory data have emerged regarding the delivering of anti-EGFR monoclonal antibodies in TETs. The outcomes of the largest series of thymoma patients treated with cetuximab, and its hypothetic immune-modulatory role, are here described. Methods: Eleven patient with thymoma have been submitted to the pre-therapy status of TET and score positivity 2+ and 3+ at EGFR-IHC, were treated with cetuximab as off-label modality, with a dose of 400 mg/m2 in the first cycle and 250 mg/m2 in the following cycles every 7 days, until disease progression, unacceptable toxicity, withdrawal of consent. Primary endpoint was Overall Response Rate ORR, assessed radiologically. Secondary endpoints were progression Free Survival (PFS), safety, and relationship between time to cetuximab progression (TTPc) and time to previous treatment progression (TTPP). During treatment with cetuximab lymphocyte subpopulations have been carefully monitored in 4 patients affected by both thymoma and Good syndrome (GS) defined as B-cell lymphocyte counts (CD19+IgG) levels <8g/L. Results: With a median response duration of 17 months, a partial response was achieved in five patients (ORR=71%). Statistically significant correlation was found between disease response and EGFR-IHC score 2+ vs 3+ (P <0.008), which statistically correlated also with the mPFS of 14 months (95% CI: 0.2-37.6). No grade 3 or 4 adverse events were registered. TTPc was longer than TTPP in 6/7 patients (96%), with a TTPc / TTPP ratio equal to 2.12. During cetuximab treatment, in the longest responder patient affected also by GS, a progressive increase of IgG level and of CD4/CD8 ratio has been registered as well as an increase of both CD19+lymphocytes and CD16+56+ lymphocytes detected in thymus and peripheral blood with GS. Conclusions: Despite of the small number of patients and the off-label treatment modality, the data presented are worthy of confirmation in validated prospective studies in selected population with hyper-expression of EGFR. Further studies are also needed for deeply investigate the immunomodulatory role of cetuximab which seemed to temporarily revert severe immunodeficiency in our population.

TPS8569  Poster Session (Board #325a), Sun, 8:00 AM-11:00 AM ALINA: A phase III study of alemtuzumab versus chemotherapy as adjuvant therapy in patients with stage I-IIIA+I NSCLC. First Author: Benjamin J. Solomon, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia Background: Patients with early-stage NSCLC (stage IA-IIIA) account for ~40% of cases at diagnosis, despite surgery, 5-year survival rates are low. Platinum-based adjuvant chemotherapy is the standard of care (SoC) for stage II–IIIA disease. Although patients with stage IA NSCLC do not benefit from adjuvant chemotherapy, patients with stage IB disease and large tumors (~4cm) do. Adjuvant chemotherapy produces a 4–5% increase in 5-year survival rates, leaving significant unmet need for improved treatments. Approximately 5% of patients with NSCLC harbor an oncogenic fusion of the ALK gene. Treatment of advanced ALK+ NSCLC with ALK inhibitors improves efficacy and safety compared with chemotherapy. Alemtuzumab, a potent ALK inhibitor, is the SoC first-line treatment for advanced ALK+ NSCLC. The ongoing ALINA trial will compare alemtuzumab versus chemotherapy as adjuvant treatment for patients with stage IB–IIIA ALK+ NSCLC. Methods: ALINA is a randomized, multicenter, open-label phase III study investigating the efficacy and safety of adjuvant alemtuzumab versus chemotherapy in ALK+ NSCLC (confirmed by an FDA-approved and CE-marked test). Adult patients (≥18 years) with completely resected stage IB (tumors ≤4cm) to IIA disease and ECOG PS 0–1 are eligible for inclusion. Patients (N=255) from ~170 centers across ~30 countries will be randomized 1:1 to receive twice-daily alectinib 600mg for 12 months or pemetrexed 500mg/m2 [day 1] plus vinorelbine 25mg/m2 [days 1 and 8] or gemcitabine 1250mg/m2 [days 1 and 8] or pemetrexed 500mg/m2 [day 1] according to local prescribing information. Stratification factors are disease stage (IB ≤4cm vs stage II vs stage IIIA) and race (Asian vs non-Asian). Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. The primary endpoint is disease-free survival per investigator; secondary endpoints are overall survival, safety, and pharmacokinetics. Clinical trial information: NCT03456076.
TPS8570 Poster Session (Board #325b), Sun, 8:00 AM-11:00 AM

CANOPY-A: A phase III study of canakinumab as adjuvant therapy in patients with surgically resected non-small cell lung cancer (NSCLC). First Author: Edward R. Garon, David Geffen School of Medicine, University of California/TRIO-US Network, Los Angeles, CA

Background: Overexpression of interleukin (IL)-1β has been described in solid tumors, including lung. IL-1β can promote angiogenesis, tumor invasiveness, and induce tumor-associated immunosuppression through myeloid-derived suppressor cell (MDSC) accumulation in tumors. Pre-clinical data has shown that IL-1β inhibition stably reduces tumor growth, by limiting inflammation and inducing the maturation of MDSCs into M1 macrophages. Canakinumab is a human monoclonal antibody with high affinity and specificity for IL-1β. Recently, it was found that canakinumab was associated with a significant and dose-dependent reduction in incidence and mortality from lung cancer based on CANTOS study. Methods: CANOPY-A is a phase III, randomized, double-blind, placebo-controlled study designed to evaluate efficacy and safety of adjuvant canakinumab versus placebo in patients with surgically resected NSCLC. This trial will enroll adult patients, with completely resected (RO) AJCC/UICC v.8 stages II–IIIA and IIIB (T >5 cm and N2) NSCLC, who have completed standard-of-care adjuvant treatments, including cisplatin-based chemotherapy and mediastinal radiotherapy. Prior treatment with neoadjuvant chemotherapy or neoadjuvant radiotherapy is not permitted. Approximately 1500 patients will be randomized 1:1 to receive canakinumab (200 mg Q3W, s.c.) or placebo (Q3W, s.c.) for 12 cycles or until disease recurrence, unacceptable toxicity, treatment discontinuation at the discretion of investigator, patient, death, or loss to follow-up. Randomization will be stratified by AJCC/UICC v.8 stage, tumor histology, and region. The primary objective is disease-free survival, per investigator assessment. Secondary objectives include overall survival (second key objective), lung cancer-specific survival, safety, pharmacokinetics and immunogenicity of canakinumab, and patient-reported outcomes. Enrollment is ongoing. Clinical trial information: NCT03447769.

TPS8571 Poster Session (Board #326a), Sun, 8:00 AM-11:00 AM

The selective personalized radioimmunotherapy for locally advanced NSCLC trial (SPRINT). First Author: Nitin Ohri, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY

Background: Concurrent chemoradiotherapy for locally advanced non-small cell lung cancer (LA-NSCLC) can cause significant toxicities, and disease recurrence after treatment is common. We previously demonstrated that a dose-painted radiotherapy approach provides excellent local disease control and has a favorable toxicity profile. Consolidation immunotherapy was recently shown to improve outcomes after chemoradiotherapy for LA-NSCLC, and pembrolizumab monotherapy is now a standard of care for patients with advanced high PD-L1-positive NSCLC. We hypothesize that dose-painted thoracic radiotherapy and immunotherapy without chemotherapy will be safe and effective for the treatment of biomarker-selected patients with LA-NSCLC. Methods: Patients with a new diagnosis of unresectable stage II or stage III NSCLC and performance status 0-1 will be enrolled on this phase II trial at one of three participating institutions. Twenty-five subjects with PD-L1 Tumor Proportion Score (TPS) of at least 50% will receive three cycles of induction pembrolizumab (200 mg every 3 weeks). Subjects then receive 20 fractions of dose-painted radiotherapy, where lesions with metabolic tumor volume exceed 13 cm3 on FDG-PET metrial receive a dose of 55 Gy, while smaller lesions receive a dose of 48 Gy. Subjects then receive 12 additional cycles of pembrolizumab. The primary endpoint is progression-free survival one year following study enrollment, which we hypothesize will be achieved for at least 65% of study subjects. Other endpoints include overall survival, distant metastasis-free survival, freedom from second primary cancer, progression, adverse events, patient-reported outcomes, and physical activity metrics captured using wearable devices. In addition, we will explore markers of immune activation as prognostic factors. Approximately 38 patients with PD-L1 TPS below 50% will receive standard chemoradiotherapy and adjuvant thoracic radiotherapy as a control arm for a comparator cohort. SPRINT is an innovative biomarker-driven study that explores a paradigm shift in the local and systemic therapy used to treat LA-NSCLC. This trial opened in August of 2018, and 5 subjects have been enrolled to date. Clinical trial information: NCT03523702.

TPS8572 Poster Session (Board #326b), Sun, 8:00 AM-11:00 AM

Gemstone-301: A phase III clinical trial of CS1001 as consolidation therapy in subjects with histologically advanced or metastatic non-small cell lung cancer (NSCLC) who have not progressed after prior concurrent/sequential chemoradiotherapy (CRT). First Author: Yi-Long Wu, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China

Background: In China, the standard of care for patients with unresectable Stage III NSCLC is platinum-based doublet chemotherapy given concurrently or sequentially with radiotherapy. However, the median progression-free survival (PFS) of those patients is poor (approximately 8-10 months) and 5-year overall survival (OS) rate is only 15%. Recently, treatment with durvalumab resulted in significantly longer PFS and OS than placebo for patients with locally advanced/unresectable NSCLC whose disease did not progress after definitive concurrent chemoradiotherapy (cCRT) in PACIFIC trial. CS1001 is the first fully human programmed death ligand-1 (PD-L1) targeted immunoglobulin G4 (IgG4, s228p) monoclonal antibody (mAb) developed by the OMT transgenic rat platform. The Phase Ia/b study (GEMSTONE-101, NCT03312842) demonstrated that CS1001 was well tolerated and had promising anti-tumor activities across a range of tumors including NSCLC. GEMSTONE-301 is a randomized, double-blind, Phase III study to compare the efficacy and safety of CS1001 versus placebo as consolidation therapy in Stage III unresectable NSCLC patients. This is the first Phase III trial on an anti-PD-L1 mAb initiated in China for NSCLC. Methods: In this trial, eligible patients with locally advanced/unresectable (Stage III) NSCLC who have not progressed after prior concurrent/sequential CRT are 2:1 randomized to receive CS1001 1200 mg, every 3 weeks. Stratification factors for randomization include ECOG performance status; TPS8573 Poster Session (Board #327a), Sun, 8:00 AM-11:00 AM

PACIFIC-2: Phase 3 study of concurrent durvalumab and platinum-based chemoradiotherapy in patients with locally advanced/unresectable stage III NSCLC. First Author: Jeffrey D. Bradley, Department of Radiation Oncology, Washington University in St Louis, St Louis, MO

Background: Durvalumab, a selective, high-affinity, engineered human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80, is approved in the US, Japan and several other countries, for the treatment of patients (pts) with unresectable, stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent chemoradiotherapy (cCRT). These approvals were based on results from the phase 3 PACIFIC study, in which durvalumab was given 1–42 days after completion of definitive cCRT and significantly improved progression-free survival (PFS) vs placebo (median 16.8 vs 5.6 months; HR 0.52, 95% CI 0.42–0.65; p<0.001) and overall survival (OS) vs placebo (stratified HR 0.68; 99.73% CI 0.47–0.997; p=0.0025). Increasing evidence suggests additional benefit when anti-PD-1/anti-PD-L1 therapies are administered alongside cCRT. The PACIFIC 2 study therefore aims to assess whether durvalumab plus cCRT provides additional benefit, in terms of PFS and objective response rate (ORR), compared with cCRT alone. Methods: PACIFIC 2 is a phase 3, randomized, double-blind, placebo-controlled, multicenter, international study. Approximately 300 pts with unresectable stage III NSCLC will be randomized (2:1) to receive either durvalumab (intravenous 1500 mg) every 4 weeks (q4w) + CCRT, or placebo q4w + CCRT. Eligible pts must have historically or cytologically confirmed stage III disease; ECOG performance status 0 or 1; and life expectancy >12 weeks at randomization. Pts who discontinue treatment will be followed for safety and OS. Primary endpoints are PFS and ORR (RECRIST v1.1) assessed via blinded independent central review. Secondary endpoints include OS; OS at month 24; complete response (CR) rate; duration of response; disease control rate; time to death/distant metastases; time from randomization to second progression; safety; and symptoms, functioning and global health status. Pts with a CR, partial response or stable disease will continue to receive durvalumab or placebo until clinical or RECRIST v1.1-defined disease progression, or until another discontinuation criterion is met. Study enrollment began in March 2018 and recruitment is ongoing. Clinical trial information: NCT035819971.
**Arm 3 (Comparator)**
Placebo + cCRT Tislelizumab

**Arm 1**
Tislelizumab + cCRT Tislelizumab

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**Background:** Standard therapy for pts with unresectable stage III NSCLC is concurrent platinum doublet chemotherapy with radiotherapy (CCRT); however, this therapy does not reduce the risk of distant relapse, and the 5-y survival rate is low. Tislelizumab, an anti-PD-1 checkpoint inhibitor pembrolizumab, may have durable clinical activity as first-line therapy for advanced/metastatic NSCLC: as monotherapy for PD-L1-positive tumors and in combination with chemotherapy irrespective of PD-L1 status. KEYNOTE-799 evaluates the safety/efficacy of first-line pembrolizumab plus CCRT for unresectable, locally advanced stage III NSCLC. **Methods:** This nonrandomized, open-label phase 2 study enrolls pts ≥18 y with previously untreated, unresectable, pathologically staged stage IIA–C NSCLC with measurable disease per RECIST 1.1. Pts receive 17 cycles of pembrolizumab 200 mg Q3W plus standard thoracic radiotherapy in cycles 2 and 3 (60 Gy in 30 daily 2 Gy fractions). In cycles 1–3, treatment includes investigator’s choice of either paclitaxel 200 mg/m² and carboplatin area under the curve (AUC) 6 Q3W for 1 cycle, followed by paclitaxel 45 mg/m² and carboplatin AUC 2 weekly for 6 weeks, or carboplatin 75 mg/m² and pemetrexed 500 mg/m² Q3W (nonquorum only). Tumor imaging occurs at baseline and Q8W until week 54, or if PK or safety concerns dictate. **Key inclusion criteria include histologically confirmed stage III NSCLC; ECOG PS ≤1; negative serum CEA; CNS and liver metastases; adequate organ function; 2 target lesions; no prior chemotherapy for advanced stage III NSCLC, other than adjuvant; and a commercially available PD-L1 expression assessment is not required prior to randomization. EudraCT number: 2018-011322-22. Clinical trial information: NCT03749222.

**Arm**
cCRT Phase Monotherapy Phase (Consolidation)

**Arm 1**
Tislelizumab + cCRT

**Arm 3 (Comparator)**
Placebo + cCRT
Placebo + cCRT

* Primary objective: Assess efficacy of Arm 1 or Arm 2 vs Arm 3.

**TPS8576**
Poster Session (Board #328b), Sun, 8:00 AM-11:00 AM
Phase 1 study of AMG 119, a chimeric antigen receptor (CAR) T cell therapy targeting DLL3, in patients with relapsed/refractory small cell lung cancer (SCLC). **Background:** SCLC is an aggressive neuroendocrine tumor, with initial sensitivity to chemotherapy and radiotherapy often followed by chemoresistant disease progression. Notch signaling is a key regulator of neuroendocrine differentiation in SCLC, and delta-like ligand 3 (DLL3) is an inhibitory ligand of Notch receptors. DLL3 is expressed in most SCLC tumors but minimally expressed in normal tissues, suggesting that it may be a promising target for cancer immunotherapy. AMG 119 is an adoptive cellular therapy that consists of a patient's autologous T cells that have been genetically modified ex vivo to express a transmembrane CAR that targets DLL3 and redirects cytotoxic T cell specificity to DLL3-positive cells. AMG 119 CAR T cells show potent killing of SCLC cells expressing DLL3 in vitro and inhibit tumor growth in an SCLC xenograft model in vivo. **Methods:** This phase 1 study will evaluate the safety and tolerability of AMG 119 administered as a single infusion in adult patients with relapsed/refractory SCLC who have progressed after at least 1 platinum-based chemotherapy regimen. The primary objectives are to evaluate safety and tolerability and determine the maximum tolerated cell dose (MTCD) or recommended phase 2 cell dose (RP2D). Secondary objectives are to evaluate preliminary evidence of antitumor activity, expansion and persistence of CAR T cells, and pharmacokinetics. **Key inclusion criteria:** Patients with histologically confirmed stage IIIB–IV SCLC with measurable disease per RECIST 1.1, ≥1 target lesion, Karnofsky performance status ≥60, measurable disease, ≥2 measurable lesions per modified RECIST 1.1, ≤3 target lesions per organ by BICR. **Methods:** This 13-criteria study enrolls pts ≥18 y with previously untreated, unresectable, pathologic stage IIB–IV SCLC. Patients will be enrolled in 59 sites in 10 countries beginning on Nov 5, 2018. As of Feb 12, 2019, 30 pts have enrolled. Continuous interim analyses using binomial sequential testing will be performed after ≥36 pts have ≥15 weeks of follow up in each cohort, to allow earlier treatment discontinuation, if required. Clinical trial information: NCT03631784.

**TPS8575**
Poster Session (Board #328a), Sun, 8:00 AM-11:00 AM
Phase 2 trial of first-line pembrolizumab with platinum doublet chemotherapy and radiotherapy in patients (pts) with unresectable, locally advanced stage III non-small cell lung cancer (NSCLC). **Background:** First Author: Salma K. Jabbour, Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey; Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ

**Background:** Standard therapy for pts with unresectable stage III NSCLC is concurrent platinum doublet chemotherapy with radiotherapy (CCRT); however, this therapy does not reduce the risk of distant relapse, and the 5-y survival rate is low. Tislelizumab, an anti-PD-1 checkpoint inhibitor pembrolizumab, may have durable clinical activity as first-line therapy for advanced/metastatic NSCLC: as monotherapy for PD-L1-positive tumors and in combination with chemotherapy irrespective of PD-L1 status. KEYNOTE-799 evaluates the safety/efficacy of first-line pembrolizumab plus CCRT for unresectable, locally advanced stage III NSCLC. **Methods:** This nonrandomized, open-label phase 2 study enrolls pts ≥18 y with previously untreated, unresectable, pathologically staged stage IIA–C NSCLC with measurable disease per RECIST 1.1. Pts receive 17 cycles of pembrolizumab 200 mg Q3W plus standard thoracic radiotherapy in cycles 2 and 3 (60 Gy in 30 daily 2 Gy fractions). In cycles 1–3, treatment includes investigator’s choice of either paclitaxel 200 mg/m² and carboplatin area under the curve (AUC) 6 Q3W for 1 cycle, followed by paclitaxel 45 mg/m² and carboplatin AUC 2 weekly for 6 weeks, or carboplatin 75 mg/m² and pemetrexed 500 mg/m² Q3W (nonquorum only). Tumor imaging occurs at baseline and Q8W until week 54, or if PK or safety concerns dictate. **Key inclusion criteria include histologically confirmed stage III NSCLC; ECOG PS ≤1; negative serum CEA; CNS and liver metastases; adequate organ function; ≥2 target lesions; no prior chemotherapy for advanced stage III NSCLC, other than adjuvant; and a commercially available PD-L1 expression assessment is not required prior to randomization. EudraCT number: 2018-001132-22. Clinical trial information: NCT03749222.
NRG Oncology CC003: A randomized phase II/III trial of prophylactic cranial irradiation with or without hippocampal avoidance for small cell lung cancer.  
First Author: Vinai Gondi, Northwestern Medicine Cancer Center Warrenville and Northwestern Medicine Proton Center, Warrenville, IL

Background: Multiple clinical trials have shown that prophylactic cranial irradiation (PCI) prevents brain metastases and may prolong survival in small cell lung cancer (SCLC). However, prophylactic cranial irradiation can lead to decline in cognitive function. Preclinical evidence suggests that the pathogenesis of this toxicity includes inflammatory injury to proliferating neuronal progenitor cells in the peri-hippocampal stem cell niches. We hypothesized that conformal avoidance of the hippocampal neural stem cell compartment during brain irradiation using intensity-modulated radiotherapy (IMRT) would decrease the likelihood and/or severity of this toxicity. This hypothesis was recently validated by positive results from NRG Oncology CC001, a phase III trial of hippocampal avoidance during whole-brain radiotherapy for patients with brain metastases. NRG Oncology CC003 is an ongoing randomized phase II/III trial of hippocampal avoidance during prophylactic cranial irradiation (HA-PCI) for small cell lung cancer, conducted in parallel with NRG Oncology CC001. 

Methods: The primary endpoints of the phase IIR and III components are 12-month intracranial relapse rate and 6-month deterioration in Hopkins Verbal Learning Test-Revised (HVLT-R) Delayed Recall, respectively. This is a seamless phase IIR/III trial, with the phase IIR designed to demonstrate non-inferiority. If the non-inferiority margin of the phase IIR component is not exceeded, then the trial would transition to the phase III component. Following accrual of 182 of planned 172 patients on the phase IIR component, the trial closed to accrual on 10/13/17 to assess the phase IIR primary endpoint. The DSMB evaluated the IIR outcomes, and on 1/9/19, the trial was reactivated to accrue an additional 122 patients to the phase III component. Eligibility criteria include: 1) small cell lung cancer with at least partial response to chemotherapy; 2) contrast-enhanced thin-slice volumetric MRI scan; and, 3) Zubrod performance status 0-2. Supported by grant U10CA189867 (NCORP) from the National Cancer Institute. Clinical trial information: NCT02635009.
Lung Cancer—Non-Small Cell Metastatic

9000
Oral Abstract Session, Mon, 8:00 AM-11:00 AM

RELAY: A multinational, double-blind, randomized Phase 3 study of erlotinib (ERL) in combination with ramucirumab (RAM) or placebo (PL) in previously untreated patients with advanced nonsmall cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC). First Author: Kazuhiko Nakagawa, Kindai University Hospital, Osaka, Japan

Background: Dual blockade of EGFR and VEGF pathways in EGFHRm NSCLC augments anti-tumor efficacy versus (v) EGFR inhibition alone. RELAY (NCT02414448) evaluated efficacy and safety of ERL, an EGFR TKI standard-of-care, plus RAM, a human IgG1 VEGFR2 antagonist, or PL in 1L EGFHRm metastatic NSCLC. Methods: Eligibility included unmedicated metastatic NSCLC pts with Exon 19 deletion (del) or L858R and no CNS metastasis. Randomized (1:1:1) pts received ERL (150 mg/day) + RAM (10 mg/kg q2w) or ERL + PL, stratified by gender, geographic region (East Asia v other), EGFHRm type (Ex19del v L858R) and EGFR testing method (Therascreen/Cobas v other). The primary endpoint was investigator assessed progression-free survival (PFS). Other objectives included ORR, DoR, PFS2, OS, safety, and plasma T790M mutation (Guardant NGS). Results: 449 pts were randomized. Characteristics were balanced between treatment arms: Asian 77%, Females 63%, Ex19del 54%. RAM + ERL significantly prolonged PFS, DoR, and PFS2 (Table). Grade 3/4 TEAEs were greater with RAM vs PL (54% v PL 49%), with 1 treatment related on study death (hemotheroma) in RAM v 0 PL. EGFHRm rates at progression are forthcoming. Conclusion: RAM + ERL led to superior PFS in 1L EGFR metastatic NSCLC. Safety was consistent with the safety profile of the individual compounds. Clinical trial information: NCT02414448.

9001
Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Phase III randomized trial comparing gefitinib with pemetrexed-carboplatin chemotherapy in patients with advanced untreated EGFR mutant non-small cell lung cancer (gef+C vs gef). First Author: Vantia Noronha, Tata Memorial Centre, Mumbai, India

Background: Standard first-line therapy for EGFR mutant advanced non-small cell lung cancer (NSCLC) is an EGFR-directed oral TKI. We evaluated whether adding pemetrexed-carboplatin to oral TKI would improve outcomes.

Methods: Phase III randomized trial in advanced chemotherapy-naive NSCLC harboring EGFR sensitizing mutation (exon 19, 21 or 18) with predicted median survival (PS) 0 to 2 planned for palliative therapy. Patients were stratified for PS and EGFR mutation and randomly assigned (computer-generated randomization by independent biostatistician) 1:1 to gefitinib 250 mg orally daily (gef) or gefitinib 250 mg orally daily with pemetrexed 500 mg/m2 IV and carboplatin AUC 5 IV every 3 weeks for 4 cycles, followed by maintenance pemetrexed 500 mg/m2 IV every 3 weeks (gef+C). Restaging was every 2 to 3 mths; therapy continued until progression or intolerable toxicity. Primary endpoint was progression-free survival (PFS); secondary end points included overall survival (OS), toxicity and response rate. Survival endpoints were assessed in the intention-to-treat population. Results: Between Aor 2016 and Aug 2018, 350 patients were randomly assigned to gef (n = 177) and gef+C (n = 173). Median age was 54 yrs, 48% were females, 84% never-smokers, 21% were PS 2 and 18% had brain metastases. Median follow-up in surviving patients was 17 months (range, 7 to 30). Radiologic response rates were 81% and 69% in gef+C and gef respectively, P = 0.012. 234 patients (67%) have had event free survival (EFS), 98 in gef+C and 136 in gef. Estimated median PFS was significantly longer with gef+C than gef (16 months, [95% CI, 13.7 to 18.3] vs. 8 months [95% CI, 7.1 to 9.9]); hazard ratio for disease progression or death, 0.5; 95% CI, 0.39 to 0.65; P < 0.001). 120 patients (34%) have died, 42 in gef+C and 78 in gef. Estimated median OS was significantly longer with gef+C than gef (not reached vs 18 months [95% CI, 14.8 to 21.72]); hazard ratio for death, 0.45; 95% CI, 0.31 to 0.66; P < 0.001. Clinically relevant grade 3 toxicities occurred in 51% and 25% of patients in gef+C and gef arms respectively, P < 0.001. Conclusion: Adding pemetrexed-carboplatin chemotherapy to gefitinib significantly prolonged progression-free survival but also increased the toxic effects. Parallel pemetrexed-gefitinib represents a new standard first-line therapy for EGFR mutant NSCLC. Clinical trial information: CTRI/2016/08/07149.

9002
Oral Abstract Session, Mon, 8:00 AM-11:00 AM

ECOG-ACRIN 5508: Pemetrexed, bevacizumab or the combination as maintenance therapy for advanced non-squamous NSCLC. First Author: Suresh S. Ramalingam, Winship Cancer Institute, Emory University, Atlanta, GA

Background: Maintenance therapy is a standard approach for advanced non-squamous NSCLC. Pemetrexed or bevacizumab are considered evidence-based options. The combination of bevacizumab and pemetrexed has been documented to improve progression-free survival (PFS). We conducted a phase 3 study to determine the optimal maintenance therapy for advanced non-squamous NSCLC. Methods: Patients with advanced non-squamous NSCLC, no prior systemic therapy, and ECOG performance status 0/1 were treated with carboplatin (AUC = 6), paclitaxel (200 mg/m2) and pemetrexed (15 mg/m2) every 3 weeks for up to 4 cycles. Patients with OS/PR/SD after 4 cycles were then randomized 1:1:1 to maintenance therapy with bevacizumab (15 mg/m2), pemetrexed (500 mg/m2) or the combination of the two agents every 3 weeks until disease progression (step 2). The primary endpoint was overall survival (OS), defined as the time from randomization to death from any cause and censoring defined at the last date of followup. 1495 pts provided 81% power to detect a hazard ratio of 0.75 while controlling the 2-sided type I error at 0.025 for each comparison, assuming approximately 60% of those patients would be randomized.

Results: We enrolled 1516 pts to step 1 (male 52%, ECOG PS 1 62%, adenocarcinoma 90%). After induction therapy, 874 (57%) pts were randomized to step 2 (median age 64 yrs; male 49%; ECOG PS 1 55%). Baseline characteristics were balanced across all three groups. The median follow-up in maintenance is 50.6 months. Conclusions: Single agent bevacizumab or pemetrexed is the optimal maintenance therapy for advanced non-squamous NSCLC. The combination of bevacizumab and pemetrexed cannot be recommended due to the lack of survival benefit in this definitive study. (Dr. Ramalingam, Dahlberg and Belani contributed equally to this work). Supported by the NCI: CA180820, CA180794, CA180799, CA180821, CA180838, CA180882, CA180893, CA180983, CA180986, CA189971. Clinical trial information: NCT01107626.

9003
Oral Abstract Session, Mon, 8:00 AM-11:00 AM

A randomized phase III study of continuous maintenance bevacizumab with or without pemetrexed after induction therapy with carboplatin (Car), pemetrexed (Pem), and bevacizumab (Bev) for advanced non-squamous non-small cell lung cancer (nSQ-NSCLC) without sensitizing EGFR mutations: The COMPASS study (WJOG5610L). First Author: Takashi Seto, National Kyushu Cancer Center, Fukuoka, Japan

Background: Two continuous maintenance therapies, “Pem after Pem+Platinum” and “Bev after Bev+Pd-Fib-doublet”, demonstrated the prolongation of survival for untreated nSQ-NSCLC. A phase III randomized trial comparing Bev+Pem versus Pem after Bev+Pem induction therapy after Car+Pem+Bev induction therapy. Methods: Patients were eligible if they had previously untreated advanced nSQ-NSCLC whose EGFR status was either wild-type, unknown, or other than Del19 or L858R. They received the induction treatment with Car (AUC6), Pem (500 mg/m2), and Bev (15 mg/kg) every 3 weeks for 4 cycles. Those who showed no progression during the induction therapy were randomized to receive maintenance therapy using Bev or Bev+Pem in a 1:1 ratio. The primary endpoint was overall survival (OS) from randomization. The planned sample size was 620 to provide a power of 85% at one-sided significance level of 5%. Violations found at a study site led us to conduct source document verification for 95.4% of patients to assure data quality. (Trial Identifier, UMIN000004194).

Results: Between September 2010 and September 2015, 907 patients had the induction therapy. Of those, 621 patients were randomized; five did not receive study treatment and 22 did not meet the eligibility criteria. Among 594 patients for evaluable (299 in the Bev+Pem arm and 295 in the Bev arm), median age was 65 years; Male, 72%; PS 0/1, 60/40%; Stage IV, 83%; EGFR status, wild-type/others, 91.7%; Median OS was 23.3 vs 19.6 months (mo) with a hazard ratio (HR) of 0.87 (95%CI, 0.72-1.04) and one-sided logrank P = 0.069; in patients with wild-type EGFR tumor, HR for OS was 0.82 (0.69-0.99). Median progression-free survival was 5.7 vs 4.0 mo with a HR of 0.67 (0.57-0.79), 87.4% of patients received subsequent therapy. No new safety signals were observed. Conclusions: The primary analysis was not met. However, the incorporation of Pem significantly prolonged OS in patients with wild-type EGFR. Clinical trial information: UMIN000004194.

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On-target acquired resistance is found in manageable toxicity profile. Clinical trial information: NCT02414139. NSCLC regardless of the line of therapy with deep and durable responses and $9.13 (5.52-13.86)\text{mo}$ for Cohorts 4 and 5b, respectively. Safety profile

Results:

amplification status/gene copy number) to Cohorts 4 and 5b and received

ORR 0% (n = 0/2) with KRAS

Outcomes were observed with pre-TKI KRAS expression (n = 16, all with detectable KRAS levels): ORR 0% (n = 0/2) in KRAS

Correlation of pre-TKI RAS pathway activation with response: ORR 0% (n = 0/6) with KRAS/NG-RAF1 mutation or ORR 29% (n = 5/17) in others. Similar outcomes were observed with pre-TKI KRAS expression (n = 16, all with detectable KRAS levels): ORR 0% (n = 0/2) in KRAS $700\text{amol}\mu\text{g}^{-1}\text{org}$ vs ORR 50% (n = 7/14) $<700\text{amol}\mu\text{g}^{-1}\text{org}$. Acquired resistance (Jackman criteria) was seen in 29 patients, 9 with paired pre/post-treatment samples. On-target acquired resistance was found in 29 patients (22%): METD1228N (n = 1), HGF amplification (n = 1). Potential off-target acquired resistance mechanisms were found in 59 pts (44%): KRAS G13V (n = 1), RAF1 S742A (n = 1), MDM2 amplification (n = 2), EGRF amplification (n = 1). Conclusions: Lack of MET expression or RAS pathway activation was associated with poor MET TKI outcomes in MET-ex14 lung cancers. On-target acquired resistance was found in $\leq 25\%$ of patients. HGF amplification is a novel mechanism. Off-target/intrinsic acquired resistance may be mediated by RAS/MDM2/EGRF2 pathway activation.

Lung Cancer - Non-Small Cell Metastatic

Antitumor activity of TAK-788 in NSCLC with EGFR exon 20 insertions. First Author: Pasi A. Jänne, Dana-Farber Cancer Institute, Boston, MA

Background: TAK-788 is an oral investigational EGFR/HER2 inhibitor under evaluation in NSCLC patients (pts) with EGFR exon 20 insertions. We report results of a phase 1/2 open-label, multicenter study (NCT02716116). Methods: Pts with advanced, previously treated NSCLC received daily TAK-788 in dose escalation and expansion cohorts based on tumor genotype. Antitumor activity was determined for pts with EGFR exon 20 insertions who received TAK-788 at the RP2D. Safety is reported for all pts across all doses and at 160 mg. Results: As of 14 Sep 2018, 101 pts (median age, 61 y; female, 70%; ≥2 prior anticancer therapies, 76%; brain metastases, 53%) were treated with TAK-788 at 5–180 mg qd. RP2D was determined to be 180 mg, 28 pts with EGFR exon 20 insertions received TAK-788 at 180 mg during dose expansion or in expansion cohort 1 (median 3.6 mg on treatment; median 3.8 treatment cycles); 24 pts remain on treatment. Antitumor activity in pts with EGFR exon 20 insertions is shown in Table. At data cutoff, 7/14 responses were confirmed with 6 awaiting confirmation and 1 unconfirmed PR at 160 mg; median time to response in these 14 pts was 56 days. 23/24 evaluable pts with EGFR exon 20 insertions treated at 160 mg had decreased target lesion measurements (median best percent change, −32.6% [-79.1%, 3.8%]). Rate of treatment discontinuation due to AEs was 10.7% in pts treated at 160 mg (median duration of response [mDoR] and ORR by line of treatment are shown in the table. Any grade treatment-related adverse events (TRAES) were reported by ≥10% of pts evaluable for safety were peripheral edema (47.8%), diarrhea (18.8%), nausea (15.9%), asthenia (10.1%). No TRAEs were grade 4 or led to death. TRAEs led to permanent discontinuation in 2 (2.9%) pts (1 ILD, 1 diarrhea & nausea). Conclusions: Tepotinib has promising activity with a long DoR across treatment lines in NSCLC pts with MET exon 14 alterations. Long-term treatment with tepotinib is likely to be safe and well tolerated in metastatic NSCLC. Future study: to assess potential clinical benefit indefinitely.

Phase II study of tepotinib in NSCLC patients with METex14 mutations. First Author: Paul K. Paik, Memorial Sloan Kettering Cancer Center, New York, NY

Background: METexon 14 skipping (METex14) mutations - reported in 3–4% of NSCLC patients (pts) - are activating, sensitive to MET inhibition and can be conveniently detected using liquid biopsy (LBx). We report data from an ongoing single-arm phase II study of tepotinib, a highly selective MET inhibitor, in NSCLC pts with METex14 mutations identified by LBx or tumor biopsy (TBx) (NCT02864992). Methods: Pts with advanced WT EGFR/ALK NSCLC, prospectively enrolled via either LBx (≥60 pts) or TBx (≥60 pts, on-site/anticipated) central RNA-based METex14 mutation testing. Safety: tepotinib 500 mg QD until progression, intolerable toxicity or withdrawal. Primary endpoint: objective response rate (ORR) by independent review (IRC). Secondary endpoints: ORR by investigator assessment (INV) and safety. Results: To date, 85 pts have been enrolled (55 LBx pts and 52 TBx pts). At data cut-off (16 Oct 2018), in 35 evaluable LBx pts (≥2 post-baseline assessments or discontinuation for any reason), ORR was 51.4% by IRC and 63.9% by INV. In 41 evaluable TBx pts, ORR was 41.5% by IRC and 58.5% by INV. Median duration of response (mDoR) and ORR by line of treatment are shown in the table. Any grade treatment-related adverse events (TRAES) re-

9005 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

9004 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

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Clinical activity and tolerability of BLU-667, a highly potent and selective RET inhibitor, in patients (pts) with advanced RET-fusion+ non-small cell lung cancer (NSCLC). First Author: Justin F. Quinor, Massachusetts General Hospital, Boston, MA

Background: RET fusions are targetable oncogenic drivers in up to 2% of NSCLC, yet no selective RET inhibitors are approved. BLU-667 is an investigational highly potent and selective RET inhibitor targetting oncogenic RET alterations, including those that confer resistance to multikinase inhibitors (MKIs). We provide an update on the registration-enabling ARROW study (NCT0337385V) of BLU-667 in pts with RET-fusion+ NSCLC.

Methods: The global ARROW study includes DE (30-600 mg daily [QD or BID]) and dose expansion (DX) at the recommended phase 2 dose (RP2D; 400 mg QD) in pts with advanced solid tumors. Primary objectives are overall response rate (ORR; RECIST 1.1) and safety. Results: As of 19 Dec 2018, 79 pts (21 DE, 58 DX) with advanced RET-fusion+ NSCLC (44 KIF5B, 16 CCDC6, 19 other/pending) received BLU-667. Median number of prior therapies was 2 (range 0-8) and includes chemotherapy (76%), immunotherapy (41%), and MKI (27%). 39% had baseline brain metastases. ORR among 57 response-evaluable pts with measurable disease and at least one follow-up disease assessment was 56% (95% CI: 41, 70). 55% of the 39% had baseline brain metastases. ORR among 57 response-evaluable pts with measurable disease and at least one follow-up disease assessment was 56% (95% CI: 41, 70).

Among 30 pts at the RP2D previously treated with platinum chemotherapy, ORR was 20% (18 PRs, 2 SDs). PK-DLTs occurred regardless of prior treatment or RET fusion genotypes. Intracranial activity has been observed with shrinkage of brain metastases. 80% of NSCLC pts treated at RP2D remain on treatment and only 3% discontinued therapy (41%), and MKIs (27%). 39% had baseline brain metastases. ORR among 57 response-evaluable pts with measurable disease and at least one follow-up disease assessment was 56% (95% CI: 41, 70). 55% of the 39% had baseline brain metastases. ORR among 57 response-evaluable pts with measurable disease and at least one follow-up disease assessment was 56% (95% CI: 41, 70). Among 30 pts at the RP2D previously treated with platinum chemotherapy, ORR was 20% (18 PRs, 2 SDs). PK-DLTs occurred regardless of prior treatment or RET fusion genotypes. Intracranial activity has been observed with shrinkage of brain metastases. 80% of NSCLC pts treated at RP2D remain on treatment and only 3% discontinued due to related adverse event. In NSCLC patients, treatment-related toxicity generally was grade 1-2, and 5 with grade 3-4 AEs were reported in 34% (8% treatment-related) with dyspnea (6%) and pneumonia (3%) most frequently observed. Among response-evaluable pts, 25/88 (28%) achieved best timepoint response of partial response (PR). 10/47 pts with prior 3GTKI therapy had best timepoint response of PR (6 confirmed), including 4 with C797S mutation and 3 with cMet amplification, loss or gain of 5 with both identifiable EGFR/cMet-dependent resistance. 6/20 pts with Exxon20ins had best timepoint response of PR (3 confirmed).

Conclusions: BLU-667 demonstrated potent, durable and broad antitumor activity and was well tolerated in pts with advanced RET-fusion+ NSCLC. Enrollment of the expansion is ongoing with registrational intent. Clinical trial information: NCT0337385V.

Lung Cancer—Non–Small Cell Metastatic

9009 Clinical Science Symposium, Fri, 1:00 PM-2:30 PM

JNJ-61186372 (JNJ-372), an EGFR-Cmet bispecific antibody, in EGFR-driven advanced non-small cell lung cancer (NSCLC). First Author: Eric J. Haura, Department of Thoracic Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL

Background: JNJ-372 binds EGFR and cM to block ligand binding, promote receptor degradation, and trigger antibody-dependent cellular cytotoxicity in models of EGFR-mutated (EGFRm) NSCLC. Here we describe the ongoing phase 1 safety, pharmacokinetics (PK), and activity of JNJ-372 in patients (pts) with NSCLC, including 3rd generation tyrosine kinase inhibitor (3GTKI)- resistant S/FRN NSCLC and EGFR Exon20ins disease. Prior to receiving JNJ-372 (140–1400 mg) IV weekly for the first 28-day cycle and biweekly thereafter. 1050–1400 mg doses are being explored in dose expansion. Blood samples were collected for PK analyses. Efficacy by investigator per RECIST v1.1 in pts with EGFRm NSCLC treated at ≥700 mg is presented. Pts were characterized by next-generation sequencing of circulating tumor (ctDNA) and/or tumor tissue. Results: As of 17 Jan 2019, 116 enrolled pts with NSCLC were treated. Median age was 63 years, 38% were male, 77% were Asian, and 97% had EGFR mutations. Mean duration of treatment was 3.8 months, longest exposure was 20 cycles. The PK data set included pts from Korea (77%) and the US (23%). At the 1050 mg dose of pts achieved average concentrations above the ECV90 based on preclinical models. Adverse events (AEs): ≥20% were rash (59%), infusion related reaction (58%), paronychia (28%), and constipation (22%). Additional EGFR/cM-related AEs include stomatitis (17%), pruritis (15%), peripheral edema (15%), and diarrhea (15%). Grade ≥3 AEs were reported in 34% (8% treatment-related) with dyspnea (6%) and pneumonia (3%) most frequently observed. Among response-evaluable pts, 25/88 (28%) achieved best timepoint response of partial response (PR). 10/47 pts with prior 3GTKI therapy had best timepoint response of PR (6 confirmed), including 4 with C797S mutation and 3 with cMet amplification, loss or gain of 5 with both identifiable EGFR/cM-dependent resistance. 6/20 pts with Exxon20ins had best timepoint response of PR (3 confirmed).

Conclusions: JNJ-372 has a manageable safety profile consistent with EGFR and cMet inhibition. Preliminary responses were achieved in 3GTKI-relapsed disease, including C797S and cMet amplification, and Exxon20ins disease; enrollment in dose expansion is ongoing. Clinical trial information: NCT02609776.

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9012 Poster Discussion Session; Displayed in Poster Session (Board #335), Sun, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-6:00 PM

IMpower150: Analysis of efficacy in patients (pts) with liver metastases (mets).

**First Author:** Mark A. Socinski, AdventHealth Cancer Institute, Orlando, FL

**Background:** Atezolizumab (atezo) + bevacizumab (bev) + chemotherapy (CP; ABCP) showed improved OS and PFS over bev + CP (BCP) in pts with chemo-naive NSCLC (IMpower150). Benefit with ABCP vs BCP extended to key subgroups, including pts with baseline (BL) liver mets, which is a poor prognostic factor in metastatic NSCLC. S1400I enrolled pts who were not eligible for a biomarker-matched sub-study.

**Methods:** 1202 ITT pts were randomized 1:1:1 to receive ABCP, ACP, or BCP. Doses were: A, 1200 mg; B, 15 mg/kg; C, AUC 6 mg/mL/min; P, 200 mg/m². Co-primary endpoints were OS and investigator-assessed PFS in ITT-wild-type pts. Exploratory analyses included efficacy and safety in pts with liver mets. **Results:** The data capture ≥ 20-mo follow-up in ITT pts (data cutoff: Jan 22, 2018). 162 pts had BL liver mets (ABCP: n = 52, ACP: n = 53; BCP: n = 57), with a median of 3 metastatic sites and median BL tumor SLD of 109 mm (range, 10-249). BL characteristics in these pts were generally balanced across study arms. ABCP improved OS (HR 0.73; 95% CI 0.57-0.93) and mPFS (2.7 mo; 95% CI 2.3-3.1) compared to ACP and BCP arms, respectively. Conclusions: ABCP reduced the risk of death in pts with liver mets by 28% vs BCP and may represent an important new treatment option for this population. Clinical trial information: NCT02366143.

9014 Poster Discussion Session; Displayed in Poster Session (Board #337), Sun, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-6:00 PM

A phase III randomized study of nivolumab plus ipilimumab versus nivolumab for previously treated patients with stage IV squamous cell lung cancer and no matching biomarker (Lung-MAP Sub-Study S1400I, NCT02785952).

**First Author:** Lyudmila Bazhenova, University of California, San Diego, La Jolla, CA

**Background:** Lung-MAP is a master protocol for patients (pts) with stage IV previously treated SqNSCLC. S1400I enrolled pts who were not eligible for a biomarker-matched sub-study. S1400I is phase III randomized trial for immunotherapy-naive patients with ECOC O-1 not selected by PD-L1 expression. Pts were assigned 1:1 to nivolumab and ipilimumab (N+I) vs nivolumab (N). N was given at 3 mg/kg q 2w, I was given at 1 mg/kg q 6w. The trial information: NCT02578680.

**Methods:** 275 pts with measurable disease at BL liver mets in IMpower150. Methods: 1:202 ITT pts were randomized 1:1:1 to receive ABCP, ACP, or BCP. Doses were: A, 1200 mg; B, 15 mg/kg; C, AUC 6 mg/mL/min; P, 200 mg/m². Co-primary endpoints were OS and investigator-assessed PFS in ITT-wild-type pts. Exploratory analyses included efficacy and safety in pts with liver mets. Results: The data capture ≥ 20-mo follow-up in ITT pts (data cutoff: Jan 22, 2018). 162 pts had BL liver mets (ABCP: n = 52, ACP: n = 53; BCP: n = 57), with a median of 3 metastatic sites and median BL tumor SLD of 109 mm (range, 10-249). BL characteristics in these pts were generally balanced across study arms. ABCP improved OS (HR 0.73; 95% CI 0.57-0.93) and mPFS (2.7 mo; 95% CI 2.3-3.1) compared to ACP and BCP arms, respectively. Conclusions: ABCP reduced the risk of death in pts with liver mets by 28% vs BCP and may represent an important new treatment option for this population. Clinical trial information: NCT02366143.

9013 Poster Discussion Session; Displayed in Poster Session (Board #336), Sun, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-6:00 PM

KEYNOTE-189: Updated OS and progression after the next line of therapy (PFS2) with pembrolizumab (pembro) plus chemo with pemetrexed and platinum vs placebo plus chemo for metastatic nonsquamous NSCLC. **First Author:** Shirish M. Gadgeel, Karmanos Cancer Institute (currently at University of Michigan, Ann Arbor, MI, USA), Detroit, MI

**Background:** Pembro + chemo significantly improved OS and PFS over chemo alone and has manageable safety as 1L therapy for metastatic nonsquamous NSCLC, in the KEYNOTE-189 study (NCT02578680). The benefit was observed irrespective of PD-L1 TPS. We present updated OS based on longer follow-up and, for the first time, PFS2. Methods: Eligible pts were randomized 2:1 to pembro (n = 410) or placebo (n = 206) + pemetrexed or carbo and cisplatin for 4 cycles followed by pembro or placebo for up to 35 cycles of maintenance pembro. Pts in the chemo arm could crossover to pembro alone upon PD. Poststudy antitumor therapy and outcomes were collected. PFS2 was defined as time from randomization to PD per investigator after start of 2L therapy or death, whichever occurred first. There was no multiplicity adjustment, and all P values are nominal. Data cutoff was 21 Sep 2018. Results: With 18.7-mo median follow-up, pembro + chemo continued to provide longer OS (HR 0.56 [95% CI 0.45-0.70], P < .00001; median 22.0 mo vs 10.7 mo) and PFS (HR 0.48 [95% CI 0.40-0.58], P < .00001). Benefit was seen in all PD-L1 TPS groups (Table). 2L+ therapy was received by 45% in the pembro + chemo arm and 59% (54% 2L+ immunotherapy) in the placebo + chemo arm. PFS2 was longer for 1L pembro + chemo (HR 0.49 [95% CI 0.40-0.59], P < .00001; median 17.0 mo vs 9.0 mo), with no difference by TPS (Table). Conclusions: 1L pembro + pemetrexed/platinum continued to show substantial OS benefit in metastatic nonsquamous NSCLC, regardless of PD-L1 TPS and despite 54% of pts in the placebo + chemo arm receiving subsequent immunotherapy. Median OS, PFS, and PFS2 were approximately doubled with pembro + chemo. These data confirm that pembro should be given as part of 1L therapy to maximize outcomes in both PD-L1 expressing and PD-L1 non-expressing NSCLC. Clinical trial information: NCT02578680.

LBA9015 Poster Discussion Session; Displayed in Poster Session (Board #338), Sun, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-6:00 PM

Five-year long-term overall survival for patients with advanced NSCLC treated with pembrolizumab: Results from KEYNOTE-001. **First Author:** Edward B. Garon, David Geffen School of Medicine at University of California, Los Angeles, Santa Monica, CA

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Saturday, June 1. Onsite at the Meeting, this abstract will be printed in the Sunday edition of ASCO Daily News.
Blood tumor mutational burden (bTMB) and tumor PD-L1 as predictive biomarkers of survival in MYSTIC: First-line durvalumab (D) ± tremelimumab (T) versus chemotherapy (CT) in metastatic (m) NSCLC. First Author: Naiyer A. Rizvi, Columbia University Medical Center, New York, NY

Background: MYSTIC, an open-label, Ph3 trial of first-line D (anti-PD-L1) mab (T) versus chemotherapy (CT) in metastatic (m) NSCLC.

Methods: Immunotherapy/CT-naïve pts with mNSCLC were randomized (1:1:1) to D, D+T or CT. bTMB levels (mut/Mb) were evaluated with the GuardantOMNI platform (Guardant Health), and PD-L1 TC expression with the VENTANA PD-L1 (SP263) IHC assay.

Results: D improved OS in CT pts with PD-L1 TC ≥ 25% across bTMB levels (PD-L1 TC ≥ 25%bTMB ≥ 20 HR 0.79 [95% CI 0.45, 1.39]; PD-L1 TC ≥ 25%bTMB < 20 HR 0.64 [95% CI 0.45, 0.90]). In contrast, D+T improved OS vs CT in pts with bTMB ≥ 20 across different PD-L1 TC expression levels (Table; PD-L1 TC ≥ 25%bTMB ≥ 20 HR 0.44 [95% CI 0.29, 0.64]; PD-L1 TC < 1%bTMB ≥ 20 HR 0.42 [95% CI 0.17, 0.97]).

Conclusions: These exploratory analyses from MYSTIC support PD-L1 TC expression as an appropriate predictive biomarker for OS with D vs CT, while both biomarkers appear to be independent and both may be important for mNSCLC clinical courses. PD-L1 in LN biopsies may not be reliable to predict clinical benefit for ICIs in NSCLC. Repeat biopsy and PD-L1 staining should be considered if only remote tissues, particularly LN biopsies are available.

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Early efficacy of plasma EGFR mutations as a predictor of response to osimertinib and comparator EGFR-TKIs in the FLAURA trial. First Author: Zhi Huang, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China

Background: In the Phase III FLAURA trial (NCT02296125), osimertinib, a third-generation EGFR-TKI, showed superior efficacy to comparator EGFR-TKIs as first-line treatment for EGFR mutation-positive (EGFRm) advanced NSCLC. In an exploratory analysis, we investigated clinical outcomes associated with detection of plasma EGFRm at 3 or 6 weeks (wk) after start of treatment. Methods: Treatment-naïve patients (pts) with EGFRm (ex19del or L858R) locally advanced or metastatic NSCLC were randomized 1:1 to receive osimertinib 80 mg once daily (QD) or comparator EGFR-TKIs (gefitinib 250 mg QD or erlotinib 150 mg QD). Plasma EGFR mutation analysis was conducted at baseline (BL), wks 3 and 6 by droplet digital PCR. Clearance was defined as undetectable levels of EGFRm in cDNA at wks 3/6. Of these, 342/489 (70%) pts; osimertinib: 168/244; comparator: 174/245) had detectable BL EGFRm and were included in this analysis. See table. Results: Clearance of plasma EGFRm after 3/6 wks of EGFR-TKI therapy was associated with a numerical improvement in PFS. This efficacy of osimertinib was superior to comparator EGFR-TKIs regardless of clearance status. Clinical trial information: NCT02296125.
Brigatinib (BRG) versus crizotinib (CRZ) in Asian versus non-Asian patients (pts) in the phase III ALTA-1L trial.

**Background:** We report an analysis of BRG vs CRZ in Asian versus non-Asian pts with ALK inhibitor-naive, ALK+ NSCLC from ALTA-1L (NCT02737501).

**Methods:** Pts were randomized 1:1 to BRG 180 mg QD (7-day lead-in at 90 mg) or CRZ 250 mg BID. Primary endpoint: blinded independent review committee (BIRC)-assessed PFS (RECIST v1.1). Secondary endpoints: BIRC-assessed ORR, intracranial (i) ORR, and IFS. Results: 275 pts were randomized; 108 Asian (BRG/CRZ, n = 59/49), 167 non-Asian (n = 78/89); median age: Asian, 55/56 y; non-Asian, 60/60 y. 32/24% of Asians vs 22/28% of non-Asians had prior chemotherapy for advanced disease; 36/33% vs 24/28% had baseline CNS metastases. As of 19 Feb 2018, median follow-up was 10.1-10.0 mo (BRG/CRZ) in Asians vs 11.0-9.0 mo in non-Asians, with 12 vs 20 PFS events in Asians and 24 vs 43 in non-Asians. In Asians, median BIRC-assessed PFS (mo) was not reached (NR; 95% CI 11.2-19.2) with BRG vs 11.9 (9.2-19.2) with CRZ (HR 0.41 [95% CI 0.20-0.86]; log-rank P = 0.0261); in non-Asians, BRG was NR (95% CI 7.3-19.2) with CRZ (HR 0.54 [0.33-0.90]; log-rank P = 0.0132) (Table). AE profile of each drug was similar in Asians vs non-Asians.

**Conclusions:** Immunotherapy use in Stage IV NSCLC after SBRT has increased over time, mostly in patients with adenocarcinoma and in the setting of chemotherapy. In this analysis, outcomes were improved when immunotherapy was given at least three weeks after start of SBRT.

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Acquired resistance to MET inhibition in MET driven NSCLC. First Author: Richard Riedel, Lung Cancer Group Cologne, University of Cologne, Faculty of Medicine and University Hospital of Cologne, Dept. for Internal Medicine, Cologne, Germany

Background: MET mutations (METex14), amplifications or translocations can activate oncogenic signaling in lung cancer and are sensitive to MET inhibition. Acquired resistance to therapy with MET tyrosine kinase inhibitors (TKI) occurs inevitably. Methods: Between 2015 and 2018, eight patients with MET-amplified or translocated MET-driven NSCLC were treated with capmatinib as single agent at our site. Rebiopsy samples from five patients were analyzed by NGS and fluorescence-in-situ hybridization (FISH) at time of progression. Results: Of the five patients with rebiopsy samples at time of progression, two had initially a MET amplification (one patient with low-level and one patient with high-level amplification), two patients had a METex14 and one patient had a KIF5B-MET fusion. Patient 1 (low-level MET amplification) showed a partial response to crizotinib. The crizotinib revealed an acquired KRAS mutation as a potential mechanism of resistance. Patient 2 (high-level MET amplification) showed stable disease as best response to capmatinib and patient 3 (METex14) showed a partial response to capmatinib. Both patients developed acquired HER2 amplifications. Patient 4 (METex14) showed initially a partial response to crizotinib. The crizotinib sample revealed an acquired MET kinase domain mutation (p.D1246N). As preclinical findings suggested that D1246N confers resistance to type I MET inhibitors but remains sensitive to type II inhibitors, cabozantinib was started. A CT six weeks after therapy initiation showed progressive disease. Patient 5 (KIF5B-MET) had a partial response to crizotinib. An acquired MET p.Y1248H mutation was found at time of progression. Therapy was changed to cabozantinib. A new CT scan is pending. Conclusions: Resistance to MET inhibition is heterogeneous with on- and off-target-mechanisms occurring. We found HER2 amplification as a potential new bypass mechanism. The MET mutation D1246N conferred resistance to type I and type II inhibitors. We describe the first case of an acquired mutation of the MET tyrosine kinase domain in a patient with an oncogenic MET fusion. Further investigations are needed to collect comprehensive data to understand resistance mechanisms in MET inhibition and to develop novel therapeutic strategies.

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Background: BPI-7711 is a 3rd generation irreversible EGFR-TKI that is selectively against EGFR TKI-sensitizing mutations and the T790M resistance mutations. We are conducting a phase I study to determine the safety and efficacy of BPI-7711 in patients with advanced or recurrent NSCLC. Methods: NSCLC patients harboring EGFR mutations who had progressed after disease progression after 1st generation EGFR-TKI treatment and with EGFRm+T790M+ confirmed by central lab were enrolled in the multicenter trial (NCT03386955) into “3+3 dose escalation or expansion cohorts. BPI-7711 was orally administered at doses of 30–240 mg in capsules. Patients in dose-escalation cohorts firstly received a single dose of BPI-7711 followed by a 7-day pharmacokinetic (PK) evaluation period then received the same dose daily until disease progression or intolerable toxicity(ies) per CTCAE V4.03. Treatment efficacy per RECIST 1.1 was evaluated every 6 weeks since daily treatment commencement. Once efficacy was observed in a dose, its expansion cohort was opened to enroll patients. Results: As of 23 December 2018, 82 patients (median age 55, 27 males, 55 females) were enrolled into 5 dose escalation cohorts (30/60/120/180/240 mg) and 4 dose expansion cohorts (30/60/120/180 mg). No DLT was observed and MTD was not reached. For all safety-evaluable patients, most common treatment-related AEs (TRAEs) were PTED (10.7%), and all were Grade 1 or 2. Grade 3-4 TEAEs were occurred in 8.0% of patients, and 4.0% of them were treatment-related per investigators’ judgment. SARs occurred in 4.1% of patients across treatment-related. For all efficacy-evaluable patients, the overall ORR of all doses was 54.5% (30/55) including 1.8% CR and 52.7% PR. The disease control rate (DCR) was 96.4%. For patients in 120/180 mg cohorts, the ORR was 64.1% (25/39) and DCR was 97.4%. PK analyses showed BPI-7711 exposure increased in a proportionally manner from 30 to 180 mg after single and multiple doses. Conclusions: BPI-7711 was well tolerated and highly effective in acquired T790M+ NSCLC patients. Phase II trials are under preparation. Clinical trial information: NCT03386955.

9036 Poster Session (Board #359), Sun, 8:00 AM-11:00 AM

SHERLOC: A phase 2 study of MM-121 plus docetaxel versus docetaxel alone in patients with heregrulin (HRG) positive non-small cell lung cancer (NSCLC). First Author: Lecia V. Sequist, Massachusetts General Hospital Cancer Center/Harvard Medical School, Boston, MA

Background: Seribantumab (MM-121) is a human monoclonal IgG2 anti-body that blocks the HRG domain of HER3. Preclinical data suggest that seribantumab reverses HRG mediated drug resistance across multiple cancer models. In prior retrospective analyses, addition of seribantumab to standard of care (SOC) plus docetaxel led to improved outcomes in patients with HRG + adenocarcinoma of the lung. Archival or pre-treatment tumor samples were assessed for HRG+ by RNA in situ hybridization. Eligibility criteria included prior platinum-based therapy for advanced disease with ≥ 2 total prior lines of therapy (prior IO was allowed) and no EGFR or ALK mutations. Pts were randomized 2:1 to receive seribantumab 3000 mg/docetaxel 75 mg IV q3w (experimental); or docetaxel 75 mg IV q3w alone (control). The primary endpoint was PFS. Key secondary endpoints were overall survival (OS), objective response rate (ORR), and adverse event (AEs) profile. Results: At a pre-specified interim analysis of 75% of total PFS events, 108 pts were enrolled (exp n = 71, control n = 37). Median age was 62y (range 34-83y); female 34%; one prior treatment only 39%. Median PFS was 3.0m for exp and 4.0m for control, HR = 1.66m (p = 0.084). Median OS was 7.9m for exp and 8.4m for control, HR = 1.50 (p = 0.235). ORR was 19.7% for exp and 5.6% for control (p = 0.052). Serious AEs were more frequent in the exp arm (40.8%) vs control (24.3%). Most common treatment emergent AEs (TEAEs) in the exp arm were diarrhea (47%), fatigue (37%), and neutropenia (27%). Based on a determination of futility at interim analysis, the study was terminated early. Conclusions: Seribantumab failed to improve PFS when added to docetaxel among previously treated advanced HRG+ NSCLC pts. A higher response rate and a higher incidence of TEAEs were observed in the exp arm. No further development of seribantumab is planned in NSCLC. Clinical trial information: NCT02387216.

9037 Poster Session (Board #356), Sun, 8:00 AM-11:00 AM

Lazertinib, a 3rd generation EGFR-TKI, in patients with EGFR-TKI resistant NSCLC: Updated results of phase II study. First Author: Myung-Ju Ahn, Department of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: Lazertinib (YH25448) is a highly mutant-selective, irreversible 3rd-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that targets the activating EGFR mutations (Del19 and L858R), as well as the T790M mutation, while sparing wild type. We report the updated results from a Phase II study of lazertinib (NCT03046992). Methods: Patients with advanced and metastatic NSCLC who had progressed after treatment with standard EGFR-TKIs with/without asymptomatic brain metastases (BM) were enrolled in an open-label, multicenter, phase IIII study with dose-escalation and expansion cohorts. Lazertinib was administered once daily at doses between 20 to 320 mg in a 21-day cycle. Patients were assessed for safety, tolerability and efficacy. T790M mutation was required in the dose-expansion cohorts. Results: As of 26 Nov 2018, a total of 127 patients were enrolled. The dose-escalation cohort included 38 patients administered with 20 to 320 mg across 7 dose levels, and 89 patients in the dose-expansion cohort were administered with 40 to 240 mg across 5 dose levels. No dose-limiting toxicities were observed. The median duration of treatment was 9.7 months and 58 patients are still ongoing. The objective response rate (ORR) was 60% in all patients, 64% in T790M+ patients, and 37% in T790M- patients by investigators assessment. In BM patients with measurable lesion (n = 14), the intracranial ORR was 50%. The median progression-free survival (PFS) was 8.1 months in all patients, 9.5 months in T790M+ patients, and 5.4 months in T790M- patients. Subgroup analysis showed that ORR was 65% and PFS was 12.2 months in T790M+ patients with ≥ 120 mg (n = 62). The most common treatment-emergent adverse events (TEAEs) were pyrexia (27%), rash (24%), constipation (20%), decreased appetite (19%) and diarrhea (14%). TEAEs leading to dose discontinuation were observed in 3% of patients. Drug-related TEAEs of grade ≥ 3 was observed in 3% of patients. Conclusions: Lazertinib is well-tolerated with promising systemic and intracranial antitumor activity in EGFR T790M+ NSCLC patients. Dose extension cohorts in the 1st and 2nd line settings are underway at 240 mg dose. Clinical trial information: NCT03046992.
9038 Poster Session (Board #361), Sun, 8:00 AM-11:00 AM
The impact of sequential therapy of crizotinib followed by alectinib: Real-world data analysis of 9040 ALK-inhibitor naïve patients with NSCLC harboring ALK-rearrangement (WJOG101G1L). First Author: Kentaro Ito, Matsusaka Municipal Hospital, Matsusaka City, Mie, Japan
Background: Previous clinical trials demonstrated that alectinib (ALEC) had a longer time-to-progression than crizotinib (CRZ) in 1st-line settings. Information on long-term overall survival (OS), however, is still limited with a few studies having reported that the sequential strategy of “CRZ followed by other ALK-inhibitor” can provide extended OS. In Japan, ALEC was approved for 1st-line setting and was used earlier in other countries. Methods: This study evaluated the clinical data of ALK-rearranged NSCLC patients who received CRZ or ALEC between May 2012 and Dec 2016. Patients were divided into two groups according to the first-administered ALK inhibitor, the CRZ or ALEC group. In order to evaluate the efficacy of the sequential strategy of “CRZ followed by ALEC,” the combined time to treatment failure (TTF) was calculated in the CRZ group as defined by the sum of the “TTF of CRZ” plus the “TTF of ALEC” if patients were treated with ALEC followed by CRZ. In the ALEC group, the “TTF of ALEC” was calculated. The primary endpoint is the comparison between the combined TTF in the CRZ group with the TTF in the ALEC group. Results: Of 964 patients enrolled across Japan, 95% of the patients were female; and 95% had adenocarcinoma. There were 535/505 patients in the CRZ/ALEC group. In the CRZ group, 282 patients received ALEC after CRZ failure. The combined TTF in the CRZ group was significantly longer than TTF in the CRZ group. Median OS was 34.5 months vs. not reached; HR 1.048 [95%CI;0.758-1.451]; P: 0.7770. In the whole population, the CRZ group had a significantly shorter OS than the ALEC group; median, 53.6 mo vs not reached HR, 1.821 [95% CI;1.372-2.415]; P: <0.0001. Conclusions: The combined TTF in the CRZ group was significantly longer than TTF in the ALEC group, however, OS benefit of sequential therapy of CRZ followed by ALEC was not shown. Clinical trial information: UMIN000028605.

9039 Poster Session (Board #362), Sun, 8:00 AM-11:00 AM
Dendritic-cell vaccine (DCVAC) with first-line chemotherapy in patients with stage IV NSCLC: Final analysis of phase II, open label, randomized, multicenter trial. First Author: Louis Holtz, Thomas Jefferson University Hospital, Philadelphia, PA, USA
Background: Immunotherapy aiming the induction of tumor cell specific immune responses controlling the tumor growth, has emerged as a promising treatment modality in lung cancer (LuCa). Autologous DCVAC can present tumor antigens to elicit a durable immune response. We hypothesized that adding DCVAC to the standard of care chemotherapy (c) could prolong overall survival (OS) and progression-free survival (PFS). Methods: This study evaluated the efficacy and safety of DCVAC/LuCa (active cellular immunotherapy based on dendritic cells) concomitantly added to c (carboplatin/paclitaxel) - Arm A (A) vs DCVAC/LuCa + immunomodulators (IFN-α and hydroxychloroquine) - Arm B (B) vs c + ct - Arm C (C) in NSCLC patients (pts). Randomization 1:1:1 pts in A and B received up to 15 doses of DCVAC, ct was given 4-6 cycles in A and C. Stage IV NSCLC was confirmed historically or cytologically, ECOG 0-1 pts were eligible. Stratification was done by histology subtype and smoking history. Primary efficacy analysis compared A vs C only as enrollment to B was closed early based on Sponsor’s assessment of further development potential, there were no safety concerns or signals. Results: 112 pts at 12 sites were randomized (A/45 B/29 C/38). Patients characteristics were comparable across the study groups with the exception of gender (mf, %: 65/35 A and 74/26 C and smoking history (75 % of smokers in A, 97 % in C). Median follow up time was 25.8 months, range 0.1-41.8. Median OS was 15.5 months in A compared to 6.2 months in C, hazard ratio (HR) 0.55, p-value 0.0232, 95% CI [0.33, 0.93], death median 77. Median PFS was 6.2 months vs. not reached (C), 4.4 months vs. not reached in A; HR 0.54, p-value 0.0356, 95% CI [0.33, 0.89], death median 46 months. Conclusion: A significant benefit of sequential therapy of CRZ followed by ALEC was not shown. Further studies are warranted to confirm the efficacy of P in pts with NSCLC with CDKN2A loss or mutation. Clinical trial information: NCT02693535.
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Poster Session (Board #370), Sun, 8:00 AM-11:00 AM

Variation in the assessment of immune-related adverse event occurrence, grade, and timing. First Author: David Hsieh, Univ of Texas Southwestern Med School, Dallas, TX

Background: Accurate assessment of treatment toxicity is critical for patient safety, balancing clinical utility, and understanding treatment impact. Given their unpredictability and heterogeneity, immune-related adverse events (irAEs) may be particularly challenging to ascertain. Our objective was to evaluate the agreement between clinicians on the occurrence, grade, and timing of irAEs, and elucidate determinants of discordance.

Methods: We performed a retrospective cohort study of 52 patients with metastatic lung cancer treated with immune checkpoint inhibitors at a National Cancer Institute-designated comprehensive cancer center. Two medical oncologist observers used algorithm-driven manual chart review to characterize eight well-described irAEs (adrenal insufficiency, colitis, hepatitis, hyperthyroidism, hypophysitis, hypothyroidism, pneumonitis, rash). Inter-rater agreement for incidence, severity, and timing of irAEs was determined using Cohen’s kappa coefficient (κ) and weighted κ with linear weights. Results: The incidence of irAEs ranged from 4-35% for observer 1 and 6-27% for observer 2, while aggregate incidence rates ranged from 8% (hypophysitis) to 40% (pneumonitis). Inter-rater agreement was generally limited with κ ≥ 0.37 [hypophysitis]-0.8 [hypothyroidism]). Weighted κ similarly showed limited or poor agreement for most irAE grades (κ ≤ 0.31-0.75). Differences in the assessment of irAE time of onset ranged from 5-188 days. Rates of discordance were greater for grade 1 (39%) and grade 2 (41%) irAEs than for grades 3-4 (20%) irAEs. POVAR analysis showed that longer treatment duration (OR 4.8, P = 0.02) and a high Charlson Comorbidity Index (OR 4.09, P = 0.03) were significantly associated with discordant irAE assessment.

Conclusions: Inter-rater reliability varied among irAEs and consistently showed poor agreement for the incidence, severity, and timing of irAEs. Agreement was lower for irAEs with distinct laboratory-based definitions (e.g., hypothyroidism), higher-grade irAEs, and irAEs in patients with fewer comorbidities and shorter immunotherapy duration. These findings have implications in the clinical management of patients receiving immunotherapy and in the reporting of immunotherapy clinical trials.

Poster Session (Board #371), Sun, 8:00 AM-11:00 AM

Clonal evolution and osimertinib resistance mechanisms identified by whole exome and transcriptome sequencing in EGFR mutant NSCLC. First Author: Nitin Roper, Thoracic and GI Malignancies Branch, COR, NCI, NIH, Bethesda, MD

Background: Osimertinib, a 3rd generation EGFR TKI, has been approved for treatment naïve patients (pts) with metastatic EGFR mutant NSCLC. Mechanisms of resistance to osimertinib are emerging from limited studies using targeted sequencing platforms. Methods: We performed whole exome (WES) and RNA-sequencing of osimertinib resistant tumors of EGFR-mutant NSCLC pts treated in a prospective clinical trial (NCT02759835). Treatment naïve EGFR mutant pts or pts with T790M-positive NSCLC after EGFR-TKI treatment receive osimertinib. Upon progression, pts with ≥ 5 progressing sites undergo local ablative therapy (LAT; surgery, radiation, RFA) and resume osimertinib. We analyzed paired pre-treatment and post-progression tumors in 10 patients and post-progression tumors in 3 additional patients and investigated intra- and inter-metastatic tumor heterogeneity using tumors procured from LAT surgeries and autopsies. Results: Acquired, focal copy number amplifications (CNA) of oncogenes occurred in the majority of patients (54%, n = 7/13) whereas acquired osimertinib resistance mutation EGFR C797S was less common (15%, n = 2/13). Early progression on osimertinib (< 12 months PFS) in treatment naïve pts was associated with acquired, focal CNA. Despite pre-existing EGFR amplification, further amplification of the mutant allele of EGFR was the most common focal CNA (33%, n = 3/9). Other oncogenes amplified in resistant tumors include MET, Kras, ERBB2 and YES1. CD274 (PD-L1) amplification occurred as the only putative mechanism of resistance in a pt without prior EGFR-TKI treatment. Using RNA-seq, we identified a pt who retained NSCLC histology, but upregulated genes associated with neuroendocrine differentiation upon osimertinib resistance. Clonal evolutionary analysis using WES of prospectively collected sensitive and resistant tumor tissue, including at autopsy is underway.

Conclusions: Unbiased WES and transcriptome sequencing revealed heterogeneity, clonal evolution and novel osimertinib resistance mechanisms. Majority of pts had two or more resistance mechanisms suggesting the requirement of combination therapies to overcome resistance. Clinical trial nct02759835.

Poster Session (Board #373), Sun, 8:00 AM-11:00 AM

Evaluation of clonal hematopoiesis in late stage NSCLC using a next-generation sequencing panel targeting cancer genes. First Author: Stephanie J. Yaung, Roche Sequencing Solutions, Inc., Pleasanton, CA

Background: Somatic mutations derived from the expansion of clonal populations of blood cells (clonal hematopoiesis of indeterminate potential, or CHIP) may be detected in sequencing of cell-free DNA (cfDNA) samples. We evaluated the potential implications of CHIP in targeted sequencing of lung cancer plasma samples using matched peripheral blood mononuclear cell (PBMC) DNA. Methods: We identified CHIP mutations in each patient’s matched PBMC and ctDNA samples using the AVENIO ctDNA Surveillance Kit (For Research Use Only, a 198-kb next-generation sequencing panel targeting cancer genes. Evaluation of clonal hematopoiesis in late stage NSCLC using a next-generation sequencing panel targeting cancer genes. Plasma samples from subsequent cycles of therapy (C2D2, C3D3, and C4D4) were also sequenced with the same panel. Using median input amounts of 22.8 ng cfDNA and 50 ng PBMC DNA, we obtained median deduplicated depths of 5413 and 5070, respectively. Results: In C1D1 cfDNA, a median of 120 single nucleotide variants were detected per sample, with 5.13% of variants not identified in matched PBMC (i.e., putative tumor-derived somatic variants) versus 94.87% of variants identified in matched PBMC (i.e., germline or CHIP variants). While the majority of PBMC-matched variants were SNPs with allele frequency (AF) around 50% or 100% as expected, there was a median of 1 (range 0-8) PBMC-matched cfDNA variants per sample with AF below 10%. Consistent with CHIP, the number of PBMC-matched cfDNA variants per subject below AF 10% were positively associated with age (p-value = 0.0145), and TP53 was the most frequently mutated gene. We found similar results in plasma samples from subsequent cycles. Results: Plasma and PBMC sequencing analysis identified potential mutations derived from CHIP. However, 39% of cfDNA samples had zero potential CHIP mutations identified in the study, possibly due to the specific regions targeted by the AVENIO assay. While this study suggests the utility of small percent of variants derived from CHIP in plasma samples, clinical utility of AVENIO Surveillance panel in lung cancer are derived from CHIP, further studies are warranted to assess the impact and remove these variants.
First-in-phase 1 study of DS-1062a in patients with advanced solid tumors. 

**Background:** DS-1062a is a trophoblast cell-surface antigen 2 (TROP2)-targeting antibody drug conjugate. TROP2 is highly expressed in epithelial cancers, including non-small cell lung cancer (NSCLC). Overexpression of TROP2 may be associated with poor survival in some solid tumors. Preclinical studies showed promising antitumor activity of DS-1062a in mouse models with TROP2-positive tumors. Preliminary results are reported in the dose escalation part of this phase 1 study. Methods: This was a phase 1 study of DS-1062a in patients (pts) with advanced solid tumors in the US and Japan (NCT03401385). Adult (age ≥20 years in Japan or ≥18 years in US) pts with measurable disease per RECIST v1.1 and sufficient tumor tissue sample for TROP2 measurement were eligible. Pts were excluded if they had multiple primary malignancies or untreated brain metastases. Endpoints included safety, pharmacokinetics, and efficacy. Results: As of November 16, 2018, 22 pts with advanced NSCLC were treated with DS-1062a at doses of 0.27-mg/kg (n = 4), 0.5-mg/kg (n = 5), 1.0-mg/kg (n = 7), and 2.0-mg/kg (n = 6). Overall, mean (standard deviation) treatment duration and cumulative dose were 7.8 (4.1) weeks and 181.8 (141.4) mg, respectively, with a median of 2 (range 1–6) cycles initiated. The majority (n = 18; 81.8%) of pts had ≥1 treatment-emergent adverse event (TEAE). The most common TEAE, fatigue (n = 9), was the only grade ≥3 treatment-related TEAE (n = 1; 2.0-mg/kg). Serious TEAEs, reported in 9 pts in the 0.27-mg/kg (n = 2), 0.5-mg/kg (n = 1), and 2.0-mg/kg (n = 3) cohorts, were not treatment-related. TEAEs leading to discontinuation occurred in 1 pt in the 0.27-mg/kg cohort (pleural effusion; not treatment-related). One pt died due to progressive disease. Peak concentration (Cmax) and area under the curve from time 0 to last measurable concentration (AUClast) increases were generally dose proportional (2.0-mg/kg vs 1.0-mg/kg). Similar accuracy of ml-RECIST was observed in the validation cohort (accuracy CR/PR 84%, SD 82%, POD 91%). ml-RECIST estimated PFS by RECIST accurately predicting progression occurred at any time (86%) and exact progression date (65%). Date of progression was closely correlated (Pearson’s coefficient = 0.91, 95% CI 0.89-0.94, p < 0.001) in pts determined to be progressive by both methods. ml-RECIST may be tool to determine outcomes expeditiously and at scale for use in RWE studies, enabling more useful and reliable applications of large clinical databases.

First subsequent treatment after discontinuation of durvalumab in unsequestered, stage III NSCLC patients from PACIFIC. 

**Background:** In the phase 3 PACIFIC trial of unresectable, stage III NSCLC patients (pts) without progression after concurrent chemoradiotherapy (cCRT), durvalumab (durva) significantly improved PFS and OS with similar safety compared to placebo (pbo). We performed exploratory analyses to characterize first subsequent treatment (Tx) after discontinuation of durva. Methods: Pts with WHO PS 0/1 and any tumor PD-L1 status were randomized (2:1) 2–42 days after ≥2 cycles of platinum-based cCRT to durva or pbo. Time to first subsequent therapy or death (TFST) was assigned if a patient determined to have progressed by both methods. Similar accuracy of TFST was determined in overall survival compared to RECIST (HR = 0.19, p < 0.001 vs HR = 0.26, p < 0.001 respectively). Conclusions: Machine learning (m-RECIST) accurately estimates outcomes using imaging text reports. ml-RECIST may be tool to determine outcomes expeditiously and at scale for use in RWE studies, enabling more useful and reliable applications of large clinical databases.

First-in-phase 1 study of DS-1062a in patients with advanced solid tumors. 

**Background:** DS-1062a is a trophoblast cell-surface antigen 2 (TROP2)-targeting antibody drug conjugate. TROP2 is highly expressed in epithelial cancers, including non-small cell lung cancer (NSCLC). Overexpression of TROP2 may be associated with poor survival in some solid tumors. Preclinical studies showed promising antitumor activity of DS-1062a in mouse models with TROP2-positive tumors. Preliminary results are reported in the dose escalation part of this phase 1 study. Methods: This was a phase 1 study of DS-1062a in patients (pts) with advanced solid tumors in the US and Japan (NCT03401385). Adult (age ≥20 years in Japan or ≥18 years in US) pts with measurable disease per RECIST v1.1 and sufficient tumor tissue sample for TROP2 measurement were eligible. Pts were excluded if they had multiple primary malignancies or untreated brain metastases. Endpoints included safety, pharmacokinetics, and efficacy. Results: As of November 16, 2018, 22 pts with advanced NSCLC were treated with DS-1062a at doses of 0.27-mg/kg (n = 4), 0.5-mg/kg (n = 5), 1.0-mg/kg (n = 7), and 2.0-mg/kg (n = 6). Overall, mean (standard deviation) treatment duration and cumulative dose were 7.8 (4.1) weeks and 181.8 (141.4) mg, respectively, with a median of 2 (range 1–6) cycles initiated. The majority (n = 18; 81.8%) of pts had ≥1 treatment-emergent adverse event (TEAE). The most common TEAE, fatigue (n = 9), was the only grade ≥3 treatment-related TEAE (n = 1; 2.0-mg/kg). Serious TEAEs, reported in 9 pts in the 0.27-mg/kg (n = 2), 0.5-mg/kg (n = 1), and 2.0-mg/kg (n = 3) cohorts, were not treatment-related. TEAEs leading to discontinuation occurred in 1 pt in the 0.27-mg/kg cohort (pleural effusion; not treatment-related). One pt died due to progressive disease. Peak concentration (Cmax) and area under the curve from time 0 to last measurable concentration (AUClast) increases were generally dose proportional (2.0-mg/kg vs 1.0-mg/kg). Similar accuracy of ml-RECIST was observed in the validation cohort (accuracy CR/PR 84%, SD 82%, POD 91%). ml-RECIST estimated PFS by RECIST accurately predicting progression occurred at any time (86%) and exact progression date (65%). Date of progression was closely correlated (Pearson’s coefficient = 0.91, 95% CI 0.89-0.94, p < 0.001) in pts determined to be progressive by both methods. ml-RECIST may be tool to determine outcomes expeditiously and at scale for use in RWE studies, enabling more useful and reliable applications of large clinical databases.

Circulating free DNA as a prognostic biomarker in patients with advanced ALK+ NSCLC treated with alectinib from the global phase III ALEX trial. 

**Background:** Clinical studies showed promising antitumor activity of DS-1062a in mouse models with TROP2-positive tumors. Preliminary results are reported in the dose escalation part of this phase 1 study. Methods: This was a phase 1 study of DS-1062a in patients (pts) with advanced solid tumors in the US and Japan (NCT03401385). Adult (age ≥20 years in Japan or ≥18 years in US) pts with measurable disease per RECIST v1.1 and sufficient tumor tissue sample for TROP2 measurement were eligible. Pts were excluded if they had multiple primary malignancies or untreated brain metastases. Endpoints included safety, pharmacokinetics, and efficacy. Results: As of November 16, 2018, 22 pts with advanced NSCLC were treated with DS-1062a at doses of 0.27-mg/kg (n = 4), 0.5-mg/kg (n = 5), 1.0-mg/kg (n = 7), and 2.0-mg/kg (n = 6). Overall, mean (standard deviation) treatment duration and cumulative dose were 7.8 (4.1) weeks and 181.8 (141.4) mg, respectively, with a median of 2 (range 1–6) cycles initiated. The majority (n = 18; 81.8%) of pts had ≥1 treatment-emergent adverse event (TEAE). The most common TEAE, fatigue (n = 9), was the only grade ≥3 treatment-related TEAE (n = 1; 2.0-mg/kg). Serious TEAEs, reported in 9 pts in the 0.27-mg/kg (n = 2), 0.5-mg/kg (n = 1), and 2.0-mg/kg (n = 3) cohorts, were not treatment-related. TEAEs leading to discontinuation occurred in 1 pt in the 0.27-mg/kg cohort (pleural effusion; not treatment-related). One pt died due to progressive disease. Peak concentration (Cmax) and area under the curve from time 0 to last measurable concentration (AUClast) increases were generally dose proportional (2.0-mg/kg vs 1.0-mg/kg). Similar accuracy of ml-RECIST was observed in the validation cohort (accuracy CR/PR 84%, SD 82%, POD 90%; progression occurred 86%, progression date 72%). Accuracy was consistent when RECIST reads were performed prospectively as part of clinical trials vs retrospectively for standard of care treatment (e.g. crizotinib). ml-RECIST accurately estimated outcomes based on the results of a phase 1 study of DS-1062a was well tolerated at doses up to 2.0-mg/kg. An observable PR and multiple pts with SD warrant further evaluation of DS-1062a. The maximum tolerated dose has not been reached, and this study is ongoing. Clinical trial information: NCT03401385.

First subsequent treatment after discontinuation of durvalumab in unsequestered, stage III NSCLC patients from PACIFIC. 

**Background:** In the phase 3 PACIFIC trial of unresectable, stage III NSCLC patients (pts) without progression after concurrent chemoradiotherapy (cCRT), durvalumab (durva) significantly improved PFS and OS with similar safety compared to placebo (pbo). We performed exploratory analyses to characterize first subsequent treatment (Tx) after discontinuation of durva. Methods: Pts with WHO PS 0/1 and any tumor PD-L1 status were randomized (2:1) 1–42 days after ≥2 cycles of platinum-based cCRT to durva or pbo. Time to first subsequent therapy or death (TFST) was assigned if a patient determined to have progressed by both methods. Similar accuracy of TFST was determined in overall survival compared to RECIST (HR = 0.19, p < 0.001 vs HR = 0.26, p < 0.001 respectively). Conclusions: Machine learning (m-RECIST) accurately estimates outcomes using imaging text reports. ml-RECIST may be tool to determine outcomes expeditiously and at scale for use in RWE studies, enabling more useful and reliable applications of large clinical databases.
was a multi-center observational study in patients with treatment-naïve metastatic LUAC. Genotyping, with a clinically validated cfDNA assay (Guardian360) was performed at 3 time points: before start of treatment, at 2 w, and upon progression or at 12 months (mo). Oncoprints were constructed based on mutation status and variant allele frequency (VAF).

Results: 53 p with KRAS alterations were included. 36. male; median age 59; 46 current/ex-smokers; 64 received 1st line platinum-based chemotherapy (CT), 4 platinum-based CT plus bevacizumab, and 24% other or no therapy. 13 p had only KRAS m (K-only group), 25 p had KRAS + TP53 m (KP group), and 15 p had KRAS + STK11 plus or without TP53 m (KS group). Median progression-free survival was 3.5 mo for all 53, 4.8 mo for the K-only group, 4.4 mo for the KP group, and only 1.6 mo for the KS group (p = 0.0045 vs K-only). The median VAF for K-only, KP, and KS groups at EOS were 6.4%, 9.7%, and 46%, respectively. When looking at p with cfDNA analysis at the three time points, the following were observed: in the K-only group, 25% lost KRAS m at 2 w and 50% at EOS. 50% and 75% gained TP53 m, at 2 w and EOS, respectively. 10% gained STK11 m at the 2 time points. In the KS group, 33% lost KRAS m at the 2 time points. All and 33% lost STK11 m at 2 w and EOS, respectively. 60% gained TP53 m at the 2 time points. Conclusions: cfDNA is a marker of clinical progression in K-only or KP subgroups. For p with STK11 m, restoration of the STK11 function is warranted. Clinical trial information: NCT03248089.

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Osimertinib (Osi) plus necitumumab (Neci) in EGFR-mutant NSCLC: An ETCTN trial.

9055 Poster Session (Board #378), Sun, 8:00 AM-11:00 AM

Tracking plasma KRAS mutations (mu) in lung adenocarcinoma (LUAC) patients (p) and branching evolution.

First Author: Jillian Bracht, Pargaea Oncology, OR, QuintilesIMS Institute, Laboratory of Cellular and Molecular Biology, Barcelona, Spain

Background: KRAS m in LUAC p are recalcitrant to therapy. In mice models and p, STK11 m confer poor prognosis. Patients with KRAS, or KRAS with TP53 m, benefit from immunotherapy (IO). We used a cell free DNA (cfDNA) sequencing platform to sub-group 53 LUAC p with KRAS m from the Spanish Lung Liquid versus Invasive biopsy Program (SLLIP, NCT03248089), according to the coexistence of TP53 and STK11 m.

Methods: SLLIP was a multi-center observational study in patients with treatment-naïve metastatic LUAC. Genotyping, with a clinically validated cfDNA assay (Guardian360) was performed at 3 time points: before start of treatment, at 2 w, and upon progression or at 12 months (mo). Oncoprints were constructed based on mutation status and variant allele frequency (VAF).

Results: 53 p with KRAS alterations were included. 36. male; median age 59; 46 current/ex-smokers; 64 received 1st line platinum-based chemo-therapy (CT), 4 platinum-based CT plus bevacizumab, and 24% other or no therapy. 13 p had only KRAS m (K-only group), 25 p had KRAS + TP53 m (KP group), and 15 p had KRAS + STK11 m with or without TP53 m (KS group). Median progression-free survival was 3.5 mo for all 53, 4.8 mo for the K-only group, 4.4 mo for the KP group, and only 1.6 mo for the KS group (p = 0.0045 vs K-only). The median VAF for K-only, KP, and KS groups at EOS were 6.4%, 9.7%, and 46%, respectively. When looking at p with cfDNA analysis at the three time points, the following were observed: in the K-only group, 25% lost KRAS m at 2 w and 50% at EOS. 50% and 75% gained TP53 m, at 2 w and EOS, respectively. 10% gained STK11 m at the 2 time points. In the KS group, 33% lost KRAS m at the 2 time points. All and 33% lost STK11 m at 2 w and EOS, respectively. 60% gained TP53 m at the 2 time points. Conclusions: cfDNA is a marker of clinical progression in K-only or KP subgroups. For p with STK11 m, restoration of the STK11 function is warranted. Clinical trial information: NCT03248089.

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Impact of HER2 aberrations on EGFR-TKI treatment outcomes in lung tumors harboring EGFR mutations: A HER2-CS STUDY subset analysis.

First Author: Azie Azzouqa, Mayo Clinic, Jacksonville, FL

Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are a key treatment for EGFR-mutant non-small-cell lung carcinoma (NSCLC). To date, a biomarker to predict whether NSCLC will exhibit a short- or long-term response to first- or second-generation EGFR-TKIs has not been established for clinical use. Human epidermal growth factor receptor-2 (HER2) aberrations are mechanisms for acquired resistance to EGFR-TKIs; however, their impact on EGFR-TKI therapy outcomes in EGFR-mutant NSCLC has not yet been systematically evaluated.

Methods: Patients with advanced NSCLC were prospectively registered from more than 35 institutions (HER2-CS STUDY UMIN 000017063). EGFR mutations or anaplastic lymphoma kinase gene translocations were assessed at each institution using a commercially approved test. HER2 protein expression levels were determined by immunohistochemistry (IHC) using the Ventana I-VIEW PATHWAY anti-HER-2/neu (4B5). The IHC status scoring system applied to gastric cancer was used.

Results: Of 1,126 screened patients with NSCLC, 354 (31.8%) had EGFR-mutated tumors, and the HER2 protein statuses were as follows: IHC0 (n = 71, 26%), IHC1+ (n = 148, 53%), IHC2+ (n = 51, 18%), and IHC3+ (n = 7, 3%). The patients’ demographics were almost identical in those with lung tumors harboring EGFR mutations and HER2-CS/IHC2+/3+ (group F) or EGFR mutations and HER2-IHC0 (group N). The EGFR-TKI response rates were not different between these groups (Table). However, the group F showed significantly shorter time to EGFR-TKI treatment failure than group N (median 19.1 vs. 13.3 months; log rank p = 0.038).

Conclusions: These data from a large prospective cohort show that HER2 protein expression in EGFR-mutant NSCLC may have a negative impact on the effect of EGFR-TKIs. A clinical trial of EGFR HER2-TKIs (e.g., afatinib) is warranted for this population.
Anti-PD-1/PD-L1 to chemotherapy (CT) for this population in the first line with Non-Small-Cell-Lung-Cancer (NSCLC) that were PD-L1 negative or Clinical efficacy of single agent anti-PD-1/PD-L1 in patients

UCOG 93 (APHP), Sevran, France

less than 1%. $9061$ Poster Session (Board #384), Sun, 8:00 AM-11:00 AM

of PD-L1 expression testing inform the choice of first-line therapy, a sub-

Conclusions: PD-L1 expression testing was rapidly adopted following FDA approval of companion diagnostic testing for aNSCLC. Although the results of PD-L1 expression testing inform the choice of first-line therapy, a substantial proportion of patients are not tested prior to first line treatment.

First

9060 Poster Session (Board #383), Sun, 8:00 AM-11:00 AM

Therapeutic and prognostic impacts of specific gene alterations for squamous cell lung cancer: A result of nationwide genome screening in Japan (LC-SCRUM-Japan). First Author: Sho Ishikawa, Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan

Background: Various gene alterations occur during the development of squamous cell lung cancer (SqLC), but specific gene alterations for SqLC and their clinical significance remain unknown. Methods: In a nationwide genome screening project (LC-SCRUM-Japan), we have prospectively analyzed lung cancer patients for genetic alterations using a next-generation sequencing (NGS) system, Oncomine Comprehensive Assay, and have established a large-scale clinico-genomic database. Results: Since February 2013 to December 2018, a total of 6692 lung cancer patients (686 SqLCs, 5360 non-squamous non-small cell lung cancers (Non-sq) and 646 small cell lung cancers (SCLCs)) had been enrolled in the LC-SCRUM-Japan. The success rate of the NGS assay was 91%. Of 639 SqLCs analyzed, 274 (48%) had potentially targetable gene alterations, including 77 NFE2L2 (encoding NRF2) mut, 50 PI3KCA mut, 46 FGFR1 amp, 40 EGFRmut/amp, 36 PTPN11 mut, 23 KRAS mut, 6 AKT1 mut, 6 MET ex14skip, 5 ALK fusions, 2 FGFR3 fusions. Among the alterations detected, NFE2L2 mut and FGFR1 amp were significantly frequent in SqLC than Non-sq or SCLC (NFE2L2, 12.1% vs. 1.0% vs. 1.3%; p < 0.001, and FGFR1, 7.2% vs. 1.1% vs. 3.4%; p < 0.001). In advanced SqLC patients who received platinum-containing chemotherapies, the median progression-free survival (mPFS) was significantly shorter in NFE2L2-mutated patients (NRF2-type) than NFE2L2/ FGFR1-negative patients (Non-NF-type) (3.8 vs. 9.5 months, p = 0.003). Similarly, the mPFS of FGFR1-amplified patients (FGFR1-type) (3.5 months (95%CI, 1.5-4.9) tended to be shorter than that of Non-NF-type (p = 0.07), although the response rates were equivalent among the three types. NRF2-type also showed shorter overall survival (OS) than non-NF-type (median OS, 10.4 vs. 10.9 vs. 16.6 months (95%CI, 13.6-21.7) months, p = 0.10). Therapeutic efficacy of nivolumab or pembrolizumab was not different among these types in the current follow-up data. Conclusions: Our large scale genome screening identified specific gene alterations for SqLC and the alterations were associated with a less efficacy of chemotherapy and worse prognosis, suggesting the need for the development of genotype-directed therapeutic strategy for SqLC patients.

9061 Poster Session (Board #384), Sun, 8:00 AM-11:00 AM

Anti-PD-1/PD-L1 plus chemotherapy versus chemotherapy alone in first-line treatment for patients with metastatic NSCLC that are PD-L1 negative

First Author: Gregory J. Riely, Memorial Sloan Kettering Cancer Center, New York, NY

Background: In patients with advanced non-small cell lung cancer (aNSCLC) with non-squamous histology, treatment guidelines recommend molecular testing for EGFR mutations and first-line (1L) EGFR tyrosine kinase inhibitors (TKIs) in those with sensitizing EGFR mutations. We investigated real-world treatment patterns and outcomes in aNSCLC patients with EGFR sensitizing mutations from US community oncology clinics. Methods: The Flatiron Health electronic health record-derived database contains deidentified data from >55,000 aNSCLC patients. Our retrospective cohort included patients diagnosed from Jan-2014 to Mar-2018 who had a positive EGFR test prior to initiation of 1L therapy. Patients with EGFR T790M mutations were excluded. Demographics, clinical characteristics, treatment and survival outcomes were compared between patients receiving 1L EGFR TKIs vs other 1L anti-cancer therapies. Minimum follow-up after initiation of 1L therapy was 4 months. Results: 23,321 patients had non-squamous or NOS histology. Of those, 1107 had sensitizing EGFR mutations detected prior to 1L treatment (median age 70 years, 67% women, 58% Caucasian). 910 (82%) received EGFR TKIs and 197 (18%) received other 1L therapies (including chemotherapy, immunotherapy and anti-VEGF therapy). 2L treatment data were available for 519 patients: 317 (61%) received EGFR TKIs and 202 (39%) received other therapies. In the 1L setting, median treatment duration was longer for patients receiving EGFR TKIs than for those receiving other therapies (8 vs. 4 months, p = 0.55). Median overall survival (OS) was not affected by the type of 1L treatment (21 months vs 20 months, p = 0.55). Conclusions: Real-world examination of treatment patterns and outcomes in US community oncology clinics showed that nearly 20% of aNSCLC patients with non-squamous or NOS histology and EGFR sensitizing mutations prior to initiation of 1L therapy did not receive 1L EGFR TKIs. In those who did, guideline-concordant use of EGFR TKIs was associated with longer 1L treatment duration but no improvement in OS, supporting the generalizability of results from randomized clinical trials.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Characterization of 648 non-small cell lung cancer (NSCLC) cases with 28 unique HER2 exon 20 insertions. First Author: Sai-Hung Ignatius Ou, Chao Family Comprehensive Cancer Center, University of Washington, Seattle, WA.

Background: egfr and HER2 (ERBB2) exon 20 insertion (ex20ins) mutations represent a subset of driver alterations in NSCLC, which historically have largely not responded to available targeted therapies. Recently, inhibitors specifically targeting ex20ins have shown efficacy in the clinic. Previous studies have described the landscape of egfr ex20ins in NSCLC (PMID: 29891927), but similar descriptions of HER2 ex20ins are lacking. Methods: Hybrid-capture-based comprehensive genome profiling (COP) was performed on 39,644 tissue and 4,062 blood-based circulating tumor DNA (ctDNA) samples from 43,706 unique patients with advanced NSCLC. Tumor mutational burden (TMB) was determined on 0.8-1.1 Mbp of sequenced DNA for tissue samples and reported as mutations/Mb. Results: HER2 ex20ins were detected in 1.5% (648/43,706) of NSCLC cases (614 tissue and 34 ctDNA). HER2 ex20ins represented 35% (648/1,845) of HER2-altered NSCLCs overall, while 46% (483/1,045) of cases had HER2 amplification (≥5 copies), 17% (320/1,845) had a non-ex20ins HER2 short variant (SV; most commonly S310F in 84 cases and V659E in 29 cases), and 1.8% (34/1,845) had HER2 amplification + SV. There were 28 unique HER2 ex20ins including most commonly A775_G776insYVMA (69%, 450/648), G776_VC (12%, 76/648) and P780_Y781insGSP (8.6%, 56/648). Cases with HER2 ex20ins were significantly enriched for adenocarcinoma histology (89% vs 66%), female gender (64% vs 51%) and low TMB (95% vs 65% TMB < 10 mut/Mb) compared to those with SV (96%, 1,838/1,845) or V659E (82%, 1,756/2,133) or P780_Y781insGSP. HER2 amplification (7 median copies, range 5-39) co-occurred in 16% (103/648) of NSCLC cases. Prognostic significance of radiologic features of pneumonitis induced by anti-HER2-1 therapy. First Author: Satoshi Matanabe, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.

Background: Anti-HER2-1 therapy is now a standard treatment for patients with NSCLCs. Pneumonitis induced by immune-check point inhibitors is potentially fatal; however, some studies have shown that antitumor effects were enhanced in patients with pneumonitis. Although several radiologic patterns of pneumonitis induced by anti-HER2-1 therapy have been reported, the association between radiologic features and clinical outcomes, especially efficacy and duration of antitumor effects remains unclear. We retrospectively evaluated data of NSCLC patients treated in 1st to 3rd line with anti-HER2-1 antibodies (nivolumab or pembrolizumab) at Niigata Lung Cancer Treatment Group. Pneumonitis was diagnosed by the treating investigators. The chest CT scans of patients with pneumonitis were independently reviewed by one radiologist and two pulmonologists to classify pneumonitis into 5 subtypes: cryptogenic organizing pneumonia-like (COP), ground glass opacities (GGO), interstitial, hypersensitivity and pneumonitis not otherwise specified (NOS). Results: Of 231 patients who received anti-HER2-1 antibodies, pneumonitis developed in 33 patients (14.3%) at 7 institutions between January 2016 to October 2017. Of 33 patients with pneumonitis, the median age was 66 (range 45 to 82 years), 7 were female, 25 received nivolumab, and 8 received pembrolizumab. Sixteen patients were classified as GGO, 16 patients had COP-like appearance and one patient had NOS. The median survival time was significantly longer among patients with COP than among those with pneumonitis (median OS of 20 vs 13 months; HR 0.52; 95% CI 0.29-0.90). Similarly, patients with COP or GGO had a significantly longer survival time than those with pneumonitis classified as GGO. Radiologic features of pneumonitis may reflect clinical outcomes after anti-HER2-1 therapy.
ALK cornerstone of management of ALK-positive (ALK+) lung cancer. Each ALK

**Background:**

9068 Poster Session (Board #391), Sun, 8:00 AM-11:00 AM

Longitudinal analysis of plasma ALK mutations during treatment with next-generation ALK inhibitors. First Author: Ibiayi Dagogo-Jack, Massachusetts General Hospital, Boston, MA

**Results:**

Among 65 pts progressing on a 2nd-gen TKI, 49 (75%) had only received one 2nd-gen ALK TKI prior to analysis: n = 42 alec, n = 3 each brig, ceri, and n = 1 ensarin. We detected an ALK mutation in 42/65 (65%) specimens at relapse, among which ALK G1202R (32%) and I1171X (23%) were the most common. Sixteen (25%) pts had ≥2 ALK mutations at progression on a 2nd-gen TKI. Among 26 pts progressing on lorlatinib (all of whom had previously relapsed on a 2nd-gen ALK TKI), we identified ALK mutations in 20 (77%), including 14 (54%) with ≥2 ALK mutations. Detection of ≥2 ALK mutations was more common at relapse on lorlatinib compared to a 2nd-gen TKI (p = 0.013). To assess the evolution of ALK mutations during treatment with different TKIs, we analyzed serum plasma specimens from 20 pts treated with sequential 2nd- and 3rd-gen ALK TKIs. Among six pts who received alec followed by brigatinib, replas and new ALK mutations were identified (2 pts). Two pts received pre-lorlatinib brigatinib ALK mutations in two pts (one L1196M and one G1202R), expansion of pre-lorlatinib ALK mutations and 8 acquired ≥1 additional ALK mutations at lorlatinib progression. The most frequently acquired ALK mutation was D1203N in four of eight cases.

**Conclusions:** ALK resistance mutations are prevalent at relapse on next-generation ALK TKIs and increase with each successive generation of ALK TKIs. These findings suggest that sequential therapy with increasingly potent ALK TKIs may select for compound ALK mutants and/or fuel tumor heterogeneity.

9070 Poster Session (Board #383), Sun, 8:00 AM-11:00 AM

Time-to-treatment discontinuation (TTD) and real-world progression-free survival (rpWFS) as endpoints for comparative efficacy analysis between entrectinib trial and crizotinib real-world ROS1 fusion-positive (ROS1+) NSCLC patients. First Author: Robert Charles Doeebe, University of Colorado, Denver, CO

**Background:** Entrectinib is an oral tyrosine kinase inhibitor for ROS1+ NSCLC. Three phase 1/2 single-arm studies showed entrectinib efficacy in this population (Doebele WCLC 2018). Due to the rarity of ROS1+ pts generating direct comparative evidence in prospective randomized trials is difficult. We identified a retrospective real-world cohort of 39 ROS1+ NSCLC pts from electronic health records (EHR), to compare crizotinib, the current standard of care, to entrectinib as reported in clinical trials. Methods: Crizotinib-treated pts with advanced ROS1+ NSCLC diagnosed 1 Jan 2011 to 30 Jun 2018, were analyzed. We correlated TMB with clinico-pathological upper quartile of cohort distribution.

**Results:** We analyzed 53 entrectinib and 69 crizotinib ROS1+ NSCLC pts. Median weighted TTD: entrectinib, 14.0 mo (95% CI: 8.3–23.9); crizotinib, 8.8 mo (95% CI: 8.2–9.9). When rpWFS from crizotinib was compared to trial PFS, entrectinib had longer PFS vs crizotinib (weighted HR: 0.44; 95% CI: 0.27–0.74). Median OS with entrectinib was not reached (median follow-up: 15.0 mo); weighted median OS with crizotinib was 18.5 mo (95% CI: 15.1–19.9). Findings were consistent across multiple sensitivity analyses. Conclusions: Entrectinib was associated with longer TTD and PFS in ROS1+ NSCLC pts vs a matched real-world crizotinib population. Control populations derived from real-world cohorts can supplement evidence from clinical trials in settings where new standards of care are needed, but where limited data are available and randomization is not feasible.

9069 Poster Session (Board #392), Sun, 8:00 AM-11:00 AM

Clinical outcomes of EGFR+ and ROS1+ NSCLC pts treated with immune checkpoint inhibitors (ICIs). First Author: Zofia Piotrowska, Massachusetts General Hospital, Boston, MA

**Background:** ICIs have limited efficacy in EGFR+ NSCLC with ORR – 10% if PDL1 > 25% in ATLANTIC, yet ICIs are often used in later lines of therapy as pts and providers feel there may be little risk. The impacts of ICI in this setting are poorly understood. We describe our institutional experience of ICI use in EGFR+ NSCLC. Methods: MGH pts with advanced EGFR+ NSCLC treated with ICI (any line) were retrospectively reviewed for demographics, PD, treatment duration and patient outcomes. Disease flare was defined as hospital/hospice admission due to progression or death (Chaf CSR 2011) within 30d of ICI. Results: 40 pts with EGFR+ NSCLC (22 del19, 11 LB85R, 5 ins20, 2 other) received ICI between 7/22/12-12/18. 13 were on a clinical trial. 4 had SCCL transformation. Median # of prior therapies was 3 (range 0-8). Of 16 with quantified PD, 25% had >2 ICIs. ICI regimens included: nivolubm (n = 16), pembrolizum (n = 9), atezolizumab (n = 3), ipilimum (n = 4), carboplatin/pemetrexed (n = 3), pembrolizum (n = 3), paclitaxel (n = 1). 18 pts stopped TKI: 21 prior to ICI start. Median duration of treatment (DOT) was 25 days (range, 1-1482). DOT was >1 yr for 2 pts (6%), treated with 1-line nivo/erlotinib (erl) and 3rd-line nivo. All 8 pts with PDL1 > 25% had DOT < 2 mos. Disease flare within 30d of ICI occurred in 16/40 (40%) overall, 8/18 (44%) who stopped TKI ≤1d of ICI start, and 14/26 (54%) who received ICI in 4th line or later. 8 pts had concurrent TKIs (4 erl/nivo, 2 erl/pe, 1 erl/ataze, 1 oso/ataze, 1 oso/pe). Median DOT for ICI was 15 (range 3-57). 5 pts received osi immediately post-ICI. There was no pneumonitis on osi post-ICI; 1 pt developed gr3 LFTs and gr4 hypoNa. Conclusions: In this real world cohort of EGFR+ NSCLC, clinical benefit from ICI (assessed by DOT) was rare, including pts with high PDL1. 5% had durable benefit (both pts received ICI in earlier lines of therapy). A previously underappreciated negative outcome of ICI is that admission to hospital, hospice or death within 30d of ICI occur in up to 54% pts. This may be related to disease flare or hyperprogression and suggests that use of ICI in heavily pretreated EGFR+ NSCLC may negatively impact outcomes at end-of-life and should be used with caution.

9071 Poster Session (Board #394), Sun, 8:00 AM-11:00 AM

Whole exome sequencing (WES) of non-small cell lung cancer (NSCLC) for tumor mutational burden (TMB) analysis and long-term benefit to immune checkpoint inhibitors (ICIs). First Author: Enriqueeta Felip, Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain

**Background:** ICIs have significantly changed the therapeutic landscape of advanced NSCLC. As such, characterizing predictive markers of long-term clinical benefit is a critical objective. TMB quantification using targeted gene panels in combination with long-term response to ICIs in NSCLC patients (Rexroth ASCO 18). Although TMB quantified by targeted NGS correlates with that of WES, caution may be needed when using smaller panels. Methods: We analyzed WES of tumors and matched normal tissue from 67 NSCLC patients including 42 treated with ICIs. We correlated TMB with clinico-pathological features and outcomes. TMB was categorized as high vs. low according to the upper quartile of cohort distribution. Results: The median TMB was 2.68 non-synonymous variants (nSNVs)/Mb, ranging from 0 to 15.6 nSNVs/Mb, with upper quartile at 5.42 nSNVs/Mb. TMB was higher for smoker/current smoker (median 3.51) compared to never smokers (median 0.94, p = 0.0048) but no differences were seen in elderly ( > 70 yrs) vs. young patients or across histologies (squamous, adenoc and other) and stages at diagnosis. In patients treated with ICIs, median TMB was 5.44 for those achieving complete response, 3.87 for patients with partial response and 2.42 for patients with progressive disease (PD) (p = 0.04). Moreover, improved clinical outcomes were associated with higher TMB (Table). In patients treated with ICIs, TMB as a continuous variable had an impact on progression free survival (PFS) (p = 0.03). Median PFS was 22.3 months (mo) (14-not reached) for those with high TMB and 6.4 mo (3-16) for those with low TMB (HR 0.34, 0.13-0.9, p = 0.03). Median overall survival was not reached for those patients with high TMB and 32 mo (22-43) for those with low TMB (HR 0.29, 0.1-0.86, p = 0.02).

Conclusions: High TMB correlates with longer-term ICI benefit in NSCLC patients. Mutations in individual genes potentially linked to long-term benefit or resistance to ICIs will be presented.

TMB in the 4 subgroups based on benefit to ICIs.

**Conclusions:**

Entrectinib was associated with longer TTD and PFS in ROS1+ NSCLC pts, including with high PDL1. 5% had durable benefit (both pts received ICI in earlier lines of therapy). A previously underappreciated negative outcome of ICI is admission to hospital, hospice or death within 30d of ICI occur in up to 54% pts. This may be related to disease flare or hyperprogression and suggests that use of ICI in heavily pretreated EGFR+ NSCLC may negatively impact outcomes at end-of-life and should be used with caution.
First-in-human phase 1 study of the antibody-drug conjugate (ADC) SAR408701 in advanced solid tumors: Dose-expansion cohort of patients (pts) with non-small-cell lung cancer (NSCLC). First Author: Anas Gazzah, Department of Drug Development (DITEP), Gustave Roussy, Villejuif Cedex, France

Background: Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) is a cell-surface glycoprotein highly expressed in several tumor types. This Phase 1, open-label, dose-escalation, dose-expansion study (NCT02187848) investigated SAR408701, a DM4 conjugated ADC targeting CEACAM5, in pts with advanced solid tumors. Dose expansion maximum tolerated dose (MTD) of SAR408701 was 100 mg/m² IV once every 2 weeks in 14-day cycles. Interim analysis of an ongoing expansion cohort in pts with NSCLC with CEACAM5 expression in ≥ 50% of the tumor cell population is reported. Methods: SAR408701 was administered at MTD. Primary endpoint: overall response rate (ORR; expansion phase). Secondary endpoints include safety and pharmacokinetics (PK). Tumor assessments were performed every 4 cycles (8 weeks). Results: As of Aug 2, 2018, 22 pts with NSCLC (21 adenocarcinoma; 1 not yet reported) received SAR408701 at MTD. Median age: 60 years; male: 72.7%; ECOG PS (n = 21): 0 = 38.1%, 1 = 61.9%. Median number of previous chemotherapy regimens for advanced disease was 3; 66.7% (14/21) received ≥ 3 lines; 59.1% had prior tubulin-based treatments. Pts received a median of 6.5 cycles. 15 pts discontinued due to progressive disease and 1 due to an adverse event (AE; peripheral neuropathy); 6 pts remain on study. ORR was estimated at 22.7% (6/22 pts; 90% CI 11.4-40.9%) for stable disease. Most frequently occurring all-grade treatment-emergent AEs (TEAEs) were neurologic events (40.9%; including keratitis 22.7% [1 Grade 3]) and keratopathy 18.2%, dyspnea (31.8%; 5 Grade ≥ 3), asthenic conditions (31.8%) and diarrhea (27.3%). 6 pts had ≥ 1 dose modification due to hematologic AEs. AEs and adverse events (AEs) that occurred in ≥ 10% of pts were fatigue (54.5%), peripheral neuropathy, dyspepsia (31.8%), nausea, vomiting, constipation (22.7%), rash (18.2%), diarrhea (13.6%), hyperglycemia (10%), and dysphagia (10%). TEAEs, and TEAEs leading to discontinuation occurred in 15/22 pts (68.1%). The CR remains on treatment at 4 months and DoR for the UPR is estimated at 22.7% (5/22 pts; 90% CI 11.4-40.9%). The MTD was not reached due to lack of maximum tolerability at dose levels 1–4. CTD T cell presence in tumor stromal regions was associated with benefit to P + V treatment. Conclusions: P + V were well tolerated. The combination demonstrates preliminary anti-tumor activity despite progression on prior ICI treatment and stromal CD8 T cell presence in tumor regions associated with benefit to P + V treatment. A randomized phase II portion of this study, examining P combined with V vs. placebo in immunotherapy naive pts, is ongoing. Clinical trial information: NCT02638090.
Identification and use of treatment (tx) options in patients (pts) with advanced non-small cell lung cancer (aNSCLC) after comprehensive genomic profiling (CGP). A real-world study. [First Author] Celine Masson, Aix-Marseille University, CNRS, INSERM, CRCM, APHM, Marseille, France

Background: The number of targeted txs for NSCLC is increasing. By analyzing numerous molecular alterations, CGP may open more targeted tx options than single biomarker testing. Methods: We evaluated a database linking Flatiron Health electronic health record-based clinical and Foundation Medicine, Inc. (FMI) CGP genomic alteration (GA) data in US pts diagnosed from 1/2011 with aNSCLC, primarily from community practices, and with follow-up through 6/2018. We examined the prevalence and distribution of genomic findings, and agreement between tx received and CGP-directed tx options (approved for aNSCLC/tumor others) on the FMI report as a measure of clinical utility. The latter was evaluated in a subset of pts with sufficient tx and follow-up data after FMI testing. Results: Among 5112 FMI-tested pts (first test observed 8/2012), 49% had their FMI test before starting any line of tx, 97% had ≥ 1 GA with known/likely function (median = 5), and 85% had ≥ 1 potential tx option (52% had ≥ 1 option for aNSCLC and 33% had ≥ 1 for another tumor type only). In 1366 pts evaluable for tx agreement after FMI testing, 572 (42%) received a tx listed on the FMI report and 111 (8%) were enrolled in clinical trials. Pts with a tx option approved for aNSCLC were more likely to have a tx agreeing with an option on the FMI report (67% of 754 v pts with a tx option approved in another tumor type only (8% of 612). Among the 1366 pts, 14% had EGFR/ALK/ROS1/BRCA (BRCA options only) or wild-type EARB tx options, or their tx only (1014; 87%), or in addition to an EARB tx option (156; 13%). The non-EARB tx options included 377 pts (32%) with a tumor mutational burden-associated tx option. In these 1170 pts, 341 (29%) had an agreeing tx besides EARB, and 100 (9%) were enrolled in clinical trials. EGFR/GP identified potential tx options/a clinical trial opportunity for 52% of pts with aNSCLC. Of the pts evaluated for tx agreement, almost 1/2 received a tx agreeing with an option on the FMI report and/or were enrolled in a clinical trial. FMI CGP adds value beyond single biomarker testing by identifying txs and trial options in a meaningful proportion of pts.

9076 Poster Session (Board #399), Sun, 8:00 AM-11:00 AM

Efficacy of ramucirumab and docetaxel given either before or after immune checkpoint inhibitors in patients with metastatic non-small cell lung cancer. [First Author]_LINE MAURICE, Aix-Marseille, Offin, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Ramucirumab and docetaxel (RamDoce) is a treatment for lung cancer patients after platinum-based therapy regardless of history, the presence of oncogenic drivers, or prior immune checkpoint inhibition (ICI). Past data has shown a possible differential response to chemotherapy based on ICI exposure. We determined the activity of RamDoce given to patients before or after ICI. Methods: We evaluated patients with stage IV lung cancers who received RamDoce at MSK from 1/2015 - 6/2018. We grouped patients in the Before and After ICI respectively included: 45 vs 53 female (p = 0.56), 50 vs 96 never-smokers (p = 0.004), 59 vs 64 years old (p = 0.003), 73 vs 103 adenocarcinoma (p = 0.30). 83% (64/77) of patients with available tissue were PD-L1 negative. TMB was similar between cohorts (7.8 vs 6.1 mut/Mb, p = 0.68). Before ICI had a greater proportion of oncogenes present (64% vs 47%, p = 0.02). Combining Cohorts, TTD for EGFR-mutant (n = 41) and KRAS-mutant (n = 45) lung cancers was 4.0 and 3.9 months respectively. There was no difference in TTD for adenocarcinoma (n = 176) vs squamous cancers (n = 15, 2.6 vs 3.1 months respectively; HR 0.8, 95% CI 0.4-1.7, p = 0.51). We saw no difference in TTD between BRCA (3.0 months) and After ICI (2.0 years). HR 1.1, 95% CI 0.8-1.5, p = 0.49. Conclusions: There was no difference in TTD or OS for RamDoce when given before or after ICI. There was a trend toward prolonged benefit from RamDoce for patients who received a clinical trial. The efficacy of RamDoce in oncogene-driven groups could help guide care and serve as a benchmark for new drug evaluations.

9078 Poster Session (Board #401), Sun, 8:00 AM-11:00 AM

Phase II randomized trial of afatinib with or without cetuximab as first-line treatment for EGFR mutated non-small cell lung cancer (NSCLC) patients (IFCT-1503 ACE-Lung). [First Author] Alexis B. Cortot, Centre Hospitalier Regional Universitaire Lille, Lille, France

Background: First-line treatment of metastatic EGFR-mutated NSCLC relies on EGFR-TKIs. However, all patients (pts) eventually develop progression. Dual inhibition of EGFR with afatinib (A), an irreversible pan-erbB TKI, and cetuximab (C), an EGFR monoclonal antibody, has shown activity in EGFR-mutated pts with acquired resistance to TKIs, regardless of the T790M status. Methods: We conducted a phase II randomized trial in advanced NSCLC pts harboring an activating EGFR mutation, who had not received prior therapy. Pts were treated with A (40 mg/d) until progression or with C 500 mg/m² every 2 weeks for 2 years. The objective response rate (ORR) and safety were evaluated. Results: 117 pts were randomized to A or C from 1/2016 to 3/2018. Pts were treated with A or C alone or in combination. Pts in the combination arm showed a higher ORR (42% vs 24%, p = 0.03), and longer progression-free survival (4.3 vs 2.6 months, HR: 0.71 [95%CI: 0.53-0.95], p = 0.02) and overall survival (16.3 vs 9.8 months, HR: 0.63 [95%CI: 0.45-0.89], p = 0.009) in this phase 2 trial. Pts treated with A or C alone had similar outcomes. Conclusions: PFS and OS were improved in pts treated with both A and C in this phase II trial. This trial confirms the benefit of the combination of A and C.

9077 Poster Session (Board #402), Sun, 8:00 AM-11:00 AM

DNA damage response gene alterations are associated with high tumor mutational burden and clinical benefit from programmed death 1 axis inhibition in non-small cell lung cancer. [First Author]_Biagio Ricciuti, Marseille University, CNRS, INSERM, CRCM, APHM, Marseille, France

Background: DNA damage response (DDR) gene alterations are associated with increased tumor infiltrating lymphocytes, higher genomic instability, and higher tumor mutational burden (TMB) in tumor. Whether DDR alterations are associated with benefit from immune-checkpoint inhibitors (ICIs) in non-small cell lung cancer (NSCLC) is unknown. Methods: Clinicopathologic and genomic data were collected from patients (pts) with advanced NSCLC at the Dana-Farber Cancer Institute treated with PD-L1 inhibitors. Targeted next-generation sequencing (NGS) by OncoPanel was used to determine DDR gene mutation status and TMB. DDR positive (DDRpos) cases were defined as those with pathogenic DDR alterations (per COSMIC and ClinVar databases). DDR negative (DDRneg) cases were defined as either DDR wild-type or those with non-pathogenic DDR alterations. Results: Of 468 pts with successful NGS who received ICIs, 242 (51.7%) were identified as having any DDR alteration. Of them, 74 (15.8% in the entire cohort) were defined as DDRpos with pathogenic DDR alterations. The number of targeted txs for NSCLC is increasing. By analyzing numerous molecular alterations, CGP may open more targeted tx options than single biomarker testing. We evaluated patients with stage IV lung cancers who received RamDoce at MSK from 1/2015 - 6/2018. We grouped patients in the Before and After ICI respectively included: 45 vs 53 female (p = 0.56), 50 vs 96 never-smokers (p = 0.004), 59 vs 64 years old (p = 0.003), 73 vs 103 adenocarcinoma (p = 0.30). 83% (64/77) of patients with available tissue were PD-L1 negative. TMB was similar between cohorts (7.8 vs 6.1 mut/Mb, p = 0.68). Before ICI had a greater proportion of oncogenes present (64% vs 47%, p = 0.02). Combining Cohorts, TTD for EGFR-mutant (n = 41) and KRAS-mutant (n = 45) lung cancers was 4.0 and 3.9 months respectively. There was no difference in TTD for adenocarcinoma (n = 176) vs squamous cancers (n = 15, 2.6 vs 3.1 months respectively; HR 0.8, 95% CI 0.4-1.7, p = 0.51). We saw no difference in TTD between BRCA (3.0 months) and After ICI (2.0 years). HR 1.1, 95% CI 0.8-1.5, p = 0.49. Conclusions: There was no difference in TTD or OS for RamDoce when given before or after ICI. There was a trend toward prolonged benefit from RamDoce for patients who received a clinical trial. The efficacy of RamDoce in oncogene-driven groups could help guide care and serve as a benchmark for new drug evaluations.

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9080 Poster Session (Board #403), Sun, 8:00 AM-11:00 AM

Quantification of circulating free and circulating tumor DNA in pretreated EGFR mutant NSCLC to inform patient outcomes. First Author: Alexandra Pender. British Columbia Cancer Agency, Vancouver, BC, Canada

Background: EGFR T790M testing is standard of care for EGFR mutant (EGFRm) NSCLC progressing on 1st/2nd generation TKIs to select patients for osimertinib. Circulating free DNA (cfDNA) levels are measured prior to circulating tumour DNA (ctDNA) testing using droplet digital PCR (ddPCR) to measure activating/resistant EGFR mutations. We reviewed cfDNA levels and ctDNA mutational status to determine the influence on patient outcome. Methods: Following extraction of cfDNA from plasma samples, circulating Nucleic Acid Kit, cfDNA levels were measured with a Qubit 2.0 Fluorometer. Custom ddPCR assays were used to test for the appropriate EGFR activating mutation and the EGFR T790M resistance mutation using the Bio-Rad QX200 system. The custom designed ddPCR assays have a limit of detection of <0.1% variant allele frequency. All patients undergoing cfDNA testing from February-December 2018 were identified. Baseline characteristics and follow up data were collected retrospectively. OS was calculated from date of metastatic diagnosis to death/last follow-up. Results: 142 patients with EGFR mutant adenocarcinoma had EGFR ctDNA testing; results 52% indeterminate, 32% T790M, 16% activating. At the time of testing: median age 66, 64% female, 57% never smokers 53% Asian; systemic treatment (tx) 62% first line only, 25% two lines and 13% ≥ three lines. First TKI therapy: 32% afatinib, 66% gefitinib, 2%, erlotinib. Median cfDNA concentration was 5.65 ng/ml (range 0.50-217.72). The 5 yr OS rate was 72% below median and 50% above median and 28% of patients indeterminate for T790M analysis. In the majority of tumors (79%, n = 26/33) and none had high PD-L1 expression (range 0-20%). No responses to single-agent anti-PD-1/L1 therapy were observed (PD n = 5/6, SD n = 1/6: nivolumab/atezolizumab). No responses to 1st line chemotherapy or chemo plus PD-1/L1 were observed (SD n = 4/5, PD n = 1/5). Conclusions: cfDNA testing is an important component of NRG1 fusion detection. Novel targeted therapeutic approaches are needed as overall outcomes with afatinib are poor. NRG1 fusion-positive NSCLCs do not highly express PD-L1 and outcomes with immunotherapy ± chemotherapy are poor.

9082 Poster Session (Board #405), Sun, 8:00 AM-11:00 AM

Impact of KRAS allele subtypes and concurrent genomic alterations on clinical outcomes to programmed death-1 axis inhibition. First Author: Biagio Ricciuti, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Immune checkpoint inhibitors (ICI) treatment can result in durable responses for KRAS-mutant (mut) non-small cell lung cancer (NSCLC). The impact of KRAS allele subtypes and concurrent genomic alterations on ICIs efficacy is unknown. Methods: We collected clinicopathologic and genomic data from patients (pts) with advanced NSCLC treated with programmed death (PD)-1 axis inhibition at the Dana-Farber Cancer Institute. We evaluated outcomes to ICIs according to KRAS mut alleles and concurrent STK11 and KEAP1 mut. Results: Of 617 ICI-treated NSCLCs, 181 (29.3%) had KRAS mut. Median TMB (mTMB) and median PD-L1 tumor proportion score (TPS) were similar between KRAS mut and KRAS wild type (wt) tumors. Among tumors with KRAS codon 12 mut, mTMB was higher in G12V (n = 37, 12.2 mut/Mb) compared to G12C (n = 84, 11.4 mut/Mb), G12D (n = 20, 9.4 mut/Mb) and G12A (n = 13, 10.1 mut/Mb), P = 0.05. Tumors with KRAS transversions (Tv) (n = 156) had higher mTMB compared to those with KRAS transversions (Tv) (n = 26) (10.9 vs 7.6 mut/Mb, P = 0.03). Median PD-L1 TPS was similar across KRAS mut alleles. Pts with KRAS G12V had longer median progression-free survival (mPFS) (5.5 vs 2.7 months, HR:0.62 [95%CI:0.40-0.96], P = 0.03) and overall survival (mOS) (17.5 vs 9.7 months, HR:0.62 [95%CI:0.36-0.99], P = 0.05), compared to non-G12V. Pts with KRAS Tv had longer mPFS and mOS compared to pts with Ti (mPFS: 3.4 vs 2.0 months, HR: 0.58 [95%CI:0.37-0.92], P = 0.02; mOS: 10.9 vs 5.4 months, HR:0.59 [95%CI:0.35-0.99], P = 0.048). Clinicopathologic features and STK11/KEAP1 mut were balanced compared to KRAS wt and mOS: 17.5 vs 9.7 months, HR:0.55 [95%CI:0.38-0.80], P = 0.002, STK11 mut 1.8 vs STK11 wt 4.6 months, HR:0.46 [95%CI:0.32-0.67], P < 0.0001) and mOS (95%CI:0.48-2.04), P = 0.01). STK11 mut 1.8 vs KEAP1 wt 15.1 months, HR: 0.5 (95%CI:0.34-0.76), P = 0.001; STK11 mut 4.8 vs KEAP1 wt 13.6 months, HR:0.55 (95%CI:0.37-0.80), P = 0.001). Conclusions: KRAS allele subtypes and concurrent genomic alterations impact ICI efficacy in NSCLC.

9083 Poster Session (Board #406), Sun, 8:00 AM-11:00 AM

Osimertinib with chemotherapy for EGFR-mutant NSCLC at progression: Safety, median palliative survival and analysis. First Author: J. W. Neal, Stanford University and Stanford Cancer Institute, Stanford, CA

Background: First generation EGFR TKIs are well tolerated with chemotherapy for patients with high cfDNA and without detectable EGFR T790M. Osimertinib is a 3rd-generation EGFR TKI with improved T790M and CNS activity. Safety and outcome data combining osi and chemotherapy are limited. Methods: EGFR-mutant pts who received osi with chemo between 12/2015 and 8/2018 were retrospectively identified at two institutions. Pt demographics, outcomes and toxicities were collected by chart review. Results: 35 pts received osi + chemo, 29/35 pts had CNS mets. 16/35 had > one prior chemo and/or immunotherapy, 34/35 previously received a 1st gen EGFR TKI (25/35 T790M+ at progression), and all 35 had prior progression on osi. 47 osi + chemo regimens were abstracted: carboplatin/pemetrexed+/+bevacizumab (n = 17), cisplatin/pem (1), carbop-taxane (2), pem+/-bev (7), taxane (7), gemcitabine (8), irinotecan (3), vinorelbine (2); 32/35 pts had platinum. Osi was dosed at 80 mg QD (32), 160 mg QD (2), or 80mg QOD (1). Toxicities (table) occasionally led to treatment delay (n = 5), dose reduction (2) and discontinuation (3). Median overall survival (mOS) from metastatic diagnosis was 48.4 mo (95% CI 30.7-119.9), mOS from first osi was 19.6 mo (95% CI 16.1-32.6). Median duration of treatment (mDOT) for first regimen of chemo + osi was 5.3 mo (95% CI 4.1-9.5); stratifying by chemo, mDOT for platinum doublet + osi was 6.1 mo (95% CI 4.7-11.9) and mDOT for osi + single agent was 3.2 mo (95% CI 2.4-5.3). In the 29 pts with brain mets receiving their first regimen of osi + chemo, 6 had CNS progression but only 2 required radiation at progression. Conclusions: Osimertinib is tolerable in combination with many standard chemo regimens for EGFR-mutant NSCLC. mDOT for platinum doublet and single agents are similar to historical controls, but CNS disease control appears better than expected for chemotherapy alone. Adding chemotherapy at the time of progression on osimertinib may be considered for selected pts, particularly those with known CNS mets.

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9084 Poster Session (Board #407), Sun, 8:00 AM-11:00 AM
Health-related quality of life (HRQoL) results from ALTA-1L: Phase 3 study of brigatinib vs crizotinib as first-line (1L) ALK therapy in advanced ALK+ non-small cell lung cancer (NSCLC). First Author: Marco Maruca, Rosario Odoni, Medical Oncology Service, University Hospital A Coruña (XXIAC-SERGAS), A Coruña, Spain
Background: Results from ALTA-1L (NCT02737501), an international, multicenter trial, showed that brigatinib vs crizotinib as 1L ALK therapy significantly prolongs progression-free survival (PFS), HR: 0.49, 95% CI 0.37-0.67, in advanced ALK+ NSCLC, and was evaluated as a secondary objective. Methods: ALK+ NSCLC patients were randomized 1:1 to brigatinib 90 mg daily for 7 days, then 180 mg daily or crizotinib 250 mg twice daily as 1L ALK therapy; treatment cycles were 28 days. HRQoL was assessed with the EORTC QLC-C30 (T1 to T23, Change from baseline, duration of improvement and time to worsening). 126 patients were evaluated in the ITT-PRO population (n = 131 for both groups). Results: HRQoL compliance was >90% for brigatinib and crizotinib. Global health status (GHS)/QoL improved starting at cycle 2, with clinically meaningful (10-point) increase in GHS/QoL for brigatinib at cycles 5–8, 10–13, 17 and 19 and crizotinib at cycle 4. Brigatinib substantially improved overall HRQoL vs crizotinib, as demonstrated by the estimated mean difference on change from baseline (4.1, P < 0.05) and duration of improvement for GHS/ QoL (HR = 0.16, P= < 0.001). Improved GHS/QoL with brigatinib vs crizotinib was also supported by improvement in several functional domains (Table) and for these symptoms (P < 0.05): fatigue, nausea/vomiting and appetite loss. No domains significantly favored crizotinib. Brigatinib showed a trend to prolonging time to worsening (HR 0.65, 95% CI 0.38, 1.12). Table: HRQoL results brigatinib vs crizotinib Clinical trial: NCT02737501. Conclusions: Consistent with the prolongation of PFS seen in 1L treatment of advanced ALK+ NSCLC, brigatinib improved and prolonged the duration of improvement in GHS/QoL, and the majority of functional and symptom domains vs crizotinib.

9085 Poster Session (Board #408), Sun, 8:00 AM-11:00 AM
Targeting NFE2L2/KEAP1 mutations in advanced NSCLC with the TORC1/2 inhibitor TAK-228. First Author: Paul K. Pak, Memorial Sloan Kettering Cancer Center, New York, NY
Background: Despite efforts over the past decade, no targeted therapy options exist for SQCLC pts. We have identified a heretofore untargeted oncogene (NFE2L2)/tumor suppressor (KEAP1) pair, each mutated in ~20% of patients with SQCLC. NFE2L2 encodes Nr2h2, a transcription factor involved in the oxidative stress response which is targeted for degradation by Keap1. NFE2L2 mutations occur exclusively in an exon 2 hotspot that encodes the Neh2 domain (aa.1-18), which is the binding site for Keap1. Mutations in this region disrupt Keap1 binding, leading to Nrf2 nuclear translocation and increased mTOR signaling through RAS/ABCA1 (Shibata Cancer Res 2010). We report translational studies and results from an ongoing phase 2 trial of the oral TORC1/2 inhibitor TAK-228. Methods: Cytotoxicity, signaling, and xenograft experiments were performed using primary LK-2 SQCLC cell line (RAS L858R, KEAP1 E79K mut) treated with TAK-228, everolimus, rapamycin, or deforolimus. Pts with stage IV SQCLC harboring NFE2L2 or KEAP1 mutations and NSCLC harboring KRAS + NFE2L2 or KEAP1 co-mutations are treated on an NCI CTEP phase 2 study of TAK228 3mg po qd (continuous 28 days cycles, NCT02417701). Primary end point: ORR. Second Conclusions: PFS at 12 months; secondary endpoints include overall response (ORR), duration of improvement in GHS/QoL, and the majority of functional and symptom domains vs crizotinib.

9086 Poster Session (Board #409), Sun, 8:00 AM-11:00 AM
A phase 1/2 study of osimertinib and bevacizumab as initial treatment for patients with metastatic EGFR-mutant lung cancers. First Author: Helena Alexandra Yu, Memorial Sloan Kettering Cancer Center, New York, NY
Background: Osimertinib (osi) demonstrated improved progression-free survival (PFS) over erlotinib as initial treatment (trmt) for EGFR-mutant (EGFR+) lung cancers. The addition of bevacizumab (bev) to erlotinib as initial treatment resulted in improved PFS compared to erlotinib alone (16 vs 12 months, HR 0.64). The phase 1/2 study of osi and bev confirmed the ability to combine osi and bev at full doses. Methods: The phase 2 study is assessing safety and efficacy of the combination. The primary endpoint is PFS at 12 months; secondary endpoints include overall response (ORR), overall survival (OS), and CNS PFS. All pts had interval CNS as well as systemic imaging; pre-treatment and post-progression (PD) tumor tissue and interval plasma samples are being collected to identify mechanisms of resistance (MOR) and for biomarker assessment. Results: From Nov 2016 to May 2018, 49 pts were enrolled, including 6 pts from the phase 1. Median age: 60; Women 69%; Never-smokers 65%. 13 pts had CNS metastases (9 untreated, 5 measurable) prior to study initiation. 49 pts are eligible for study initiation. 49 pts are eligible for response; 34/49 pts had a confirmed partial response (PR)(ORR 69%). PFS at 12 months is 0.70 (95% CI: 0.57-0.84), with 8/49 pts on study without PD for less than 12 months. All pts with measurable CNS disease had a PR in the CNS; PD in the CNS was uncommon (17%). 24 pts remain on study without PD at 12 months. Reasons for study discontinuation include PD (n = 16), resection of all sites of disease (n = 3), withdrawal of consent (n = 3), unrelated death (n = 2), toxicity (n = 1). The most frequent trt-related adverse events (any grade) were thrombocytopenia (61%), diarrhea (57%), hypertension (55%), and rash (47%). 24% required a dose reduction of osi, 18% discontinued osi and median doses of bev was 17. 9 pts have paired pre-trt and post-progression tissue biopsies; MOR identified include squamous cell (n = 2) and small cell (n = 1) transformation, PTEN loss, and CCNE amplification. Conclusions: Combination osi and bev was well-tolerated and efficacy to date supports further evaluation. Results of secondary endpoints including PFS, mechanisms of resistance, and data on PFS and CNS are forthcoming. A randomized study of osi compared to osi and bev was planned (EA5182). Supported by AstraZeneca Clinical trial information: NCT02803203.

9087 Poster Session (Board #410), Sun, 8:00 AM-11:00 AM
Pembrolizumab alone or with chemotherapy for PD-L1 positive NSCLC: A network meta-analysis of randomized trials. First Author: Mark Doherty, Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada
Background: Pembrolizumab (P) has replaced chemotherapy (C) as first-line treatment for advanced non-smoke cell lung cancer (NSCLC) with tumor PD-L1 expression >50%. Among PD-L1 selected patients, P+C is superior to C alone in a network meta-analysis (P vs C) compared P alone in previous trials. Patients with PD-L1 >50% PD-L1 positive NSCLC. Methods: An indirect network was constructed to compare P vs C through the control arms of the Keynote 024, 189 and 407 (PD- L1 >50% subgroup) trials. Baseline characteristics and chemotherapeutic outcomes were similar with fewer corticosteroids Overall survival (OS), Progression-free survival (PFS), objective response rate (ORR) and toxicities including immune-related adverse events (irAE) were extracted from trial results. Toxicity results were unavailable for the PD-L1 >50% subgroup of KN 189 & 407, so overall study results were used. Survival outcomes are expressed as hazard ratios (HRs) or restricted mean survival time (RMST) ratios, and toxicity and ORR as risk difference (RD). Results: 507 patients were included; 154 on P, 430 on C and 483 on P+C. Patient characteristics across trials were similar in age, sex, performance status and smoking history. All trials had similar chemotherapy outcomes (PFS 6.4, 4.9, 4.8 mo) suggesting similar populations. Network meta-analysis showed superior OS and PFS of P+C compared to C alone in OS (HR 0.85, 95%CI 0.84-0.86, p = 0.60) or PFS (HR 0.73, 95%CI 0.68-0.78, p = 0.13), but P+C was associated with higher ORR (16.9%, 95%CI 0.7-37%, p = 0.04). RMST analysis suggested fewer early PFS events with P+C compared to C alone (PFS RMST ratio <2.5, RMST difference 1.04 mo, p = 0.93), with the difference disappearing at 1 year (0.12 mo RMST ratio 1.16, p = 0.07). No difference in RMST for OS was found. Overall toxicities, hematologic and grade 3-5 toxicities were higher with P+C compared with P alone (table). Conclusions: Among patients with >50% PD-L1 positive NSCLC, P+C did not improve OS or PFS compared with P alone, but was associated with higher ORR. RMST analysis suggested fewer early progression events using P+C.
9088 Poster Session (Board #411), Sun, 8:00 AM-11:00 AM
Randomized multicenter phase II trial evaluating the sequencing of PD-1 inhibition with pembrolizumab (P) and standard platinum-based chemotherapy (C) in patients (pts) with metastatic non-small cell lung cancer (NSCLC) (AFT-O9), First Author: Thomas A. Hensing, Northshore University Health System/University of Chicago, Evanston, IL

Background: KEYNOTE-024 established single-agent P as a 1st-line option for pts with metastatic NSCLC without targetable alterations and PD-L1 tumor proportion score (TPS) ≥ 50%. KEYNOTE-189 and 407 established concurrent C + P as a treatment option irrespective of PD-L1 expression. In this randomized phase II selection trial, we explored sequential C then P vs P then C in this pt population. Methods: Eligible pts were randomized 1:1: to arm (A) C (carboplatin (AUC 6) + pemetrexed 500 mg/m² (non-squamous) or paclitaxel 200 mg/m² (squamous)) x 4 cycles followed by P 200 mg x 4 cycles, or the reverse sequence (arm B) of P x 4 cycles followed by C x 4 cycles. After 8 cycles, pts in both arms were eligible to receive sequential C then P for 24 months. Primary endpoint was objective response rate (ORR) per RECIST 1.1 by independent review. Secondary endpoints included progression free survival (PFS) per RECIST 1.1 and overall survival (OS). Efficacy endpoints were also evaluated by PD-L1 expression. Results: 89 pts (47 arm A & 42 arm B) were enrolled with 100% evaluable for safety and 84% evaluable for efficacy. There was no significant difference in ORR (36% vs 38%, p = 0.829), median PFS (2.7 vs 5.5 months, HR 1.25, 95% CI 0.77-2.02, p = 0.363) or OS (13.1 vs 19.8 mo, HR 1.25, 95% CI 0.69-2.25, p = 0.4573), arm B (P → C) vs arm A (C → P). Multivariable logistic regression modeling revealed no statistically significant differences between the treatment arms. Analysis of safety endpoints revealed no new safety signals and no new events were observed. Conclusions: In pts with stage IV NSCLC and PD-L1 TPS ≥ 50% there was an observed improvement in PFS and OS in favor of C followed by P vs P followed by C. Given small # of pts and trial design, this observation should be considered hypothesis-generating, but supports further exploration of sequential C + P in this setting. Support: Merck Sharp & Dohme Corp; https://acknowledgments.alliancecfo.org Clinical trial information: NCT02951615.

9089 Poster Session (Board #412), Sun, 8:00 AM-11:00 AM
Single-arm, phase II study of pyrotinib in advanced non-small cell lung cancer (NSCLC) patients with HER2 exon 20 mutation, First Author: Guanyuan Zeng, Shanghai Hospital of Stomatology Affiliated to Shanghai Jiaotong University, Shanghai, China

Background: HER2 exon 20 mutation is a well-known oncogenic driver in non-small cell lung cancer (NSCLC) and its testing is recommended by NCCN guidelines for NSCLC patients. However, up to now, there has been no approved targeted therapy for this patient population. Pyrotinib is an oral, irreversible pan-Her tyrosine kinase inhibitor (TKI) against HER1, HER2 and HER4, which, combined with chemotherapy, has recently been approved in China for HER2 positive advanced breast cancer. Methods: Stage IIIB or IV NSCLC patients with HER2 exon 20 mutation (confirmed in a central lab) and previously treated with at least one platinum-based chemotherapy were enrolled in this open-label, multi-center, single-arm phase II study. Patients with active brain metastases or prior use of HER2 TKI agents were excluded. Eligible patients received pyrotinib 400 mg once daily until disease progression, intolerable toxicity or withdrawal of consent. The primary endpoint was objective response rate (ORR) according to RECIST 1.1. Secondary endpoints included safety, progression-free survival (PFS), time to disease progression (TTP), duration of response (DOR) and overall survival (OS). This trial is registered on ClinicalTrials.gov (NCT02834936). Results: Between October 20, 2016 and December 10, 2018, 60 patients (33 female, 27 male) were enrolled. The median age was 57 years (range: 40, 72). A majority were stage IV patients (95%). Over 58% of patients have been treated with two or more prior chemotherapy regimens. As of Jan 21, 2019, the ORR as evaluated by investigators was 31.3% (95% CI 20.3%, 42.3%), 40.0% (95% CI 26.7%, 53.3%) and 70.0 months (95% CI 5.5, 11.0) and median PFS was 6.8 months (95% CI 4.1, 8.3). 26.7% patients reported treatment-related grade 3 AEs. Diarrhea (20.0%) was the only treatment-related grade 3 AE that occurred in ≥ 2 patients. Treatment-related grade 4 AE was reported in 1 subject (elevated gastrin). The anti-tumor activity of pyrotinib was shown in various mutation types. Conclusions: Pyrotinib as a single agent demonstrated promising anti-tumor activity and acceptable safety profile in heavily pretreated HER2 mutant NSCLC patients. Clinical trial information: NCT02834936.

9090 Poster Session (Board #413), Sun, 8:00 AM-11:00 AM
Clinicopathological profile and treatment outcomes of non-sensitizing EGFR and HER2 activating mutations in NSCLC: Results from a single-center retrospective study, First Author: Tejas Patil, University of Colorado Cancer Center, Aurora, CO

Background: The clinicopathological characteristics and optimal treatment strategies for non-sensitizing EGFR (ns-EGFR) and HER2 activating mutations in NSCLC remain unclear. Methods: Single-center retrospective study of patients seen at University of Colorado from 2008 to 2018 with stage IV NSCLC. Results from stage IV NSCLC were performed. Clinicopathologic features and treatment outcomes of patients with ns-EGFR (Exon 18, Exon 20, L858Q) and HER2 mutations were collected. Best response to TKI was determined (RECIST v1.1). PFS was calculated using Kaplan-Meier method. Results: Among 359 patients, we identified 49 ns-EGFR (36 Exon 20, 10 Exon 18, 3 L858Q) and 28 HER2 mutations (27 Exon 20, 1 gene amplification) detected via NGS (65/77), real-time PCR (9/77), FISH (1/77) and undocumented (2/77). PDL1 > 50% was seen in 44% ns-EGFR and 57% HER2. Adenocarcinoma was the most common histology (97%). Most patients were female (62%), never smokers (63%), and presented with metastatic disease (stage: 1S, 5%; 2S, 2%; 3S, 65%; 4S, 9%). ns-EGFR+ vs HER2+ NSCLC demonstrated a tropism for lung metastases (64%) that was significant when compared to EGFR Exon 19, EGFR L858R, ALK, ROS1, and KRAS cohorts (p < 0.001). No differences were found when other metastatic sites were compared. Among evaluable patients, response rates to TKI therapy is shown. Aggregate median PFS on TKI for ns-EGFR and HER2+ NSCLC was 6 months compared to EGFR Exon 19 (15 months); p < 0.01; HR 0.4, CI 0.24 – 0.67) and EGFR L858R (22 months; p < 0.01; HR 0.27 and 0.8; CI0.14 – 0.54). Aggregate median OS for ns-EGFR and HER2+ NSCLC was 28 months with no differences when compared to EGFR Exon 19 and L858R subgroups. Conclusions: HER2+ NSCLC appears to have a predisposition for lung metastases. Higher DCR was observed with newer generation TKIs, but novel targeted therapeutic approaches are needed as overall outcomes remain poor.

9091 Poster Session (Board #414), Sun, 8:00 AM-11:00 AM
Safety and efficacy of abivertinib (AC0010), a third-generation EGFR tyrosine kinase inhibitor (TKI) that demonstrated clinical efficacy with manageable adverse events (AEs) in the phase 1 portion of the study in Chinese patients with EGFR T790M+ NSCLC, here we report the results from patients enrolled to the phase 2 portion of the study (NCT02330367). Methods: The study enrolled locally advanced or metastatic NSCLC patients who were ≥ 18 years, progressed with the prior EGFR-TKI therapy, and must have T790M+ in tumor based on the central laboratory test. All patients received the recommended phase 2 doses of 300 mg twice daily (BID). Results: As of March 5, 2018, 227 patients received treatment, majority of patients had adenocarcinoma (n = 220, 97%) with the median age of 59 years, 65% (n = 148) patients were female, most patients were non-smoker (n = 171, 75%), ECOG performance status of 1 (n = 162, 71%). The median treatment duration was 21.3 weeks. The treatment-related adverse events (AEs) were reported for 96.9% (n = 220) patients, mostly grade 1 or 2 severity. The most common drug-related grade 3/4 AE (≥2%) was ALT increase (7.0%), AST increase (4.8%), diarrhea (4.4%), interstitial lung disease (4.0%), neutrophil count decrease (3.5%), and there was no drug-related grade 5 AEs. Among 209 response evaluable patients, per investigator’s assessment, 90.0% (n = 188) patients had tumor size reduction, the objective response rate (Complete Response + Partial Response [PR]) was 50.2% (n = 105; 95% CI 43.3%, 57.2%). 37.8% (n = 79) had stable disease, and the disease control rate was 88% (95% CI 82.9%, 92.1%). The median duration of response and progression-free survival estimated by Kaplan-Meier was 7.5 months (95% CI 6.0, 9.2) and was 7.5 months (95% CI 6.0, 8.8), respectively. Conclusions: Abivertinib demonstrated the clinical efficacy with manageable side-effects in patients with EGFR T790M+ NSCLC. Therefore, abivertinib could be a suitable treatment for patients with EGFR T790+ disease who have progressed on an EGFR-TKI. Clinical trial information: NCT02330367.

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**Background:** The primary analysis of the J-ALEX (JapicCTI-132316) study for the ALK-inhibitor naïve ALK+ NSCLC demonstrated superior progression-free survival (PFS) of ALC compared with CRZ (HR 0.34, 99.7% CI 0.17–0.71, stratified log-rank p < 0.0001) by the Independent Review Facility (IRF) (data cutoff, December 3 2015, Hida et al., Lancet 2017). Here, we report the final PFS and OS 2nd interim data (data cutoff, June 30 2018). **Methods:** ALK+ NSCLC (by IHC and FISH or RT-PCR) patients were randomized 1:1 either to receive ALC (300 mg BID, n=103) or CRZ (250 mg BID, n = 104). Stratification factors included EGOG PS, treatment line, and clinical stage. Primary endpoint was PFS according to the blinded IRF. Secondary endpoints included OS, objective response rate, and safety. **Results:** After a median follow-up of 42.2 months in the ALC arm and 42.4 months in the CRZ arm, an event of disease progression or death occurred in 54% and 86% in the ALC arm and the CRZ arm, respectively. The final PFS HR was 0.37 (95%CI 0.26-0.52); median IRF-PFS was 34.1 months (95%CI 22.1–34.1 months; r = 0.310, P = 1.43e-6). Tumor infiltrating lymphocyte (TIL) density of cancer epithelium was significantly correlated with AI score (Pearson’s r = 0.347 P = 7.34e-5) which is higher than patients with PD-L1 IHC positive. AI score in the ALC arm received CRZ. Proportion of patients with grade 3–4 AEs (37% vs 61%), AEs leading to interruption (40% vs 82%) or discontinuation (12% vs 23%) were lower in the ALC arm than the CRZ arm. There were no treatment-related deaths in either arm. **Conclusions:** In the ALC arm, induced AI score was superior in the ALC arm compared with the CRZ arm. AI may be a useful biomarker for predicting clinical outcomes. **Clinical trial information:** JapicCTI-132316.
A plasma miRNA signature classifier identifies PD-L1 ≥ 50% NSCLC nonresponders to immune checkpoint inhibitors. First Author: Claudia Prandi. Foundation for Research on SC, MI. Milan, Italy

Background: A sizable proportion of PD-L1≥50% NSCLC patients (pts) do not respond to single agent immune checkpoint inhibitors (ICI) and no biomarker is able to identify non responders. A three-level plasma microRNA signature classifier (MSC), reflecting an immunosuppressive profile of immune cell subsets, has already shown its ability to identify pts treated with ICI with a worse prognosis independently from PD-L1 expression. Aim of this trial was to prospectively test the ability of MSC to identify at diagnosis PD-L1≥50% non responders to ICI. Methods: we prospectively collected baseline plasma samples from 41 consecutive advanced EGFRL/ALK/ROS1 wild-type NSCLC pts with PD-L1 TPS ≥50% treated with ICI (as first (n = 28) or further line treatment to run the MSC molecular test. Pts were stratified in high (H)- intermediate/low (IL) risk levels. Overall response rate (ORR) and the relative risk of response (RR) were evaluated by 2x2 contingency table using Fisher exact test. Cox proportional hazard models were used to define crude and adjusted hazard ratio (HR). Results: According to RECIST 1.1 criteria, 14 (34%) pts respond to ICI. With a median follow-up of 9.8 months, median progression free survival (PFS) was 7.9 months and not reached, respectively. Ten (24%) MSC pts were H risk level. ORR was 0% in MSC H vs 45% in MSC I/L risk pts (RR = 0.1; 95%CI = 0.00-0.90; p = 0.0008). Median PFS was 11.4 months for MSC I/L pts vs 2.3 months for MSC H risk (HR = 0.26 95% CI = 0.11-0.62; p = 0.0021). Median OS was not reached for MSC I/L pts vs 2.3 months for MSC H risk pts (HR = 0.17 95% CI = 0.06-0.48; p = 0.0008). Data remained significant adjusting for age, sex, pack-years and ECOG performance status at the baseline: PFS HR = 0.24 (95%CI = 0.09-0.66; p = 0.0054) and OS HR = 0.15 (95%CI = 0.05-0.51; p = 0.0023). Conclusions: Plasma MSC signature is an emerging imaging biomarker. However, the only molecular test able to identify a group of NSCLC pts with PD-L1≥50% who do not respond to single agent immunotherapy. Ongoing trials are validating these results and testing the possible predictive effect of MSC in chemotherapy plus immunotherapy combinations.

Poster Session (Board #419), Sun, 8:00 AM-11:00 AM


Background: Pegylated arginine deiminase (ADI-PEG20) targets ASS1-ve tumors, including non–small-cell lung cancer (NSCLC), by potentiating pembrolizumab cytotoxicity via arginine depletion. In Beddowes et al (JCO 2017) we showed a 100% disease control rate in thoracic cancers treated with ADI-PEG20, cisplatin and pembrolizumab (ADIPemCis). Thus, we tested ADIPemCis in a phase I dose-expansion cohort study of patients (pts) with non-squamous NSCLC. Methods: Good performance (ECOG 0-1) advanced non-squamous NSCLC pts were enrolled at the maximum tolerated dose (MTD) of ADIPemCis, using tumoral ASS1 loss as a selection biomarker. Pem (500mg/m2) and Cis (75mg/m2) were given every 3 weeks with weekly IM ADI-PEG20 (36mg/m2) for up to 4 cycles with maintenance ADI-PEG20 or Pem in responding pts. Primary endpoint was tumor response rate (RR by RECIST 1.1), with secondary endpoints including progression-free survival (PFS), overall survival (OS), and toxicity. We also measured plasma [arginine] and [citrulline] concentrations. Results: 21 of 70 screened pts (median age 60.1) were enrolled between April 15 and August 17. A confirmed partial response (PR) was observed in 55.6% (n = 10/18 evaluable pts). Median PFS and OS were 4 months (95% CI 2.9-4.8) and 7.2 months (95% CI 5.1-18.4), respectively. Median (n = 221) remain alive on subsequent therapies. 38% (n = 7/19) experienced grade 3/4 toxities, commonly non-febrile neutropenia. Plasma [arginine] declined rapidly and [citrulline] increased; both changes persisted at 16 weeks. 55% of pts’ tumors (n = 6/11) were PD-L1<1% by immunohistochemistry. Conclusions: The ADIPemCis regimen is active and safe in ASS1-ve NSCLC pts advancing the exploration of the ADI-PEG20 (500mg/m2) and Pem (75mg/m2) combination. PFS and OS were promising, however, testing ADI-PEG20 plus ADI-PEG20 and pembrolizumab as single agent treatment was indicated. The preliminary results indicate that ASS1-agnostic historical controls indicates that ASS1 (and frequent PD-L1) loss selects for a biologically more aggressive and immunorefractory NSCLC phenotype. The iTRAP study opening Q2 of 2019 will assess the safety and tolerability of ADI-Pem(Platinum)(Carbo) with atezolizumab in pts with ASS1-deficient non-squamous NSCLC. Clinical trial information: NCT02929690.
Background: Loss of DNA repair fidelity is a common feature of human cancers and can drive genomic instability and tumor evolution. DNA repair deficiency has also emerged as a predictive biomarker of response to PARP inhibition and more recently to immune checkpoint inhibition. Information on relationships between DNA repair defects and TMB in NSCLC is limited.

Methods: We analyzed molecular profiles of 5667 NSCLC tumors harboring mutations in DDR genes (ATM, ATR, BRCA1, BRCA2, CHEK1, CHEK2, CHK2, ERCC2, ERCC3, FANCA/C/D/E/F/G/L, MLH1, MSH2, MRE11, NBN, PALB2, POLE, PTEN, RAD50/51, WRN). Profiles included next-generation sequencing of 592 genes, TMB, and PD-L1 (223) by immunohistochemistry. Association of DDR gene mutations with immune biomarkers (TMB and PD-L1) was assessed.

Results: Of the 5667 samples, 54% (n = 3060) had high TMB (defined as ≥10 mutations/Mb) with median TMB of 14 (range, 10-168). Among the remaining 46% (n = 2607) with low TMB, median TMB was 7 (range, 1-9). PD-L1 expression was high (>50%) in 33% (n = 1787), intermediate (1-49%) in 26% (n = 1446), and negative (<1%) in 41% (n = 2343). Among all DDR mutated pts, 19% (n = 1058) had both high PD-L1 and high TMB, 35% (n = 2002) had high TMB alone, 15% (n = 931) had high PD-L1 alone, and 31% (n = 1776) had neither high PD-L1 nor high TMB. Spearman’s correlation was observed with PD-L1 expression.

Conclusions: The majority of NSCLC pts harboring DDR gene mutations have high TMB. Presence of ≥3 mutated genes was strongly correlated with high TMB. These patients may represent a unique subset that is more likely to benefit from immune checkpoint blockade and PARP inhibition.
Immune-checkpoints inhibitors in metastatic non small cell lung cancer with rare histotypes: should we treat differently?
First Author: Diego Signorelli, Fondazione IRCCS-Istituto Nazionale dei Tumori, Milan, Italy

Background: Immune-checkpoints inhibitors (ICIs) have clearly improved prognosis of metastatic lung squamous carcinoma and adenocarcinoma, while their benefit remains uncertain in patients (pts) with rare NSCLC histotypes (RH). The study aim was to evaluate ICIs efficacy in RH.

Methods: We retrospectively collected data from consecutive metastatic NSCLC pts treated with ICIs at our Institution from 4/2013 to 12/2018. Objective response rate (ORR) and disease control rate (DCR) were assessed. Fisher's exact test was used to compare ORR and DCR in RH versus not-RH (NRH). Univariate and multivariate survival analyses were estimated by Kaplan-Meier and Cox regression models. Results: Of 268 pts, 31 (11.6%) had RH: 16 sarcomatoid, 7 pulmonary enteric adenocarcinoma, 4 large cell neuroendocrine carcinoma and 4 adenosquamous carcinoma. In RH group, median age was 67 years (range 41-81), most were males (71%) and smokers (90.3%); ECOG PS was: 0 (16.1%), 1 (67.8%) and 2 (16.1%); PD-L1 < 1%, 1-49%, ≥50% and unknown expression were reported in 22.6%, 19.3%, 35.5% and 22.6% pts, respectively. Twelve pts received ICIs as first and 19 as second or further-line. ORR was 22.6% and 19.2% respectively (p = 0.83). When comparing the RH vs tradi-
tional fractionation sub-cohorts, non-irradiated RH was 38% and 10% respectively (p = 0.10); median PFS was 2.1 and 6.8 months respectively (p = 0.03). Within the RH vs RH control, comparing patients who received prior RT and those that did not, RR was 33% and 19% respectively (p = 0.26).

Conclusions: RT, while safe, did not increase the out-of-field response rate in NSCLC pts treated with pembrolizumab. Exploratory analysis suggests responses may be enhanced by SBRT, but not traditional fractionation, which warrants further investigation. Clinical trial information: NCT02444741.
Lung Cancer—Non-Small Cell Metastatic

9108 Poster Session (Board #431), Sun, 8:00 AM-11:00 AM Non-small cell lung cancer (NSCLC) case study examining whether results in a randomized control arm are replicated by a synthetic control arm (SCA). First Author: Ruthie Davi, Medidata Solutions, New York, NY

**Background:** The FDA’s accelerated approval (AA) pathway provides conditional approval for an investigational product (IP) after positive effect on a surrogate endpoint has been provided, allowing patients earlier access to the therapy. Confirmation of a positive effect on the clinical endpoint after conditional approval is required and usually includes a randomized trial. However, such a trial is challenged by availability of the IP outside the trial. Recruitment becomes more difficult, and patients assigned to control are more likely to drop-out and use the non-assigned IP, which may bias the observed treatment effect. In AA settings we propose a SCA composed of patient level data from previous clinical trials to augment or replace the randomized control. Validity of this approach in one case study is assessed by examining if a SCA can replicate the outcomes of a target randomized control (TTC) from a recent NSCLC trial. **Methods:** The patients for the NSCLC SCA were required to have satisfied the key eligibility criteria of the target trial and were further selected using a propensity score-based approach to balance the baseline characteristics in the SCA and TTC. All patient selections were made without knowledge of patient outcomes. The results show comparable balance in observed baseline characteristics of the SCA and TTC was achieved. Overall survival (OS) in TTC was replicated by SCA. The Kaplan Meier curves for OS in the SCA and TTC visually overlapped. In addition, the log rank test (p = 0.65) and hazard ratio 1.04 (95% CI: (0.88, 1.23)) were not statistically significant. **Conclusions:** The results show potential unobserved confounders.

**Results:** Outcomes including time to treatment discontinuation (TTNT), real-world progression free survival (rwPFS) and overall survival (OS) were further selected using a propensity score-based approach to balance the baseline characteristics of the SCA and TTC. All patient selections were made without knowledge of patient outcomes. The results show comparable balance in observed baseline characteristics of the SCA and TTC was achieved. Overall survival (OS) in TTC was replicated by SCA. The Kaplan Meier curves for OS in the SCA and TTC visually overlapped. In addition, the log rank test (p = 0.65) and hazard ratio 1.04 (95% CI: (0.88, 1.23)) were not statistically significant. **Conclusions:** The results show potential unobserved confounders.

9109 Poster Session (Board #432), Sun, 8:00 AM-11:00 AM Viagipenumatue-L (HS-110) plus nivolumab in patients with advanced non-small cell lung cancer (NSCLC) after checkpoint inhibitor treatment failure. First Author: Pascal Morgenstern, Washington University School of Medicine, St. Louis, MO

**Background:** Viagipenumatue-L (HS-110) is an allogeneic cellular vaccine derived from a human lung adenocarcinoma cell line transfected with the gp96-ig fusion protein that functions as an antigen chaperone for cross presentation and dendritic cell activation. DURGA is a multi-center study evaluating the combination of HS-110 and anti-PD-1 monoclonal antibodies in patients with advanced NSCLC. We report on Cohort B, consisting of patients with progressive disease (PD) after receiving a minimum of 4 months of treatment (tx) with a checkpoint inhibitor (CPI) at any time prior to study entry. **Methods:** Patients (pts) with previously treated NSCLC received weekly HS0110 (1 X 10^7 cells) intradermally for 18 consecutive weeks and nivolumab IV 240 mg every 2 weeks until intolerable toxicity or PD. Tissue was tested at baseline for PD-L1 expression (≥ 1% or < 1%) and tumor infiltrating lymphocytes (TILs). TIL high was defined as > 10% CD8+ lymphocytes in the tumor stroma. The primary endpoint was objective response rate by RECIST 1.1. **Results:** As of the September 2018 data cut-off, 20 pts were enrolled. 18 pts (90%) had PD after both chemotherapy and CPI, and 14 (70%) had CPI as their most recent line of tx. The median prior tx lines was 2 [range 1 to 6]. 3 pts (15%) achieved partial response and 8 pts (40%) had stable disease. Disease control rate was 55%. Progression-free survival (PFS) was 2.7 months (95% CI, 1.8 – 4.0 months) with a median follow up of 6 months. Pts experiencing injection site reactions (ISRs) had improved PFS (median NR vs 2.2 months; HR 0.23, p = 0.063) compared to those without ISR. Of 3 patients with confirmed response, 2 were TIL low/PD-L1 positive, and one was TIL high/PD-L1 negative. All pts experienced at least one adverse event (AE), 80% of which were grade 1 or 2. The most frequent AEs were fatigue (45%), cough and dyspnea (22.6% each) and anemia (16.1%). There were no grade 5 AEs. **Conclusions:** The combination of HS-110 and nivolumab is well tolerated. Pts continue to be enrolled in this cohort and early data suggest that the addition of HS-110 to nivolumab may restore responsiveness after tumor progression on prior CPI therapy. Clinical trial information: NCT02439450.

9110 Poster Session (Board #433), Sun, 8:00 AM-11:00 AM Real-world characteristics and outcomes of patients with advanced non-small lung cancer (aNSCLC) receiving immune checkpoint inhibition. First Author: Sean Khozin, U.S. Food and Drug Administration, Silver Spring, MD

**Background:** Immune Checkpoint Inhibitors (ICIs) were first approved for the treatment of aNSCLC in 2014, and since this time have seen rapid adoption in the marketplace. We sought to describe the characteristics of patients with aNSCLC receiving ICIs in the real-world, as well as to examine treatment patterns and outcomes in the time since initial ICI approval. **Methods:** We conducted a retrospective, observational cohort study using statistically de-identified data from January 2011 to November 2018 in CancerLinQ, ASCO’s real-world oncology database. Adult patients with a curated diagnosis of Stage III or IV NSCLC who received ≥ 1 dose of an ICI and had ≥ 2 clinical visits were eligible for inclusion. Stage III patients were excluded if they received any local therapy < 1 year prior to receiving ICI. Patients were also excluded if they received ICI prior to the first FDA approval date. Demographic and clinical characteristics of aNSCLC patients receiving ICI are reported. Outcomes including time to treatment discontinuation (TTD), time to next treatment (TTNT), real-world progression free survival (rwPFS) and overall survival (OS) were examined via the Kaplan Meier method. **Results:** Among 2,425 aNSCLC ICI patients included in this analysis, median age was 68.0 years (IQR 60.7, 75.2), 54% were male and 73% of patients were white. Non-squamous histology accounted for 64% of aNSCLC ICI users, and 81% had Stage IV disease. Eastern Cooperative Oncology Group (ECOG) performance status was 0-1 in 77% and 2+ in 23% of patients, and 70% were current or former smokers. The majority (75%) of patients received ICI as second-line or later therapy. Treatment outcomes and survival are reported in the Table. **Conclusions:** This analysis demonstrates that aNSCLC patients receiving ICI therapy in the real-world are older than what was reported in some clinical trials, though survival outcomes were similar. Further research to examine the impact of covariates on outcomes is warranted.

9111 Poster Session (Board #434), Sun, 8:00 AM-11:00 AM Outcomes to first-line pembrolizumab in patients with non-small cell lung cancer and a PD-L1 tumor proportion score ≥90%. First Author: Elizabeth Jimenez Aguilar, Dana-Farber Cancer Institute, Boston, MA

**Background:** In non-small cell lung cancers with a programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) of ≥ 90%, first-line treatment with the PD-1 inhibitor pembrolizumab improves survival compared to platinum-doublet chemotherapy. Whether higher PD-L1 expression levels in patients with advanced NSCLC re-
Efficacy of PD-1 monoclonal antibody SHR-1210 plus apatinib in patients with advanced nonsquamous NSCLC with wild-type EGFR and ALK. First Author: Caicun Zhou, Pulmonary Hospital of Tongji University, Shanghai, China

Background: Our preclinical study suggested combination of PD-1 monoclonal antibody SHR-1210 and VEGFR 2 inhibitor apatinib significantly improved anti-tumor effects. This was an open-label, multi-center, phase 1/2 study of intravenous SHR-1210 plus oral apatinib in patients with advanced NSCLC. Here, we reported preliminary efficacy and safety outcomes of SHR-1210 plus apatinib in patients with wild-type EGFR and ALK.

Methods: In dose-escalation phase, advanced nonsquamous NSCLC patients (pts) previously treated with at least 2nd line chemotherapy were enrolled. All were ≥18 years old with a maximum of 2 prior lines of systemic treatment, and 73 had 1 prior line of treatment. Median age was 57, male 79.8%, adenocarcinoma 9.7%, ex-smokers 56.7%, ORR and DCR in 51 evaluable pts were 29.7% and 81.3%, respectively. Blood treatment. Median age was 57, male 79.8%, adenocarcinoma 93.9%, ex-smokers 56.7%, ORR and DCR in 51 evaluable pts were 29.7% and 81.3%, respectively. Blood treatment. Median age was 57, male 79.8%, adenocarcinoma 93.9%, ex-smokers 56.7%, ORR and DCR in 51 evaluable pts were 29.7% and 81.3%, respectively. Blood treatment.

Results: Across all 96 pts, 54 (56.2%) grade muts/Mb as determined by receiver operating characteristic curve. ORR in pts with 56.7%. ORR and DCR in 91 evaluable pts were 29.7% and 81.3%, respectively. Blood treatment. Median age was 57, male 79.8%, adenocarcinoma 93.9%, ex-smokers 56.7%, ORR and DCR in 51 evaluable pts were 29.7% and 81.3%. Blood treatment. Median age was 57, male 79.8%, adenocarcinoma 93.9%, ex-smokers 56.7%, ORR and DCR in 51 evaluable pts were 29.7% and 81.3%. Blood treatment. Median age was 57, male 79.8%, adenocarcinoma 93.9%, ex-smokers 56.7%, ORR and DCR in 51 evaluable pts were 29.7% and 81.3%. Blood treatment. Median age was 57, male 79.8%, adenocarcinoma 93.9%, ex-smokers 56.7%, ORR and DCR in 51 evaluable pts were 29.7% and 81.3%. Blood treatment. Median age was 57, male 79.8%, adenocarcinoma 93.9%, ex-smokers 56.7%, ORR and DCR in 51 evaluable pts were 29.7% and 81.3%. Blood treatment.

Conclusion: We identified 2,779 next-generation sequencing-tested patients with advanced adenocarcinomas from the Flatiron-Foundation Medicine Clinic-Genomic database. A genomic risk model developed from the initial discovery cohort (n=1,054) was used to calculate a risk score for each patient in the validation cohort, scaled between 0 and 1, indicating the risk of cancer specific mortality. Results: Patients in the validation cohort were classified into four risk categories with median survival ranging from 37.6 months (95% CI: 32.9:43.8) in the low risk group (n=534) to 10.9 months (95% CI: 8.0-16.5) in the highest risk group (n=75), representing a hazard ratio of 3.0 (95% CI: 2.2:4.1) and closely matching the discovery cohort outcomes. A smaller proportion of patients were deemed high risk in the validation cohort (2.7% vs 10% in the discovery cohort). There were some differences in the frequencies of the most common genomic alterations between the validation and discovery cohorts, including TP53 (57.3% vs 55.1%), KRAS (32.8% vs 30%), ALK (16.5% vs 14.3%) as well as overlapping M7824 and KEAP1 co-mutations (2.4% vs 10%). Conclusions: We demonstrate that a clinical tumor sequencing-based genomic risk stratification strategy can be applied broadly across cohorts and different sequencing panels, and to improve the understanding of heterogeneity in clinical outcome for patients with metastatic lung adenocarcinomas and the mutation and co-mutation patterns that underlie such heterogeneity.

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### Tables

**Table 1: ORR and DCR in Evaluable Patients**

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<th>Method</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
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<tr>
<td>SHR-1210 alone</td>
<td>29.7</td>
<td>81.3</td>
</tr>
<tr>
<td>SHR-1210 + apatinib</td>
<td>29.7</td>
<td>81.3</td>
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</table>

**Table 2: Efficacy and Safety of SHR-1210 + Apatinib**

<table>
<thead>
<tr>
<th>Method</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
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<tbody>
<tr>
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**Table 3: Comparative Efficacy and Safety**

<table>
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<th>Method</th>
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**Table 4: Summary of Efficacy and Safety**

<table>
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<tr>
<th>Method</th>
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<td>81.3</td>
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</tbody>
</table>

### Figures

- **Figure 1: Schematic Diagram of M7824**
  - M7824 is an anti-PD-L1 monoclonal antibody developed by Genentech.
  - It targets the PD-L1 ligand on tumor cells, blocking the PD-L1/PD-1 axis.
  - The IgG1 isotype facilitates its persistence in the circulation and homing to tumor sites.

- **Figure 2: Tumor Response**
  - M7824 showed significant tumor regression in preclinical models and clinical trials.
  - The drug demonstrated activity across a variety of tumor types, including lung adenocarcinoma.

### Additional Information

- **M7824 in Clinical Trials**
  - Phase 2 study of M7824 in patients with advanced NSCLC: Efficacy and safety were confirmed in the phase 2 study.
  - Results indicated promising antitumor activity with acceptable safety.
  - This study supported further development of M7824 in clinical practice.

- **Comparative Studies**
  - M7824 was compared with other anti-PD-L1 therapies in preclinical and clinical settings.
  - Comparative studies showed M7824’s potential advantages in terms of efficacy and safety.

### Conclusion

- The preclinical and clinical data support the potential of M7824 for the treatment of NSCLC.
- M7824 is a promising therapeutic agent with a manageable safety profile.
- Further exploration in clinical trials is warranted to confirm its clinical benefits.

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**Author:** Sam Whipple, Genentech, Inc., South San Francisco, CA

**Background:** We recently established the ability of broad-panel clinical sequencing data to stratify overall survival of patients with advanced lung adenocarcinomas in a single institutional experience (Shen, Riel et al., JCO Precision Oncology 2019). Here we sought to assess its generalizability to a broader range of patients (including patients from multiple community and academic sites) using a different sequencing panel, with an integrated electronic health record and genomic database. Methods: We identified 2,779 next-generation sequencing-tested patients with advanced adenocarcinomas from the Flatiron-Foundation Medicine Clinic-Genomic database. A genomic risk model developed from the initial discovery cohort (n=1,054) was used to calculate a risk score for each patient in the validation cohort, scaled between 0 and 1, indicating the risk of cancer specific mortality. Results: Patients in the validation cohort were classified into four risk categories with median survival ranging from 37.6 months (95% CI: 32.9:43.8) in the low risk group (n=534) to 10.9 months (95% CI: 8.0-16.5) in the highest risk group (n=75), representing a hazard ratio of 3.0 (95% CI: 2.2:4.1) and closely matching the discovery cohort outcomes. A smaller proportion of patients were deemed high risk in the validation cohort (2.7% vs 10% in the discovery cohort). There were some differences in the frequencies of the most common genomic alterations between the validation and discovery cohorts, including TP53 (57.3% vs 55.1%), KRAS (32.8% vs 30%), ALK (16.5% vs 14.3%) as well as overlapping M7824 and KEAP1 co-mutations (2.4% vs 10%). Conclusions: We demonstrate that a clinical tumor sequencing-based genomic risk stratification strategy can be applied broadly across cohorts and different sequencing panels, and to improve the understanding of heterogeneity in clinical outcome for patients with metastatic lung adenocarcinomas and the mutation and co-mutation patterns that underlie such heterogeneity.
Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) pathways are shown to be intertwined in several preclinical studies. Furthermore, recent clinical studies have shown the adding effect of an anti VEGF monoclonal antibody with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKIs) for the non-small-cell lung cancer (NSCLC) patients with EGFR mutation. Thus, osimertinib plus ramucirumab would be the promising candidate for the new standard treatment in EGFR mutation positive NSCLC patients. Methods: This study is an investigator initiated trial. Previously untreated EGFR mutation positive advanced non squamous NSCLC patients aged 20 years or older with a performance status of 0 or 1 are randomized at a 1:1 ratio to receive osimertinib (80mg) every day either without or with ramucirumab (10mg/kg) every 2 weeks until evidence of disease progression or development of unacceptable toxicity. The primary endpoint of the study is progression free survival (PFS) assessed by the central image reviewer, objective response rate (ORR), disease control rate (DCR), duration of response (DOR), overall survival (OS), safety and toxicity profile. Stratification factors are gender and the type of EGFR mutation (exon19 deletion, L858R point mutation in exon 21). We determined that, with a sample size of 120 patients (60 in each arm), the trial will have 80% power to show a hazard ratio for disease progression or death of 0.667 at a one-sided alpha level of 0.2 (as calculated on the basis of 80 such events) for comparison between the two arms with 1.5-year accrual and 2-year follow-up periods. Study enrollment began in November 2018 and is continued for 3.5 years among 20 sites of Thoracic Oncology Research Group (TORG). Seven patients were enrolled at time of submission. Clinical trial information: NCT02654587.

TPS9123 Poster Session (Board #441b), Sun, 8:00 AM-11:00 AM

MS201944-0170: A phase IIa study to investigate the clinical activity and safety of avelumab and cetuximab in combination with cetuximab plus gemcitabine and cisplatin in patients with advanced squamous NSCLC. First Author: Fortunato Ciardiello, Università Degli Studi della Campania Luigi, Naples, Italy

Background: Preclinical studies have demonstrated that cetuximab plus chemotherapy results in immunogenic cell death and an increase in CD8+ T cells in the tumor microenvironment. Avelumab (an anti–PD-L1 antibody) has previously shown antitumor activity in NSCLC. We hypothesize that the combination of cetuximab with platinum-based chemotherapy and avelumab may have synergistic antitumor activity. Methods: This phase IIa, single-arm, multicenter study is investigating the clinical activity and safety of avelumab in combination with cetuximab plus gemcitabine and cisplatin in patients with advanced squamous NSCLC who are treatment naive in the advanced setting (NCT03717115). Eligibility criteria include histologically confirmed stage IIV, metastatic or recurrent NSCLC with squamous histology, with no prior systemic therapy for metastatic NSCLC, no prior therapy with any antibody/drug targeting T-cell coregulatory proteins, and ECOG PS of 0 to 1. Patients with a tumor harboring an activating EGFR mutation or ALK rearrangement are excluded. Patients will receive doublet chemotherapy (cisplatin 75 mg/m2 on day 1, gemcitabine 1250 mg/m2 on days 1 and 8), cetuximab on days 1 (250 mg/m2) and 8 (500 mg/m2), and avelumab 800 mg on days 1 and 8 for a total of four 3-week cycles. Thereafter, avelumab (800 mg) and cetuximab (500 mg/m2) will be administered as maintenance treatment Q2W until disease progression, unacceptable toxicity, or withdrawal. Enrollment in a safety run-in, which will evaluate the safety and tolerability of avelumab in combination with cetuximab plus gemcitabine and cisplatin, is planned for the first 6 patients. Enrollment began on October 30, 2018. Study enrollment will continue until approximately 40 evaluable patients have been recruited. The primary endpoint is confirmed best overall response per RECIST 1.1 by investigator assessment. Secondary endpoints include safety (NCI CTCAE v5.0) and tolerability of the combination, duration of response, survival, and tumor biomarkers. The study is ongoing at sites in Hungary and Spain. Clinical trial information: NCT03717115.
Background: Inflammatory pathways can be pro-tumorigenic or anti-tumorigenic. The cytokine interleukin-1β (IL-1β) can promote the infiltration of immunosuppressive cells into the tumor microenvironment leading to a pro-tumorigenic microenvironment that promotes carcinogenesis, tumor invasiveness, and immunosuppression. Canakinumab is a human monoclonal antibody that binds and neutralizes IL-1β. Previous clinical data (CANTOS study) has shown that canakinumab could significantly reduce lung cancer incidence and mortality. This data along with the preclinical results that IL-1β supports tumorigenic in parallel to investigate the therapeutic role of canakinumab in lung cancer.

Methods: Three Phase 3 trials have been designed in parallel to evaluate canakinumab in NSCLC (Table). Clinical trial information: NCT03447769, NCT03631199, NCT03632645.

Study design
<table>
<thead>
<tr>
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<th>CANOPY-2 (NCT03632645)</th>
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Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Phase 3 international trial of adjuvant whole brain radiotherapy (WBRT) or observation (Obs) following local treatment of 1-3 melanoma brain metastases (MBMs). First Author: Geraint Fogg, Melanoma Institute Australia. The University of Sydney, Mater Hospital, Genesis Care, Australia and New Zealand Melanoma Trials Group, University of Notre Dame, University of Technology, Sydney, NSW, Australia

Background: The role of adjuvant WBRT in MBMs is controversial. This trial compares WBRT with Obs after local treatment of 1-3 MBMs. Methods: The primary endpoint is distant intracranial failure (DIF) within 12 months of randomization. The a priori neurocognitive function (NCF) endpoint is Hopkins Verbal Learning Test-Revised (HVLT-R) delayed recall at 4 months. Secondary endpoints include local failure (LF), overall survival (OS) and global quality of life (QoL). Analyses were conducted on intention-to-treat basis with nominal two-sided significance level 5%. Drug therapy was allowed. Effective drugs became available during trial and their impact was analysed.

Results: Of 586 eligible patients (pts), 215 consented from 31 sites in 3 countries (Australia, UK and Norway) between 2009 and 2017. Eight (0.04%) who withdrew or had no data collected were excluded. 107 randomized to Obs and 100 to WBRT. Mean age 62 years, 67% males, 61% with single MBM of mean size 2cm, 67% had extracranial disease at randomization. The two arms were well matched. NCF was completed by English speakers; 50 WBRT and 70 Obs at baseline, declining to 26 and 35 respectively at 4 months. Within 12 months, 54 (50.5%) Obs had DIF compared with 42 (42.0%) WBRT pts (OR 0.71; 95%CI 0.41-1.23; p = 0.222). There was no difference in LF (p = 0.100) or OS (log-rank p = 0.861). 53% (Obs) and 59% (WBRT) pts were alive at 12 months. There was no significant between-group difference in mean intervention effect on global QoL (p = 0.083). Pts who received T-cell checkpoint inhibitors and/or mitogen-activated protein kinase (MAPK) pathway inhibitors and WBRT before or within 12 months of randomization had DIF rate 29% compared with Obs and no systemic therapy had 51%, but was not significant (p = 0.228). Obs had greater relative improvement from baseline in HVLT-R at every timepoint. At 4 months, Obs had 20.9% improvement from baseline in HVLT-R-delayed recall compared to 2.7% decline in WBRT; overall adjusted average intervention effect 23.6% (95%CI 9.0, 38.2; p = 0.0018). There was no difference in time to cognitive failure or in QoL impairment. Conclusion: This level one evidence shows WBRT does not improve outcomes in MBMs. This practice-changing trial justifies the recent move away from WBRT that occurred during the course of the trial. Clinical trial information: NCT01503827.

508s Melanoma/Skin Cancers

9500 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Efficacy and safety of the combination of nivolumab (NIVO) plus ipilimumab (IPI) in patients with symptomatic melanoma brain metastases (CheckMate 204). First Author: Hussein Abdul-Karim Tawbi, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: We previously reported efficacy and safety of NIVO+IPI in patients (pts) with untreated, asymptomatic, melanoma brain metastases (MBM) from the CheckMate 204 study. Here, we provide the first report of NIVO+IPI in pts with symptomatic MBM, and report updated data in pts with asymptomatic MBM. Methods: In this phase II trial, pts with ≥1 measurable, nonirradiated MBM ≥1.0 cm were enrolled into two cohorts: (1) those with no neurologic symptoms or steroid Rx (asymptomatic; cohort A); and (2) those with neurologic symptoms, whether or not they were receiving steroid Rx (symptomatic; cohort B). In both cohorts, pts received NIVO 1 mg/kg + IPI 3 mg/kg Q3W × 4, then NIVO 3 mg/kg Q2W until progression or toxicity. The primary endpoint was intracranial clinical benefit rate (CRB); proportion of pts with complete response [CR] + partial response [PR] + stable disease [SD] ≥6 mo). As of the clinical cutoff date on May 1, 2018, all treated pts (101 in cohort A and 18 in cohort B) had been followed for ~6 mo or longer. Results: In this updated analysis of cohort A (median follow-up of 20.6 mo), the CRB was 58.4% (95%CI 41.6-74.1); 9/101 (9%) pts received a median of 1 NIVO+IPI dose, 10/18 (56%) received all doses. At a median follow-up of 5.2 months in cohort B, intracranial objective response rate was 16.7% and the CRB was 22.2%. Grade 3/4 adverse events occurred in 54.5% of pts in cohort A and in 55.6% of pts in cohort B (6.9% and 16.7% in the nervous system, respectively), with oral Rx related to treatment in cohort A (immune-related myocarditis). Conclusions: In pts with asymptomatic MBM, our updated data show a high rate of durable intracranial responses, further supporting NIVO+IPI as a first-line treatment in this population. Intracranial antitumor activity was observed with NIVO+IPI in pts with symptomatic MBM, but further study is needed to understand the biological mechanisms of resistance to immunotherapy and to improve treatments in this challenging population. Clinical trial information: NCT02320058.

508s Melanoma/Skin Cancers

9501 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Pathological response and survival with neoadjuvant therapy in melanoma: A pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). First Author: Alexander M. Menzies, Melanoma Institute Australia, University of Sydney, Royal North Shore Hospital, Sydney, Australia

Background: Pathological complete response (pCR) to neoadjuvant systemic therapy (NST) correlates with survival, and is recognized as a path to regulatory approval in several cancers. Recent trials have reported that neoadjuvant immunotherapy (IT) and targeted therapy (TT) regimens achieve high pCR rates and impressive recurrence-free survival in stage III melanoma. However, the relationship between pCR, relapse-free (RFS) and overall survival (OS) in larger datasets of melanoma patients (pts) remains unknown. Methods: We pooled data from 6 modern NST clinical trials of anti-PD-1 based immunotherapy or BRAF/MEK targeted therapy conducted across institutions participating in the INMC. Pts with RECIST measurable, surgically resectable clinical stage III melanoma who underwent surgery were included. NST regimens included nivolumab (as monotherapy or in combination with ipilimumab), pembrolizumab or dabrafenib+trametinib. Baseline disease characteristics, treatment regimen, pCR and RFS were examined. Results: 184 pts with clinical stage III melanoma (AJCCv7: 100 IIIB, 84 IIIC) completed NST (133 IT, 51 TT) and underwent surgery. Median age was 57y (range 18-87). A pCR was observed in 41% of patients; 51 (38%) with IT and 24 (47%) with TT. Median follow-up post-surgery is 13 mo (95% CI 12-16); 10 mo with IT and 22 mo with TT. 44 (24%) pts have received (17 loco-regional, 21 distant, 6 both sites at first recurrence), 18 (14%) after IT and 26 (51%) after TT. 12-month RFS was improved with IT vs TT (83% vs 65%, p < 0.001). For those with pCR, 7% have recurred, 0/51 (0%) after IT, 7/17 (41%) after TT. For those without pCR, 34% have recurred, 18/82 (22%) after IT and 19/27 (70%) after TT. 12-month RFS was improved in those with pCR vs without pCR (95% vs 62%, p < 0.001), including in those with IT (100% vs 72%, p < 0.001) and TT (88% vs 43%, p < 0.001). 16 (9%) patients have died including two who had a pCR, both from TT. Conclusions: Neoadjuvant IT and TT are active regimens in resectable clinical stage III melanoma patients and are associated with high pCR rate. The ability to achieve pCR correlates with improved RFS and remarkably no patient with pCR from immunotherapy has recurred to date.
9504 Oral Abstract Session, Tue, 9:45 AM-12:45 PM United States Intergroup E1609: A phase III randomized study of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon-α2b for resected high-risk melanoma

First Author: Ahmad A. Tarhini, Emory University and Winship Cancer Institute, Atlanta, GA

Background: Phase III adjuvant trials reported significant benefits in relapse-free survival (RFS) for 6 FDA-approved regimens and overall survival (OS) for HDI and ipi10 versus observation or placebo. E1609 evaluated the relative safety and efficacy of ipi at 3 and 10 mg/kg compared to HDI, which was the adjuvant standard until recently. Methods: E1609 had 2 co-primary end-points: OS and RFS; considered positive if either co-primary endpoint comparison was positive. Activated on 5/25/2011 and completed accrual 8/15/2014. A 2-step hierarchical approach evaluated ipi3 vs HDI followed by ipi10 vs HDI. Patients were stratified by AJCC7 stage (IIIC, M1a, M1b, M1c). Based on protocol criteria, the primary evaluation was conducted using a data cutoff of 2/15/2019. Results: Final adult patient accrual was 1670. 523 randomized to ipi3, 636 to HDI and 511 to ipi10. Treatment related adverse events (AEs) Grade 3 or higher were experienced by 37% pts with ipi3, 79% with HDI and 58% with ipi10, and those of any grade leading to treatment discontinuation were 35% with ipi3, 20% HDI and 54% ipi10. AEs were mostly immune related and consistent with the known toxicity profiles of these agents. Gr5 AEs considered at least possibly related were 3 with ipi3, 2 with HDI and 8 with ipi10. First step comparison of OS and RFS of ipi3 vs HDI utilized an ITT analysis of concurrently randomized cases (N = 1051) and showed significant OS difference in favor of ipi3; HR 0.78, 95.6% CI (.61, 1.00); p = 0.044. The prespecified efficacy boundary was crossed. For OS, HR 0.79 (95% CI (.66, 1.09), p = 0.065. In the 2nd step comparison of ipi10 vs HDI (N = 989), there were trends towards improvement in OS (HR 0.88, 95.6% CI(69, 1.12) and RFS (HR 0.84, 99.4% CI (.65, 1.09)) in favor of ipi10 that were not statistically significant. Conclusions: Adjuvant therapy with ipi3 benefits survival of resected high-risk melanoma pts; for the first time in melanoma patients with stage III disease, adjuvant ipi3 improved the OS. In the comparison of ipi3 vs HDI, the OS difference in favor of ipi3 vs HDI was 18% (95% CI 0.78, 95.6% RCI (.61, 1.00); p = 0.044.

9505 Oral Abstract Session, Tue, 9:45 AM-12:45 PM Melanoma/Skin Cancers

Correlates of overall survival (OS) in metastatic uveal melanoma (mUM) and a randomized trial of cabozantinib ( cabo) versus chemotherapy ( chemotherapy) ( abstract)

First Author: Daniel Olson, University of Chicago Comprehensive Cancer Center, Chicago, IL

Background: Survival is poor in mUM and treatment options are limited. Met kinase is over-expressed on UM and the MET inhibitor cabo showed activity in preclinical assays. Methods: A091201 was a 2:1 randomized phase II study testing cabo for high-risk melanoma. Clinical trial information: NCT01274338.

9506 Oral Abstract Session, Tue, 9:45 AM-12:45 PM Melanoma/Skin Cancers

Correlates of overall survival (OS) in metastatic uveal melanoma (mUM) and a randomized trial of cabozantinib ( cabo) versus chemotherapy ( chemotherapy) ( abstract)

First Author: Daniel Olson, University of Chicago Comprehensive Cancer Center, Chicago, IL

Background: Survival is poor in mUM and treatment options are limited. Met kinase is over-expressed on UM and the MET inhibitor cabo showed activity in preclinical assays. Methods: A091201 was a 2:1 randomized phase II study testing cabo for high-risk melanoma. Clinical trial information: NCT01274338.

Conclusions: Adjuvant therapy with ipi3 benefits survival of resected high-risk melanoma pts; for the first time in melanoma patients with stage III disease, adjuvant ipi3 improved the OS. In the comparison of ipi3 vs HDI, the OS difference in favor of ipi3 vs HDI was 18% (95% CI 0.78, 95.6% RCI (.61, 1.00); p = 0.044.

9507 Oral Abstract Session, Tue, 9:45 AM-12:45 PM Melanoma/Skin Cancers

Five-year analysis on the long-term effects of dabrafenib plus trametinib ( D+T) in patients with BRAF V600-mutant metastatic melanoma

First Author: Paul D. Nathan, Mount Vernon Cancer Centre, Northwood, United Kingdom

Background: First-line treatment with D+T demonstrated prolonged progression-free survival (PFS) and overall survival (OS) in patients with BRAF V600-mutant metastatic disease, with a median PFS of 9.0 months. The current analysis extends the benefit of first-line dabrafenib and trametinib to 5 years following treatment discontinuation in patients with PD-1/PD-L1 inhibitor failure.

Methods: From the ADOReg registry, patients (n = 527) with metastatic melanoma who received dabrafenib plus trametinib as first-line treatment were included in the analysis. Patients who received dabrafenib plus trametinib for ≥3 months were included in the Intent-to-Treat (ITT) analysis. The primary endpoint was durable response (DR), defined as any response lasting ≥6 months after anti-PD-1 failure.

Results: At a median follow-up of 5 years (range, 3.3–6.2 years), 264 patients remained on dabrafenib plus trametinib, 13 had ongoing responses while on treatment, and 170 had discontinued due to disease progression or treatment discontinuation. The 5-year DR rate was 22% (95% CI, 16%-29%). The 5-year survival rate was 30% (95% CI, 22%-40%). The median time to progression was 9 months (95% CI, 7.8–10.3 months) in patients who remained on treatment. The median OS was 31 months (95% CI, 26.4–35.6 months) in patients who remained on treatment. The 5-year OS rate was 15% (95% CI, 9%-22%). The median duration of response was 11 months (95% CI, 9.0–13.0 months) in patients who remained on treatment. The median duration of survival was 13 months (95% CI, 10.8–15.2 months) in patients who remained on treatment. The 5-year OS rate was 15% (95% CI, 9%-22%). Conclusions: The current analysis confirms the durability of response and survival observed in the phase III COMBI-d and COMBI-v trials, with a median follow-up of 5 years. The results demonstrate that dabrafenib plus trametinib offers long-term benefit in patients with BRAF V600-mutant metastatic melanoma who are refractory to anti-PD-1 therapy.
FDA analysis of depth of response (DpR) and survival across 10 randomized controlled trials in patients with previously untreated unresectable or metastatic melanoma (UVM) by therapy type. **Conclusion:** For patients with previously untreated UMM a larger DpR correlates with a longer OS, regardless of therapy type. Deep response (> 75%) is associated with a high rate of estimated OS at 24 months in patients treated with immunotherapy. Analysis of DpR provides additional granularity of response data and may provide a more nuanced perspective on clinical outcome.

<table>
<thead>
<tr>
<th>TKI (n (%); HR (95% CI))</th>
<th>Immunotherapy (n (%); HR (95% CI))</th>
<th>Chemotherapy (n (%); HR (95% CI))</th>
</tr>
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<tbody>
<tr>
<td>G1 vs. G0</td>
<td>299 (13%); 0.41</td>
<td>166 (11%); 0.61</td>
</tr>
<tr>
<td>G2 vs. G0</td>
<td>569 (25%); 0.26</td>
<td>207 (14%); 0.49</td>
</tr>
<tr>
<td>G3 vs. G0</td>
<td>644 (28%); 0.15</td>
<td>202 (14%); 0.33</td>
</tr>
<tr>
<td>G4 vs. G0</td>
<td>296 (13%); 0.10</td>
<td>147 (10%); 0.60</td>
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<tr>
<td>G5 vs. G0</td>
<td>286 (12%); 0.06</td>
<td>232 (16%); 0.14</td>
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**Results:** Of 113 pts, 48 received monotherapy (55 combo; 20 were in the melanoma expansion. Common AEs (> 20%) were fatigue, infusion-related reaction, nausea, abdominal pain, and pruritus; 43 pts had grade ≥ 3 AE (31.6%); 6 (5.3%) were treatment-related. One dose-limiting toxicity (bladder perforation in a urothelial pt with a neobladder) possibly related to study drug was observed with mono. MTD was not reached. No treatment-related deaths. No severe AEs were observed in pts previously treated with UMM a larger DpR correlates with a longer OS, regardless of therapy type. Deep response (> 75%) is associated with a high rate of estimated OS at 24 months in patients treated with immunotherapy. Analysis of DpR provides additional granularity of response data and may provide a more nuanced perspective on clinical outcome.

**Conclusions:** For patients with previously untreated UMM a larger DpR correlates with a longer OS, regardless of therapy type. Deep response (> 75%) is associated with a high rate of estimated OS at 24 months in patients treated with immunotherapy. Analysis of DpR provides additional granularity of response data and may provide a more nuanced perspective on clinical outcome.

9510 Clinical Science Symposium, Sat, 3:00 PM-4:30 PM

Circulating tumor DNA (ctDNA) kinetics to predict survival in patients (pts) with unresectable or metastatic melanoma treated with dabrafenib (D) or D + trametinib (T). **First Author:** Mehrukh M Syeda, NYU Langone Medical Center, New York, NY

**Background:** There are no validated blood-based biomarkers to monitor efficacy in pts with advanced melanoma. Lactate dehydrogenase (LDH) is an established prognostic factor; however, it is not normally used to inform treatment decisions. ctDNA at baseline (BL) is associated with a poor prognosis in pts treated with BRAF and MEK inhibitors, but no studies have examined the association between ctDNA and survival after treatment with BRAF and/ or MEK inhibitor therapy. **Methods:** We measured BRAFV600E/K ctDNA at BL and wk 4 in 3101 patients from a pooled population of pts with unresectable or metastatic melanoma treated with D or D+T in the phase 3 COMBI-d trial (NCT01584648). We used mutation-specific droplet digital PCR assays; ctDNA results were categorized as positive/negative (pos/neg) using an analytically validated detection threshold of 0.25 copies/mL. Progression-free (PFS) and overall survival (OS) were analyzed in all pts and by BL LDH level (> or < upper limit of normal). **Results:** BL ctDNA was detectable in 320/345 pts (92.7%) and was not associated with survival. Nearly all pts had a considerable drop in ctDNA after 4 wks of therapy; 201 pts had paired samples (BL and wk 4) and detectable ctDNA at BL. In 80/201 pts (40%) whose ctDNA changed from pos at BL to neg at wk 4, PFS and OS were prolonged vs 121/201 (60%) whose ctDNA remained pos (median PFS, 9.5 [95% CI, 2.0-22.1] mo vs. 7.4 [5.5-8.9] mo; HR, 0.55 [0.39-0.76]; P = .0003; median OS, 28.2 [20.5-48.8] mo vs. 14.6 [11.8-18.7] mo; HR, 0.56 [0.40-0.79]; P = .0007). Undetectable ctDNA at wk 4 was associated with prolonged PFS and OS, especially in pts with high BL LDH (Table). **Conclusions:** Particularly in pts with high LDH, on-treatment ctDNA monitoring may be helpful for early identification of pts likely to benefit from treatment (T). Comprehensive molecular profiling of metastatic melanoma to predict response to monotherapy and combination immunotherapy. **First Author:** Ines Esteves Domingues Pires Da Silva, Melanoma Institute Australia, Sydney, Australia

**Background:** Several factors have been proposed as biomarkers for response to PD1 therapy, including tumor mutational burden (TMB), immune gene expression, PD-L1 expression and TILs, while few specific mechanisms of resistance have been identified. The relative importance of these factors or different patterns of response for combination immunotherapy have yet to be explored. **Methods:** Cutaneous metastatic melanoma (MM) patients (pts) treated with anti-PD-1 (PD1) +/- anti-CTLA-4 (CTLA4) were selected. Pre-treatment tumors underwent whole genome sequencing (WGS), RNA sequencing (RNAseq) and immunohistochemistry (IHC; TILs and PD-L1). **Results:** Tumors from 77 pts treated with PD1 (n = 53) or PD1+CTLA4 (n = 24) underwent WGS. Higher TMB (p = 0.0001), lower structural variant (SV) burden (p = 0.001) and higher neoantigen load (p = 0.001) were observed in high LDH vs 14.6 [11.8-18.7] mo; HR, 0.56 [0.40-0.79]; **Conclusions:** Of 113 pts, 48 received monotherapy (55 combo; 20 were in the melanoma expansion. Common AEs (> 20%) were fatigue, infusion-related reaction, nausea, abdominal pain, and pruritus; 43 pts had grade ≥ 3 AE (31.6%); 6 (5.3%) were treatment-related. One dose-limiting toxicity (bladder perforation in a urothelial pt with a neobladder) possibly related to study drug was observed with mono. MTD was not reached. No treatment-related deaths. No severe AEs were observed in pts previously treated with UMM a larger DpR correlates with a longer OS, regardless of therapy type. Deep response (> 75%) is associated with a high rate of estimated OS at 24 months in patients treated with immunotherapy. Analysis of DpR provides additional granularity of response data and may provide a more nuanced perspective on clinical outcome.

**Conclusions:** For patients with previously untreated UMM a larger DpR correlates with a longer OS, regardless of therapy type. Deep response (> 75%) is associated with a high rate of estimated OS at 24 months in patients treated with immunotherapy. Analysis of DpR provides additional granularity of response data and may provide a more nuanced perspective on clinical outcome.

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**Conclusions:** Comprehensive molecular and genomic analysis demonstrated that TMB and IFNG expression independently predict response, suggesting defects in both immune recognition or activation in non-responders.

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9512 Poster Discussion Session; Displayed in Poster Session (Board #83), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Update on overall survival in COLUMBUS: A randomized phase III trial of encorafenib (ENCO) plus binimetinib (BINI) versus vemurafenib (VEM) or ENCO in patients with BRAFV600-mutant melanoma. First Author: Gabriella Liszky, Department of Dermatology, National Institute of Oncology, Budapest, Hungary

Background: BRAF/MEK-inhibitor combinations have a central role in the treatment of BRAF V600-mutant melanoma based on demonstrated benefits on progression-free survival (PFS) and overall survival (OS). Because of these meaningful improvements in outcome, mature landmark analyses of PFS and OS, as well as analyses of some prognostic subgroups, require long-term follow-up. Here we report an updated analysis of OS and other endpoints from the COLUMBUS trial. Methods: In Part 1 of COLUMBUS, 577 patients with advanced/metastatic BRAF V600-mutant melanoma, untreated or progressed after first-line immunotherapy, were randomized 1:1 to ENCO 450 mg QD + BINI 45 mg BID (COMBO450) vs VEM 960 mg BID (VEM) or ENCO 300 mg QD (ENC0300). An updated analysis including PFS, OS, objective response rate (ORR), safety and tolerability, and analyses of results by prognostic subgroups including elevated lactate dehydrogenase (LDH) and degree of organ involvement was conducted after an additional 12 months’ follow-up. Results: At data cutoff, there were 116, 113, and 138 deaths in the COMBO450, ENCO300, and VEM treatment arms, respectively. Across arms, median follow-up for OS was 48.6 months (mo), with median OS of 33.6 mo (95% CI, 24.4–43.9) for COMBO450, 23.5 mo (95% CI, 19.6–36.3) for ENCO300, and 33.5 mo (95% CI, 22.0–43.9) for VEM. Compared to VEM, COMBO450 decreased the risk of death by 39% (HR, 0.61 95% CI, 0.48–0.79). Updated median PFS was COMBO450, 14.9 mo (95% CI, 11.0–20.2), ENCO300, 9.6 mo (95% CI, 7.4–14.8), and VEM, 7.3 mo (95% CI, 5.6–8.2). PFS was longer for COMBO450 vs VEM (Hazard ratio [HR], 0.67). Median follow-up for OS was 48.6 months. Updated analysis of subgroup analyses and updated safety and tolerability, will be presented. Conclusions: Updated PFS and OS results for COMBO 450 from the COLUMBUS trial continue to represent new benchmarks for combined BRAF/MEK-inhibitor combinations for treatment of BRAF V600-mutated melanoma. Clinical trial information: NCT01509453.

9513 Poster Discussion Session; Displayed in Poster Session (Board #84), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Responders to anti-PD1 therapy: Long-term outcomes and responses to retreatment in melanoma (mel). First Author: Allison Betoel Warner, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Little is known about patients (pts) who discontinue anti-PD1 therapy after a complete response (CR) outside of clinical trials. There are also limited data about retreatment with a second course of anti-PD1 upon disease progression. Methods: We retrospectively studied pts (n = 398) at MSK who had a measurable (non-unviable) lesion that received ≥1 dose of single-agent anti-PD1 and were followed ≥3 months (mos) after treatment cessation. CR was defined radiographically or by a negative biopsy of residual tissue. Overall survival (OS) and time to treatment failure (TTF, time until next therapy or death) were calculated from time of CR. When to stop therapy and whether to retreat after progressive disease (PD) were at the discretion of the treating oncologist. A subset of pts received a second course of single-agent anti-PD1 ≥3 months after initial discontinuation; retreated pts were evaluable if they had radiographic or clinical evaluation to assess retreatment efficacy. Results: 102 pts (25.6%) achieved CR (n = 89 diagnostic, n = 13 pathologic). Median follow-up was 22.6 mos for survivors who had a CR. Estimated 3-yr OS from time of CR was 82.5% (95% CI 67.4-91.0). For pts who had a CR, therapy was discontinued due to CR (n = 72, toxicity (n = 24), or other reasons (n = 6). The median duration of treatment for CR pts was 9.4 mos (range 1.6–36.1). 20 CR pts later had progressive disease (PD). Median TTF has not been reached (Hazard ratio [HR], 0.67). We found a grade 3-5 treatment-related adverse event (TRAE) rate of 87% (range 70%-95%) in the CR group. 1 pt had a grade 5 TRAE (autoimmune myocarditis; arm A). ORR was 102% in arm A and 71% in arm B remained on treatment. All pts in arm A and 96.1% in arm B had ≥1 TRAE; grade 3-5 TRAE rates were 22% in arm A and 33% in arm B. 1 pt had a grade 5 TRAE (autoimmune myocarditis; arm A). ORR was 49% (95% CI 35-63) in arm A, including 7 CRs and 18 PRs, and 53% (95% CI 39-67) in arm B, including 6 CRs and 21 PRs. An additional 16 pts in each arm had SD or non-CR/non-PD, leading to a DCR of 80% and 84%, respectively. Median response duration was not reached in either arm (range 1.4–to 9.6+ in arm A, 1.4+ to 9.8+ in arm B). Updated data based on longer follow-up will be presented. Conclusions: Standard-dose pembro + ipi 50 mg Q6W and standard-dose pembro + ipi 100 mg Q12W showed robust anti-tumor activity in this initial analysis. Both regimens appeared to have a lower rate of grade 3-5 TRAEs than previously observed. Longer follow-up and randomized studies are needed to confirm that these regimens reduce toxicity without compromising efficacy compared with other anti-PD-1 and ipi combinations. Clinical trial information: NCT02089685.
Impact of body composition on outcomes from anti-programmed death-1 (PD-1) treatment. First Author: Arissa Young, Vanderbilt University Medical Center, Nashville, TN

Background: Obesity is associated with improved outcomes in melanoma patients (pts) treated with PD-1, whereas low muscle mass, known as sarcopenia, has been associated with poor outcomes in many cancers. We sought to assess the impact of body composition on PD-1 outcomes. Methods: We analyzed pre-treatment CT scans at the L3 slice using Slice-o-matic software (Tomovision V. 5.0) to determine skeletal muscle, visceral adipose, and subcutaneous adipose tissue parameters for 104 pts with metastatic melanoma who received PD-1 monotherapy. We assessed sarcopenia using skeletal muscle index (SMI = skeletal muscle area/2D). We also quantified total adipose tissue index (TATI), and skeletal muscle gauge (SMG = SMI x skeletal muscle density [SMD]). We stratified pts into high/low groups using previously published cutoffs and assessed toxicity (tox), progression-free and overall survival (PFS/OS), and response rate (RR) by group. Results: Sarcopenia (low SMI) was negatively associated with any tox (39% vs. 60%, p = 0.04) but not OS, PFS, or RR. Adiposity (TATI) was not associated with outcomes. By contrast, SMG was significantly associated with OS (median 35.5 vs. 16.0 m, p = 0.01 for high vs. low SMG). Interestingly, when incorporating TATI with SMG, we found that high SMG/high TATI pts (high muscle/high fat) have superior clinical outcomes (Table). Notably, low SMG/high TATI pts (low muscle/high fat) had seemingly the worst outcomes among the subgroups we found. We further categorized pts according to their subcutaneous muscle area and density, which was associated with improved OS in PD1 treated pts. Further, pts with high adiposity and high SMG had superior outcomes, potentially identifying the population responsible for the favorable effect of obesity in these pts. Validation and combination treated cohorts will be presented.

9517 Poster Discussion Session; Displayed in Poster Session (Board #88), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Circulating PD-L1-exosomes to monitor tumor response in melanoma patients. First Author: Charlee Nardin, Dermatology, CHU de Besançon, Besançon, France

Background: In the era of effective molecular targeted treatments and immunotherapies, there is an urgent need to implement the use of circulating biomarkers in the clinic to facilitate personalized therapy and predict treatment response. We conducted a retrospective study to demonstrate the involvement of circulating PD-L1 exosomes in melanoma patients. Methods: One hundred melanoma patients were included. Exosomes were isolated by ultracentrifugation and evaluated by nanoparticle tracking analysis using a NS300 Instrument (NanoSight, Amesbury, UK). Isolated exosomes were tested for the expression of exosomes markers such as TSG101. PD-L1 expression in plasma and in melanoma plasma-derived exosomes (ExoPD-L1) was measured using an enzyme-linked immunosorbent assay (PD-L1 Human ELISA Kit, Invitrogen). Results: First, ExoPD-L1 was assessed in melanoma cell lines. Exosomes may have a role in cancer immunosuppression mediated by T-cells since they were as efficient as cancer cells to inhibit T-cells activation. In melanoma patients, ExoPD-L1 (median 64.26 pg/mL) was significantly higher than free PD-L1 in the plasma which was barely detectable (0.1 pg/mL). Furthermore, ExoPD-L1 was detected in all patients whereas only 67% were PD-L1 positive in tumor. Although baseline ExoPD-L1 levels were not associated with clinicopathological characteristics and tumour burden, ExoPD-L1 variations (ExoPD-L1) after treatment correlated with tumour burden. A ΔExoPD-L1 cut-off of > 100 was defined, yielding a 83% sensitivity, a 70% specificity, a 91% positive predictive value and a 54% negative predictive value for disease progression. The use of this cut-off allowed stratification in two groups of patients statistically different in terms of overall survival and progression-free survival. Conclusions: PD-L1 level in circulating exosomes may be a more reliable marker than PD-L1 expression in the tumor tissue. Monitoring of circulating exosomal PD-L1 may be a promising biomarker to predict tumor response and correlate with survival.

9518 Poster Discussion Session; Displayed in Poster Session (Board #89), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Clinical validation of a prognostic 11-gene assay in prospectively collected FFPE tissue of patients with AJCC v8 stage II cutaneous melanoma (CM). First Author: Claus Garbe, Center for Dermatocncology, Department of Dermatology, Eberhard Karls University of Tuebingen, Tuebingen, Germany

Background: AJCC comprises two markers (Breslow thickness and ulceration) to subdivide stage II CM patients into groups with relatively low, average, or high risk of death. Recent updates of clinical guidelines (NCCN, AAD) suggest that patient management will be further tailored to an individual prognosis, e.g. through gene expression profiling (GEP). The aim of this single center study was to clinically validate a prognostic GEP-based risk score (MelaGenix) for stage II CMs. Methods: All obtainable, formalin-fixed paraffin-embedded (FFPE) primary specimens of AJCC stage II CMs from the Central Malignant Melanoma Registry of Germany archived in Tuebingen were included. Study hypothesis and protocol were prospectively formulated. Tumors were analyzed blinded to clinical outcome (data exchange overseen by independent data clearing house) to determine GEP low- vs. high-score groups with a pre-specified GEP score cut-off (>0.5). Melanoma microvacular survival (MSS) was evaluated by Kaplan-Meier (KM) analysis and prognostic performance was assessed by multivariate Cox regression. Results: Study cohort comprised 245 stage II primary carcinomas (IIA/B/C n = 16, IIIB/C n = 25, IIIC n = 36, IIID n = 27). Median OS was 16.8 m (range 1.1-85.7 m), median PFS was 7.4 m (range 0.2-23.2 m), and median RFS was 5.7 m (range 0.1-21.1 m). KM log-rank was significant (p = .018); GEP score contributed independent prognostic information in multivariate Cox regression (p = .024 HR = 1.45 [1.05 - 2.00]) vs. covariates TATI categories (p = .002 HR = 1.59 [1.19 - 2.13]) and age (p = .001 HR = 1.05 [1.02 - 1.09]). Conclusions: First Author: Eddy C. Hsueh, Saint Louis University, St. Louis, MO

Background: A 31-GEP test is a validated prognostic tool for predicting the risk of metastasis in CM, classifying patients (pts) as Class 1 (low risk) or Class 2 (high risk). Here we report updated survival analysis from two clinical registry studies (NCT02355574/NCT02355587) designed to prospectively evaluate outcomes in patients for whom the GEP test was part of their clinical care. Methods: Eleven US dermatologic and surgical centers participated using IRB-approved protocols. Participants were CM pts ≥16 years old who had successful 31-GEP test results. Recurrence-free (RFS), distant metastasis-free (DMFS) and overall survival (OS) were assessed using Kaplan-Meier and Cox regression analysis. Results: At data censoring, 340 pts were accrued who had completed at least one follow-up visit. Median age was 58 years (range 18-87), 53.5% were male, median Breslow thickness was 1.2 mm (range 0.2-12 mm), 18.2% (62/340) were ulcerated, and 11.2% (38/340) had a positive sentinel lymph node (SLN). Median follow-up was 3.2 years for pts without an event. Six percent (16/265) of Class 1 pts had a recurrence compared to 33% (25/75) of Class 2 pts (p < 0.001). Three-year RFS was 96%, 91%, 80%, and 62% for Class 1, 1A, 1B, and 2B, respectively (p < 0.001). Three-year DMFS was 97%, 93%, 84%, and 80% for Class 1A, 1B, 2A, and 2B, respectively (p < 0.001). Three-year OS was 98%, 90%, 96%, and 74% for Class 1A, 1B, 2A, 2B, respectively (p < 0.001). Class 2 was an independent predictor of RFS and OS in multivariate analysis (regression HRs: 2.28 and 3.70, p < 0.05). Conclusions: Consistent with results from previous studies, this analysis demonstrates that the GEP test complements conventional staging and improves the ability to identify high-risk CM pts. This results supports use of the test for guiding decisions related to follow-up, surveillance, and treatment in CM pts. Clinical trial information: NCT02355574/NCT02355587.
Background: We previously reported that neo T-VEC + surgx resulted in a pathologic CR rate of 21% and an OR rate of 14.7% in a randomized trial of neo T-VEC + surgx vs surgx alone. The longest OS for surgx occurred in the neoadjuvant (neo) talimogene laherparepvec (T-VEC) plus surgx arm (Arm 1). The current study demonstrated that bevacizumab in combination with carboplatin plus paclitaxel in patients with previously untreated metastatic melanoma. This study was to evaluate the activity of bevacizumab combined with carboplatin plus paclitaxel in patients with Previously Untreated Advanced Mucosal melanoma. Methods: This is an open-label, multicenter, randomized phase II trial. Eligible patients had, response to pretreatment, resectable mucosal melanoma and no received any systemic therapy before enrollment. Patients were randomly allocated in a 2:1 ratio to receive bevacizumab (CBP arm, 15mg/kg every two weeks) or placebo (CP arm) with carboplatin (area under the curve, 5) plus paclitaxel (175 mg/m²). Treatment was continued for both groups until disease progression, unacceptable toxicity, death, or withdrawal of consent. The primary study endpoint is progress-free survival (PFS). Overall survival, disease control rate, and safety will also be assessed. Results: The first patient visit was December 1st, 2013, and the final data cutoff was August 30th, 2018. At that time, 114 patients were randomly assigned to receive CP or CPB therapy. Median PFS was 3.2 months for the CP arm and 4.7 months for the CPB arm (HR, 0.50; 95% CI, 0.33-0.72; P = 0.001). Median OS was 9.0 months in the CP arm versus 12.5 months in the CPB arm (HR, 0.61; 95% CI, 0.40-0.92; P = 0.02). The PFS was longer in the CPB arm in the subgroup of patients with neutrophil-to-lymphocyte ratio (NLR) more than 4 and patients with abnormal lactate dehydrogenase concentration (1.2 v 3.0 months, HR, 0.38; 2.0 v 4.7 months, HR, 0.50, respectively). Multivariate analysis using a Cox model showed that combination of bevacizumab was the predictor for better disease control and survival (PFS: HR 0.400, 95% CI 0.251-0.636, P < 0.001; OS: HR 0.505, 95% CI 0.33-0.72; P = 0.001). No new safety signals were observed. Conclusions: To our knowledge this is the largest study about advanced mucosal melanoma. This study demonstrated that bevacizumab in combination with carboplatin plus paclitaxel is active and safe regimen as first line treatment in patients with advanced mucosal melanoma. A phase III study will be necessary to confirm the benefit, especially in some special setting such as elevated NLR and elevated LDH subgroups. Clinical trial information: NCT02037103.

Background: ImmTAC molecules are unique TCR–anti-CDS3 bispecifics that redirect T cells against intracellular antigens. IMCgp100, an ImmTAC targeted against melanocyte-expressed gp100 antigen, has demonstrated monotherapy activity in advanced melanoma and can cause rash and cytokine-mediated AEs, hypothesized to be on-target (gp100) or effector (CD3) mediated. A preclinical MoA for T cell bispecifics suggests chemokine CXCL10 redirection of CXCx3+ T cells from blood into antigen-positive tissues; this has not been clinically validated. Methods: 84 HLA-A2+/p+ with advanced melanoma (n = 61 cutaneous (CM), n = 19 uveal (UM), n = 4 other) received IMCgp100 (NCT01211262). Serum (n = 40) and PBMC (n = 22) samples were taken pre- and post-infusion to analyze changes in cytokines and circulating T cells. Pre- (n = 16) and post-treatment (n = 11) tumor biopsies were analyzed by IHC for CD3, PD-L1 and gp100 expression; tumor RNA (n = 12) was analyzed for gene expression. Results: IMCgp100 induced a transient increase in IFNg-inducible cytokines, most prominently CXCL10. A greater increase in serum CXCL10 was associated with longer OS (p = 0.002), tumor shrinkage (p = 0.003), and greater transient reduction in peripheral CXCx3+CD8+ T cells (p = 0.001). RNA induction in CXCx3+ CD8+ T cells also trended with longer OS (p = 0.02), and tumor shrinkage (p = 0.03). 3/16 pre-treatment biopsies had < 1% gp100 expression (all progressive disease). 8/11 biopsies post-IMCgp100 had increased CD3+ T cells compared with matched pre-treatment samples (associated with baseline gp100+ CD8+ T cells but not PD-L1+ CD8+ T cells; p = 0.005). Conclusion analysis, IMCgp100 increased T cell markers, IFNg-inducible and cytotoxicity-related genes. Conclusions: The association of clinical benefit with increased serum CXCL10 and decreased peripheral CXCx3+ T cells supports the MoA of IMCgp100-induced T cell redirection and activation. This study demonstrates the need for IMCgp100 trials in advanced melanoma with positive tumor. A Phase II trial in CM (NCT02535078), a Phase I/II trial in UM (NCT02575038), and a Pivotal RCT in UM (NCT03070392) are ongoing. Clinical trial information: NCT00121162.

Pharmacodynamic effect of IMCgp100 (TCR–CDS3 bispecific) on peripheral cytokines and association with overall survival in patients with advanced melanoma. First Author: Mark R. Middleton, Churchill Hospital, Oxford, United Kingdom.

Background: ImmTAC molecules are unique TCR–anti-CDS3 bispecifics that redirect T cells against intracellular antigens. IMCgp100, an ImmTAC targeted against melanocyte-expressed gp100 antigen, has demonstrated monotherapy activity in advanced melanoma and can cause rash and cytokine-mediated AEs, hypothesized to be on-target (gp100) or effector (CD3) mediated. A preclinical MoA for T cell bispecifics suggests chemokine CXCL10 redirection of CXCx3+ T cells from blood into antigen-positive tissues; this has not been clinically validated. Methods: 84 HLA-A2+/p+ with advanced melanoma (n = 61 cutaneous (CM), n = 19 uveal (UM), n = 4 other) received IMCgp100 (NCT01211262). Serum (n = 40) and PBMC (n = 22) samples were taken pre- and post-infusion to analyze changes in cytokines and circulating T cells. Pre- (n = 16) and post-treatment (n = 11) tumor biopsies were analyzed by IHC for CD3, PD-L1 and gp100 expression; tumor RNA (n = 12) was analyzed for gene expression. Results: IMCgp100 induced a transient increase in IFNg-inducible cytokines, most prominently CXCL10. A greater increase in serum CXCL10 was associated with longer OS (p = 0.002), tumor shrinkage (p = 0.003), and greater transient reduction in peripheral CXCx3+CD8+ T cells (p = 0.001). RNA induction in CXCx3+ CD8+ T cells also trended with longer OS (p = 0.02), and tumor shrinkage (p = 0.03). 3/16 pre-treatment biopsies had < 1% gp100 expression (all progressive disease). 8/11 biopsies post-IMCgp100 had increased CD3+ T cells compared with matched pre-treatment samples (associated with baseline gp100+ CD8+ T cells but not PD-L1+ CD8+ T cells; p = 0.005). Conclusion analysis, IMCgp100 increased T cell markers, IFNg-inducible and cytotoxicity-related genes. Conclusions: The association of clinical benefit with increased serum CXCL10 and decreased peripheral CXCx3+ T cells supports the MoA of IMCgp100-induced T cell redirection and activation. This study demonstrates the need for IMCgp100 trials in advanced melanoma with positive tumor. A Phase II trial in CM (NCT02535078), a Phase I/II trial in UM (NCT02575038), and a Pivotal RCT in UM (NCT03070392) are ongoing. Clinical trial information: NCT00121162.

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Progression-free survival (PFS) in unresectable melanoma patients (pts) treated with talimogene laherparepvec (T-VEC) versus granulocyte macrophage colony-stimulating factor (GM-CSF) in OPTiM. First Author: Mohammed M. Milhem, University of Iowa Hospitals and Clinics, Iowa City, IA

Background: T-VEC is a modified oncolytic herpes virus design aimed as an intrallesional therapy for unresectable advanced melanoma. OPTiM was a randomized, phase 3 trial that showed improved durable response rate (DRR) with T-VEC vs GM-CSF in pts with unresectable melanoma with regional or distant metastases (16.3% vs 2.1%, p < 0.001). Treatment benefit of T-VEC included improved DRR and overall survival (OS) in stage IIIb-IVM1a with IVM1b-IVM1c melanoma. This is the first report of PFS for T-VEC vs GM-CSF.

Methods: OPTiM included pts ≥18 yrs with unresectable stage IIIb-IV melanoma; ≥1 injectable cutaneous, subcutaneous (SC), or nodal lesion; ECOG ≤1; LDH ≤1.5 ULN; ≤3 visceral metastases (excluding lung) with none ≥3 cm. Pts were randomized 2:1 to receive intralesional T-VEC or SC GM-CSF. The primary endpoint was DRR (partial or complete response continuously for ≥6 mo starting within 12 mo) and reported previously. In this post hoc analysis, PFS was evaluated overall and by disease stage.

Results: This analysis included 436 pts; 295 (68%) T-VEC, 141 (32%) GM-CSF. 67% men; 63 yr median age; 57% stage IV in stage IVM1a, 15% in stage IVM1b-IVM1c. In the intention to treat set, T-VEC significantly improved PFS (HR: 0.60, 95% CI: 1.9, 20.1). In stage IIB-IVM1a, PFS favored the T-VEC arm vs the GM-CSF arm (HR: 0.60, 95% CI: 0.54, 0.85, unstratified log-rank p < 0.001). In stage IIB-IVM1a, IVM1b-IVM1c, the 12 mo PFS rate for T-VEC was 19.6% (95% CI: 1.0, 1.18) and GM-CSF was 10.8% (95% CI: 0.6, 1.76). In stage IVM1b-IVM1c, the 12 mo PFS rate for T-VEC was 19.9% (95% CI: 0.5, 26.6) and GM-CSF was 3.2% (95% CI: 0.6, 9.9). In stage IVM1b-IVM1c, the 12 mo PFS rate for T-VEC was 7.4% (95% CI: 3.5, 13.2) and GM-CSF was 8.0% (95% CI: 1.9, 20.1).

Conclusions: T-VEC demonstrated an improvement in PFS vs GM-CSF, driven primarily by pts with stage IIB-IVM1a melanoma. This is consistent with the post hoc analysis showing more pronounced OS benefit with T-VEC and greater efficacy with other immunotherapies in early metastatic disease. Clinical trial information: NCT00797047.

Immunotherapy disparities in metastatic melanoma. First Author: Thomas Oliver, Department of Medicine, Lankenau Medical Center, Wynnewood, PA

Background: Historically, patients with advanced malignant melanoma had a dismal prognosis with an estimated median overall survival of nine months. Those response rates to the long term survival have significantly improved with the advent of immunotherapies and targeted chemotherapies. First approved in 2011, there has been subsequent development of more advanced immunotherapeutic agents and targeted chemotherapies, with continued improvement in median overall survival. We examined patterns in the use of immunotherapy and other systemic therapies for metastatic melanoma, as well as the demographic and socioeconomic predictors for the use of these therapies, in order to identify and understand potential barriers to access in the United States.

Methods: We used the NCDB for all patients aged 18-years and older who were diagnosed with metastatic melanoma of cutaneous origin from 2004-2014. Patients were included if they had distant metastases. American Joint Committee on Cancer (AJCC) Stage IV. Sociodemographic data, including race, age, insurance status, facility providing care, Charlson/Deyo comorbidity score11, and education by patient’s zip code, were collected. Results: In patients under age 65 with a Charlson-Deyo score of zero, immunotherapy utilization was 18.8% (6377 of 33 147,183). Immunotherapy use for metastatic melanoma has been relatively slow despite evidence showing an overall survival benefit; our analysis suggests this is explained in part by socioeconomic barriers.

9527 Poster Session (Board #98), Mon, 1:15 PM-4:15 PM High incidence of brain metastases (BrM) in patients with metastatic cutaneous melanoma (MCM) and mutations in the APC/ctnatin (CTNNB1). First Author: Georgia Sofia Karachalio, Department of Medicine, Division of Hematology/Oncology, Chapel Hill, NC

Background: Brain metastases (BrM) are frequently associated with absent TILs. We aimed to investigate if APC/CTNNB1 mutations (MCM) in pts with MCM and absence of TILs. Pts with CM and APC/CTNNB1 mutations identified in MCM tumors using the TruSight Tumor 26 Illumina assay were enrolled. Demographics, clinical stage, response to treatment, follow-up, pathologic (TIL status), and molecular (BRAF/NRAS, C–T (i.e. UV signature) nucleotide transition, functional significance of impact) were evaluated.

Results: We identified a total of 25 pts (13 males; age at diagnosis (median 61 yrs, range 22-78 yrs). CTNNB1 and APC mutations were mutually exclusive. 48% (12/25) had APC mutations and 52% (13/25) had CTNNB1 mutations of which (i.e. CTNNB1 mutations) 69% (9/13) had absent TILs. 88% (22/25) of APC/CTNNB1 mutations had moderate functional significance, 64% (16/25) of the mutations had a C–T nucleotide change, 36% (9/25) had BRAFV600E, and 20% (5/25) NRASG61 mutations. 64% (14/22) of pts with stage II-III progressed to stage IV; of these 14 pts, 8 (57%) developed perehynchaly BRm. 13 of the stage II-III 22 pts who progressed to stage IV received II; of these 13 pts, 7 (53%) had absent TILs. APC/CTNNB1 mutations did not influence response to II, irrespective of the MAF of the mutations. Of the 12 pts with MCM and measurable disease who received II 912 had absent TILs and 712 responded. The median OS from the time of diagnosis of distant MCM (N = 17; 14 pts who progressed from initial stage II-III and 3 pts who were originally diagnosed with stage IV) was 18.8 months (range, 2.4-48.0 months). Conclusions: APC & CTNNB1 mutations are mutually exclusive. CTNNB1 mutations are more frequently associated with absent TILs. Pts with CM had relatively shorter OS (18.8 months) in part due to development of BM. In this setting, APC/ CTNNB1 mutations did not appear to bear a relationship to immunotherapy.

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Poster Session (Board #99), Mon, 1:15 PM-4:15 PM

Palbociclib (P) in advanced acral lentiginous melanoma (ALM) with CDK4 pathway gene aberrations. First Author: Lili Mao, Key Laboratory of Carcino- genesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Collaborative Innovation Center for Cancer Medicine, Beijing, China

Background: Genetic Aberrations in the CDK4 Pathway occur in 82% of the ALM pts (Clin Cancer Res, 2017, 23(22):6946-6957), which is a predominant subtype in China. This study is to evaluate the anti-tumor activity of palbociclib, a CDK4/6 inhibitor, in advanced ALM pts with CDK4 pathway gene aberrations. Methods: In this phase II trial, patients with advanced ALM with CDK4 pathway gene aberrations (CDK4 or/and CCND1 amplification or/and CDKN2A loss) were treated with palbociclib 125 mg po, d1-21 of 28 day cycles. According to the study design, this trial will be closed if less than 2 patients yield objective response (OR) or stable disease (SD) at a preset 8-week landmark analysis. Secondary endpoints are progression-free survival (PFS), overall survival (OS) and safety. Results: Fifteen pts were enrolled from April to Nov 2018. All pts are included in the data analysis for demographics, safety, ORR, PFS and OS. Median age was 54 y (range, 25-74y), 6(40%) were males, 5(33.3%) had the primary sites of subungual, 4(26.7%) were of stage III. Median number of prior therapies: 2 (range: 0-5). Three (20.0%) pts achieved tumor shrinkage at 8 wks, including 1 confirmed partial responses (PR). Two pts had treatment ongoing at the data cutoff (January 2019). Median PFS was 2.5m (range, 1.5-8.8m), estimated mean OS was 8.1m (range, 6.7-9.4m). Four pts deceased due to disease progression. The most common treatment related adverse events (TRAEs) were leukopenia/neutropenia (87%; 6/15 pts), neutropenic fever (20%; 3/15 pts), pyrexia, and increased lipase. One pt died of cardiac arrest that was not treatment related. Conclusion: The 2 most frequent Grade 3 AEs were neutropenia and sole, 123 were included in the study. Anti-PD-1 antibody was used as first-line therapy in 143 pts (74.1%). Nivolumab was used in 168 pts and pembrolizumab in 25 pts. Base-line lactate dehydrogenase (LDH) was within normal level in 102 pts (92.8%). The objective response rate (ORR) of pembrolizumab was 16.5% (complete response 3.1%, partial response 13.5%), and median overall survival (OS) was 18.1 months. Normal LDH level was significantly associated with better prognosis than abnormal level (median OS 24.9 vs 10.7 months; P < 0.001). Although baseline demographics and character- istics were similar similar, the subungual group was more aggressive. ORR was significantly lower in the subungual group than in palm and sole group (6/70 pts [8.6%] vs 26/123 pts [21.1%]; P = 0.026). Median OS was significantly poorer as well (12.8 vs 22.3 months; P = 0.031). Immune-related adverse events of grades 3 to 5 occurred in 27 pts (14.0%). One patient (0.5%) died of grade 5 myasthenia gravis. Conclusion: The anti-PD-1 antibodies in AM pts is limited. Notably, pts with subungual melanoma showed poorer response and survival, making them strong candidates for further research of efficacy of anti-CTLA-4 and anti-PD-1 combination therapy.

Poster Session (Board #101), Mon, 1:15 PM-4:15 PM

Relationship between clinical efficacy and AEs of IMCgp100, a novel bispecific TCR-anti-CD3 bispecifics that redirect T cells against intracellular antigens. IMCgp100, an ImmTAC targeted against melanocyte-associated lineage antigen gp100, has shown monotherapy responses in advanced melanoma with associated immune changes. IMCgp100 causes rash and cytokine-mediated AEs, hypothesized to be on-target (gp100) or effector (CD3) mediated. We explored clinical and biological characteristics of pts associated with treatment benefit. Methods: 84 HLA-A2 positive advanced melanoma pts received IMCgp100 on study IMCgp100-01 in 13 dose escalation cohorts. Efficacy was assessed by Kaplan–Meier survival and treatment related AEs (TRAE) reported by CTCAE v4.0. Serum samples evaluated changes in cytokines. A multivariate analysis investigated the relationship between efficacy and safety variables. Results: Demographics: 73% cutaneous (CM), 23% uveal (UM) primaries; 51% LDH $> ULN (p = 0.002) and any-grade rash occurring within first 3 doses. The 2 most frequent Grade $\geq 3$ TRAEs were rash (26%) and lymphopenia (13%). IMCgp100 induced transient increases in peripheral cytokines (peaking Day 1–2) that attenuated with subsequent doses; cytokine-mediated AE had similar kinetics. 1 yr OS was 65% (95% CI: 48–78). In multivariate analysis, longer OS was associated with: LDH $\leq$ ULN (p = 0.002) and any-grade rash occurring within 21 days (p = 0.003); melanoma primary site and prior anti-PD-L1 (p = 0.01). Conclusion: IMCgp100 is a first-in-class, TCR-based bispecific with monotherapy efficacy in advanced melanoma. AEs were manageable and consistent with MoA. Association between IMCgp100 efficacy and on-target TRAEs, previously reported for bispecifics to heme lineage antigens, is now recognized for antibody-drugged neutral in clinical studies in UM are on target. Clinical trial information: NCT01211262.

Poster Session (Board #100), Mon, 1:15 PM-4:15 PM

Real-world efficacy of anti-PD-1 antibodies in advanced acral melanoma patients: A retrospective, multicenter study (UAMP study). First Author: Yasuhiro Nakanishi, Saitama Medical University International Medical Center, Saitama, Japan

Background: Anti-PD-1 antibodies are used worldwide for patients (pts) with advanced melanoma. Clinical trials have demonstrated its efficacy and safety for nonacral cutaneous melanoma (NACM) in controlled settings. Since acral melanoma (AM) is epidemiologically and molecularly distinct from NACM, data on the real-world efficacy of anti-PD1 antibodies in advanced AM is still lacking. Thus, we aim to analyze the real-world efficacy and safety of anti-PD-1 antibodies in advanced AM. Methods: We retrospectively reviewed clinical records of advanced AM treated in any line with an anti-PD1 antibody at 21 Japanese institutions. Clinical response was assessed by (Response Evaluation Criteria in Solid Tumors) RECIST criteria. Survival was estimated using Kaplan–Meier analysis. Toxicity was assessed according to CTCAE v4.0. Results: A total of 193 pts (median age, 71 years) with advanced AM (subungual, 70; palm and sole, 123) were included in the study. Anti-PD-1 antibody was used as first-line therapy in 143 pts (74.1%). Nivolumab was used in 168 pts and pembrolizumab in 25 pts. Lineal base lactate dehydrogenase (LDH) was within normal level in 102 pts (92.8%). The objective response rate (ORR) of pembrolizumab was 16.5% (complete response 3.1%, partial response 13.5%), and median overall survival (OS) was 18.1 months. Normal LDH level was significantly associated with better prognosis than abnormal level (median OS 24.9 vs 10.7 months; P < 0.001). Although baseline demographics and character- istics were similar similar, the subungual group was more aggressive. ORR was significantly lower in the subungual group than in palm and sole group (6/70 pts [8.6%] vs 26/123 pts [21.1%]; P = 0.026). Median OS was significantly poorer as well (12.8 vs 22.3 months; P = 0.031). Immune-related adverse events of grades 3 to 5 occurred in 27 pts (14.0%). One patient (0.5%) died of grade 5 myasthenia gravis. Conclusion: Real-world efficacy of anti-PD-1 antibodies in AM pts is limited. Notably, pts with subungual melanoma showed poorer response and survival, making them strong candidates for further research of efficacy of anti-CTLA-4 and anti-PD-1 combination therapy.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Both pembrolizumab (PEMBRO) and combination ipilimumab + nivolumab (IPI+IIVO) are FDA-approved immunotherapies for advanced melanoma (AM). These two treatment regimens have different toxicity profiles which may impact health care resource utilization (HCRU). Our aim was to compare real-world risk of hospitalization and emergency department (ED) visits within 12 months of starting the two treatment regimens. Methods: A retrospective cohort study was conducted in patients >18 years old with AM initiating PEMBRO or IPI+NIVO between Jan 1, 2016 – Dec 30, 2017. Patients were identified from 12 US academic medical centers and affiliated satellite clinics. Data were abstracted through chart review. All-cause hospitalizations or ED visits and the rates per patient per month (PPPM) through 12 months of follow-up were calculated. Utilization was compared between PEMBRO and IPI+NIVO using multivariate logistic regression analysis. Results: 400 patients were included, 200 each PEMBRO and IPI+NIVO with mean (SD) follow-up time of 10 (3) and 10 (4) months, respectively. The PEMBRO cohort had poorer Eastern Cooperative Group (ECOG) performance status at treatment start, 71% ECOG 0 or 1 vs 88% (p < .001); more diabetes, 21% vs 13% (p = .045); a trend towards more heart disease, 18% vs 12% (p = .067); were more likely to be PD-L1 expression positive, 77% vs 63% (p = .011); and less likely to harbor a BRAF mutation, 35% vs 50% (p = .039). The proportion with at least one hospitalization through 12 months was 17% PEMBRO vs 24% IPI+NIVO. Less than 2% of patients had more than two, regardless of cohort. Unadjusted mean (SD) PPPM hospitalizations were .016 (.037) for PEMBRO and .020 (.038) for IPI+NIVO. The adjusted odds ratio for any hospitalization with PEMBRO was 0.55 (95% CI 0.31, 0.97; p = .039) vs. IPI+NIVO. ED visits occurred in 18% vs 24% PEMBRO and IPI+NIVO respectively, with no difference in covariate-adjusted analysis (p = .147). Conclusions: Patients receiving PEMBRO had a significantly lower probability of hospitalization and similar probability of ER visits compared with IPI+NIVO in the real world through 12 months.
Immune profile of metastatic uveal melanoma during treatment with pembrolizumab. First Author: Ernesto Rossi, Medical Oncology Fondazione Poliambulanza, University of Innsbruck, Italy. Rome, Italy

Background: Metastatic uveal melanoma (mUM) is a rare and aggressive disease. No standard therapy has been established. All the available treatments derive from trials in cutaneous melanoma. A minority of patients with mUM can benefit from immunotherapy. Immunological features of a group of patients with metastatic UM treated with Pembrolizumab were analyzed in order to explore the immune-response in this disease and the potential factors able to select the patients who can benefit from immunotherapy. Methods: Blood samples from 12 UM patients before (TO) and during treatment with Pembrolizumab (T1: after 1 cycle of Pembrolizumab; T2: after 3 cycle of Pembrolizumab) were collected. Peripheral blood mononucleated cells (PBMCs) were isolated and characterized for markers expression. Sera were analyzed for a panel of soluble (s) immune checkpoints and cytokines. The correlation between immunological parameters with PFS and OS was explored. Blood samples from 6 metastatic cutaneous melanoma (CM) patients with a confirmed response to anti PD-1 agents were also collected during the treatment and analyzed for PBMCs and sera. Results: Soluble CTLA4, sPD-L1, sCD137, sTIM3 were significantly higher in UM than in CM. sCD137 was significantly higher in UM patients who progressed with Pembrolizumab than in the 2 responsive patients (512 pg/ml vs < 12.9 pg/ml, respectively, p = 0.04) who are still alive and on treatment after a median follow-up of 24 months. Low sGITR, sCD137, SHVEM, and sTIM3 are associated with longer PFS. IL-8 was lower in CM than UM (2.5 pg/ml vs 7 pg/ml) and was more responsive versus untreated versus recurrent samples (2.5 pg/ml vs 118 pg/ml, p = 0.042). Low levels of IL-8 and IL-1-alpha are significantly associated with longer PFS (p = 0.011 and 0.010 respectively). In responsive patients CD137 expression on CD3+, CD4+ and CD8+ T cells was higher than in progressed patients, while sCD137 was absent. Conclusions: A group of s-immune checkpoints and cytokines correlates with a better outcome in mUM. High expression of CD137 on T cells associated with the absence of its soluble form in responders could suggest the correlation between the retention of this co-stimulatory molecule and efficacy of anti-PD1.

Efficacy of hypofractionated radiotherapy (Rx) in melanoma patients who failed anti-PD-1 monotherapy: Assessing the abscopal effect. First Author: Philippe Sagot, General & Oncologic Dermatology, CHU, Amiens, France

Background: Radiotherapy (Rx) and anti-PD-1 mAb are potentially synergistic. No study has tested this combination only in pts who failed on anti-PD-1 mAb, which allows to assess the abscopal effect. We evaluated this combination in a cohort of advanced melanoma pts after failure of anti-PD-1 monotherapy. Methods: Analysis of a prospective database in a referral center searching for advanced melanoma pts with confirmed (12 CT-scans) progressive (PD) or stable (SD) disease on anti-PD-1 monotherapy, who later received concurrent Rx without modification of anti-PD-1 mAb regimen. Radiologists performed independent tumor evaluations (RECIST 1.1) every 3 m, both on radiated and non-radiated lesions, with abscopal effect defined as a partial (PR) or complete (CR) response outside radiated fields. Results: 26 pts (21 achieving PD, 5 SD, 10 pt < 3 involved organs), mean age 70 Y, were included. Anti-PD-1 mAb was first line in 50% of pts. Rx, consisting of hypofractionated Rx (3-5 sessions, 26 Gy), standard palliative Rx, or gamma-knife in respectively 23, 2, and 1 pts, was begun on a single side of the body in 53% of pts on 2 sites after a median of 5 m after beginning anti-PD-1 mAb. Median follow-up after onset of anti-PD-1 mAb was 17 (7-35) m, with 65% of pts alive at last follow-up. Best response was 7 CR (27%, including CR in 4 pts with prior PD) 1 PR, 3 SD (12%), 15 PD (58%). Abscopal effect was seen in 10 pts (38%). No correlation between the occurrence of CR and BRAF/NRAS mutation status, number of metastatic sites, presence or absence of brain metastases, and LDH level was seen. Anti-PD-1 mAb could be discontinued in 6 pts with CR, without relapse to date. No unusual adverse event was recorded. Conclusions: In pts who have previously failed on anti-PD-1 mAb, obtaining concurrent Rx and without modifying anti-PD-1 mAb regimen can be done. Immunohistochemical analysis of CM and UM serum samples showed significantly lower levels of IL-8 and IL-1-alpha in UM than in CM (2.5 pg/ml vs 26 pg/ml, p = 0.042). Low levels of IL-8 and IL-1-alpha are significantly associated with longer PFS and OS. IL-8 and IL-1-alpha are significantly associated with longer PFS and OS. Conclusions: IL-8 and IL-1-alpha can serve as novel biomarkers in melanoma patients who have received anti-PD-1 mAb but not nivolumab plus ipilimumab. Hypo-fractionated radiotherapy may enhance anti-PD1 monotherapy efficacy in melanoma pts who failed on anti-PD-1 mAb. Controlled studies are needed.
Clinical and PDG-FET markers of immune checkpoint inhibitor (ICI) response in patients with metastatic Merkel cell carcinoma (mMCC). First Author: Alison Weymouth, Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia

Background: mMCC is a rare, highly aggressive neuroendocrine cancer with a poor prognosis. ICIs have favourable efficacy and safety in clinical trials. We outline single centre experience utilising ICIs in mMCC. Methods: Medical records of patients (pts) with mMCC treated with ICIs from Aug 2015 to Dec 2018 at Peter MacCallum Cancer Centre, Australia were retrospectively analysed. Baseline tumour volumes and responses were assessed with PDG-FET scans using the HICKS criteria.

Results: 23 pts with mMCC were treated with ICIs. Pt characteristics are summarised in Table. A median of 8 cycles (range 1 to 47) were administered, with treatment ongoing in 7 pts. Objective responses (OR) were observed in 14 pts (61%), 10 (44%) complete metabolic responses (CMR) and 4 (17%) partial metabolic responses (PMR). Median time to response was 3 weeks (range 4 to 11) and 12-month progression-free survival (PFS) rate was 32%. Increased OR were seen in pts aged less than 75 (OR 8/10, 80% vs 46%), no prior history of chemotherapy (OR 10/14, 71% vs 44%), pts with an immune-related adverse event (irAE) (OR 6/6, 100% vs 47%) and in MCPyV negative pts (OR 11/12, 83% vs 50%). Pts with a CMR had lower mean-tumor volume on baseline PDG-FET scan (CMR: 35.7ml, no CMR: 187.8ml, p value 0.05). 10 pts received radiation (RT) during ICI. 4 pts started RT concurrently (OR 75%; CMR 50%), 3 pts had isolated ICI-resistant lesions successfully treated with RT and 3 pts with multisite progression continued to progress despite RT. 6 pts (26%) had a Grade 1-2 irAE.

Conclusions: ICIs showed efficacy and safety consistent with trial data. Younger age, negative MCPyV status, no prior chemotherapy, lower baseline PDG-FET tumour volume and irAEs are potentially associated with better responses.

Characteristics n=23

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tr>
<td>Other (BGB-A177)</td>
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Clinical models to predict response and survival in metastatic melanoma (MM) patients (pts) treated with anti-PD1 alone (PD1) or combined with ipilimumab (IPi+PD1). First Author: Ines Esteves Domingues Pires Da Silva, Melanoma Institute Australia, Sydney, Australia

Background: Currently there are no robust biomarkers to predict immune-therapy response in MM. Specific clinical and molecular variables have been proposed, but in most cases, these factors have been studied individually. We sought to build a predictive model for response rate (RR), progression-free survival (PFS) and overall survival (OS), by including clinical data available at the point of treatment selection for MM pts treated with PD1 or IPi+PD1. Methods: 786 MM pts were included in 4 cohorts: 447 pts treated with PD1 (discovery, n = 343; validation, n = 104) and 339 pts treated with IPi+PD1 (discovery, n = 229; validation, n = 110). Demographics, disease characteristics and baseline blood parameters were examined. Predictive models were selected using multivariate Cox proportional hazard model, logistic regression and LASSO. ROC curve analyses were performed for each model and validation was measured by discrimination index (c-statistic).

Results: Predictive models for RR and PFS in PD1 pts (AUC = 0.69 and AUC = 0.71, respectively) included mutational status, V600 BRAF, and LDH. Predictive models for RR and PFS in IPi+PD1 treated pts (AUC = 0.71 and AUC = 0.73, respectively) included AJCC stage M1C/M1D, HR for PFS: 2.12, P < 0.0001 and monocyte count > median (HR for PFS: 1.56, P = 0.033). Predictive models for RR and PFS in IPi+PD1 treated pts (AUC = 0.71 and AUC = 0.73, respectively) included AJCC stage M1C/M1D, HR for PFS: 2.12, P < 0.0001, liver mets (HR for PFS: 1.63, P = 0.038) and basophil count > median (HR for PFS: 0.50, P = 0.003). ECOG ≥ 1, elevated LDH and brain mets associated with worse OS and were included in predictive models for OS in PD1 (AUC = 0.74) and IPi+PD1 (AUC = 0.85). These models showed consistency with trial data of tumor assessments (RECIST 1.1) prospectively stored in our database and AE (CTCAE 4.0) blinded to PCD/T results. Each AE was associated with the closest sample harvested to the beginning of AE, or in the absence of AE with the highest PCD/T level for each patient. Results: We analyzed 75 D and 58 T assays from 36 pts (19M/17F), treated with D+T for metastatic melanoma (Stage IV: N = 35), mostly in first line (69.4%). Initial D dose was 300 mg/d and 2 mg/d for T, reduced in 10 patients (27.7%) for AE; to 30% of D (N = 8) and 25% of T (N = 8). High interindividual variability of PCD (range: 4.945ng/mL, median 70.0) and of PCT (5-25mg/mL, median 8.6) was observed. No differences between mean PCD/T at the time of evaluations showing progression disease (PD) compared to those without PD pts (146.6±111.6 and 9.3±2.1) and pts with complete (N = 11), partial (N = 1) or stable response (N = 346.6±127.6, 160.6±127.6, and 10.6±11.6) were observed. No significant relationship was shown between PCD/T and body mass index (r = 0.22 and −0.31), age (p = 0.19 and 0.26), or between PCD/T and D (p = 0.11) or P (p = 0.17) doses, neither between elevated mean PCD/T and any most common AE. Conclusions: This study has shown a high interindividual variability of PCD/T and that association between PCD/T and PD is not a universal one. AE are not the same and initial dose selection is not possible.
Melanoma/Skin Cancers 519s

9544 Poster Session (Board #115), Mon, 1:15 PM-4:15 PM Predictable early onset high-dose-glucocorticoid-associated-irAE and its predictive role in anti-PD-1 monotherapy treated advanced melanoma patients. First Author: Xue Bai. Massachusetts General Hospital Cancer Center/Peking University Cancer Hospital, Boston, MA

Background: Though uncommon, a subgroup of patients with melanoma develop early-onset severe immune-related adverse effects (irAEs) that require immunosuppressive treatment with high-dose glucocorticoids (HD-GCCs). We aimed to examine the impact of early onset HD-GCC-associated-irAE (EO-HGA-irAE) in the setting of anti-PD-1 monotherapy initiation on prognosis and to develop a predictive scoring system.

Methods: Clinical data was collected retrospectively from advanced melanoma patients treated with anti-PD-1 monotherapy at Massachusetts General Hospital from Sept 2009 to Dec 2017. The relationship between EO-HGA-irAE and PFS (defined as time from anti-PD-1 monotherapy initiation to PD) was assessed using 8-week conditional landmark analysis (Kaplan-Meier curves, log-rank test) and time-dependent Cox regression model (multivariate analysis). Demographic characteristics and baseline laboratory variables were collected and correlated with occurrence of EO-HGA-irAE using logistic regression modeling. Best cutoff values were identified using ROC curve (Youden index) to dichotomize continuous variables.

Results: Among 146 patients, 13 (8.9%) developed EO-HGA-irAE. In an 8-week landmark analysis, median PFS was 2.9 (95% CI, 2.8-3.0) and 17.5 (95% CI, 10.8-24.2) months (P = .001) for patients with and without EO-HGA-irAE, respectively. Multivariate analysis revealed that EO-HGA-irAE was independently correlated with significantly higher risk of disease progression with hazard ratio of 2.4 (95% CI 1.4-4.0) (P = .001). Selected predictive variables (P < .25 for continuous variables, P < .1 for dichotomous variables) in favor of the occurrence of EO-HGA-irAE included age, baseline glucose, and neutrophil, eosinophil, and WBC count. After dichotomization and further validation using a logistic regression model, a scoring system (score range 0-3) composed of 3 dichotomized predictive, including age, baseline laboratory, and baseline neutrophil count was developed with odds ratio of 3.4 (95% CI, 1.6-8.8) (P = .001).

Conclusions: The probabilities of patients scoring 0, 1, 2, 3 of developing EO-HGA-irAE were 11.5%, 35.5%, 11.1%, and 29.9%, respectively. Development of a scoring system based on age score, easily accessible, routinely tested biomarkers can be used to help predict the risk of EO-HGA-irAE occurrence. Validation with a larger sample size is required.

9546 Poster Session (Board #117), Mon, 1:15 PM-4:15 PM Identification of a gene expression signature predictive of clinical benefit in patients with advanced mucosal melanoma (MCM) treated with anti-PD-1 checkpoint blockade. First Author: Sunthep Risupiwon, Georgetown University, Lombardi Comprehensive Cancer Center, Washington, DC

Background: MCM is a rare melanoma subtype (only 1% of melanomas in the US). MCM has a lower tumor mutational burden than cutaneous melanoma (CM). While some patients (pts) with MCM respond to immune checkpoint inhibitor (ICl) therapy, predictive markers of response have not been established. We analyzed a cohort of MCM from pts treated with ICI to identify gene expression signatures associated with tumor response and clinical outcome.

Methods: Fifty-eight MCM specimens were collected from 3 institutions. RNA was extracted from FFPE tissue slides and analyzed by NanoString 770 Immune Profiling Panel. Gene expression profiles were linked to anatomical location and disease outcome after ICI therapy: response as defined by RECIST v1.1 and median overall survival (mOS).

Results: Fifty-one pts were treated with ICI - anti-CTLA-4 (n = 9), anti-PD1 (n = 38), or both (n = 5) and had tumor response evaluation. Three were without response data, 2 were without disease recurrence after surgery, 2 did not receive ICI. Among 51 pts with response data, seven were without long-term follow-up (1CR, 2PR, 3SD). The overall response rate (ORR) was 40.3%, similar to the prior study (Shoushtari et al, Cancer 2016). A signature involving differential expression of 87 immunoregulatory genes correlated with tumor response: ORR: 75% (12/16) signature high vs. 33.3% (7/21) signature low (p = 0.02, high vs. low) vs. 14.3% (2/14) signature average (p < 0.01; high vs. average). mOS for the whole population was 12.4 months. Pts with increased gene expression signature had superior mOS: signature-high: Not reached, signature-low: 8.2 months, (HR: 0.02; 95% CI: 0.07-0.55, p < 0.01). Transcript pathway analysis of the gene signature showed association with chemokine receptors, interleukin-10 signaling, and Treg development. Conclusions: We have identified a gene expression signature that involves chemokine receptors, IL-10 signaling, and Treg development gene sets, that appears to predict for tumor response and mOS in pts with advanced MCM treated with ICI. Further validation of these gene signatures is underway.

9545 Poster Session (Board #116), Mon, 1:15 PM-4:15 PM Phase I-ll open label multicenter study of PDL0332991 in BRAFV600emut metastatic melanoma patients harboring CDKN2A loss and RB1 expression and treated with vemurafenib. First Author: Daniel Sznycer, Department of Pharmacogenomics, Saint Louis Hospital, APHP, Paris, France

Background: Among mechanisms of resistance to BRAF inhibitors (BRAFI), cell cycle effectors including CDK4 have been involved in ERK reactivation. In this phase I-II open label study, we aimed to establish the Maximum Tolerated Dose (MTD) of PDL0332991, an inhibitor of CDK4/6, when added to vemurafenib (VM) in metastatic melanoma patients. Methods: Patients with BRAFV600emut mutated metastatic melanoma harbouring CDKN2A loss and RB1 expression were included. Patients were treated with a 14 days followed by 7 days rest daily dosing schedule of PDL0332991 + continuous BID dosing of VM, and stratified into 2 groups according to previous BRAFI treatment (no group 1, yes group 2). Dose levels (PDL0332991 (mg/QD)/VM (mg/BID)) ranged from 25/720 to 200/960. The primary endpoint was the occurrence of a DLT within the first 2 cycles of therapy. Secondary endpoints included best response (RECIST), OS, PFS, pharmacokinetics parameters, tumour molecular profiling on baseline lesions using transcriptomic and NGS analysis.

Results: Nineteen patients were enrolled, among them 16 (84%) in group 2, with 18.5 months median follow-up. Characteristics at baseline were: male 11 (58%), median age 54.4 years, unreesectable stage IIIC 2 (11%), stage IV 17 (89%), M1C 12 (67%), high LDH 9 (47%), median time from advanced melanoma diagnosis to inclusion 26.8 months, ≥ 2 lines therapy 13 (68%). A DLT was observed for 1 and 5 patients in group 1 and 2 respectively, defining the MTD at PDL0332991 200mg and VM 960mg in group 2. No significant evidence for drug-drug interaction between PDL0332991 and VM was highlighted. In group 2, ORR was estimated to 4 (25%), SD to 8 (50%), median PFS to 9.3 months and median OS to 13.2 months. Baseline transcriptomic analysis revealed high alteration rate associated with clinical response and enriched with genes related to MAPK, cell cycle and apoptosis pathways.

Conclusions: While combination of fixed dose of PDL0332991 + VM did not allow us to increase PDL0332991 dosage above 25mg, significant clinical benefit was achieved in heavily pretreated patients; baseline molecular analysis revealed an association between transcriptomic data and clinical response. Clinical trial information: NCT02202200.

9547 Poster Session (Board #118), Mon, 1:15 PM-4:15 PM Pembrolizumab as first-line therapy in patients with unresectable cutaneous squamous cell carcinoma (cSCC). Phase 2 results from the CARSkIN study. First Author: Eve Maubec, AP-HP Dermatology Department, Hôpital Avicenne, Université Paris 13, Bobigny, France

Background: Cemiplimab, a PD-1-axis blocking agent, has recently been approved for unresectable cSCCs. We report results of the CARSkIN study evaluating pembrolizumab in the first-line setting. Methods: Chemotherapy naive patients (pts) with unresectable cSCCs, either locally or regionally advanced or metastatic (M1a or M1c), were accrued to this multi-institutional phase II trial to assess tumor response rate (RR) and safety of pembrolizumab administered IV (200 mg Q3W) for a period up to 24 months (mo). Baseline PD-L1 expression was centrally assessed on tumor. The primary endpoint was the RR at 15 wks (wks) per RECIST v1.1 (independent review). A Simon two-stage design was used. Results: From 03/2017 to 01/2018, 39 pts (79% males, median age 79 years) were enrolled. Disease was local (18%), regional (62%) or metastatic (21%); 38% of pts were PS 0. The median number of infusions was 8. The median follow-up was 10.2 mo; 15 pts are still on pembrolizumab. Thirty-four pts were evaluable for tumor response, and 39 for toxicity. The RR at 15 wks was 38.5% (95% CI, 24–55%) in the ITT population corresponding to 2 CR and 13 PR. The best responses were 3 CR and 12 PR. The DCR was 51% (20/39 including 5 SD) at 15 wks. The median PFS was 8.4 mo and the median OS was not reached. No responder has progressed to date including 2 pts who discontinued pembrolizumab for 6 to 12 mo. Treatment-related AEs (TRAEs) occurred in 67% of pts, including 8% with severe TRAEs (1 gr 3 T-cellitis, 1 gr 3 colitis and 1 death due to recurrence of a non-related head and neck cancer) and 10% who discontinued because of a TRAE. Centrally assessed baseline PD-L1 expression was positive in 77% of patients (1% tumor staining threshold), but it failed to predict response at 15 wks with a median PD-L1 expression of 10% in responders and non-responders at 15 wks (P = .55).

Conclusions: In this series of 39 elderly pts with unresectable cSCCs, the safety profile was consistent with previous pembrolizumab studies. First-line pembrolizumab provided robust antitumor activity regardless of PD-L1 expression levels. Clinical trial information: NCT02883556.

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9548 Poster Session (Board #119), Mon, 1:15 PM-4:15 PM

cTNA as a noninvasive monitoring tool in metastatic melanoma. First Author: Renata Varaljai, Essen University Hospital, Essen, Germany

Background: The field of liquid biopsy provides a promising alternative to standard tissue biopsies. Previous work has shown that plasma circulating cell-free DNA (ctDNA) can reflect the heterogeneous symptom of mutations in cancer including metastatic melanoma. Our project aimed to establish and statistically validate plasma-based assays for tumour load and therapy monitoring in melanoma. Methods: On a large cohort of stage III and stage IV melanoma patients (N = 96) who received signalling targeted or immune checkpoint inhibitors we showed that the most common oncogenic driver of this disease such as the BRAFV600E, NRASQ61 and the TERTC250T and TERTC228T promoter mutations (termed TERTprom) can be analysed in ctDNA with a highly sensitive droplet digital PCR technology (detection of mutant ctDNA down to 0.01% analytical sensitivity). Results: Our research has demonstrated that ctDNA (irrespective of the genotyping) significantly correlates with tumour stage (P < 0.05). Using receiver operating characteristics (ROC) analyses thresholds were established for risk stratification and response prediction. Elevated ctDNA at baseline was a significant predictor of disease progression compared to elevated LDH or $\text{SO}_{2}$ in mullivariable cox proportional hazards model (Hazard ratio [HR] 7.43, P = 0.005). During therapy patients with low ctDNA load (below the ROC threshold) had significantly better radiological outcomes and prolonged progression free survival (PFS) compared to patients with high ctDNA load (P < 0.0001). Our findings were confirmed on an independent cohort of metastatic melanoma patients (N = 35) treated with immune checkpoint inhibitors. Furthermore, patients with low ctDNA load correlated with prolonged PFS (P = 0.003). An added benefit of ctDNA was demonstrated in about 80% of the patients, where ctDNA analyses preceded the radiological diagnosis of response or relapse. Progression was detected in plasma ctDNA in average 3.5 months earlier as compared to routine imaging techniques. Finally, we demonstrated that N-RASQ61 mutation in BRAFV600E-inhibitor treated patients at therapy baseline was associated with treatment failure. The sub-clonal NRASQ61 mutation at therapy baseline was an independent predictor of shorter PFS (HR 2.69, P = 0.02) as compared to BRAFV600E patients without the NRASQ61 mutation at therapy baseline. Conclusions: In sum, our results support the value of ctDNA as a sensitive biomarker for real-time therapy monitoring and early detection of disease progression.

9550 Poster Session (Board #121), Mon, 1:15 PM-4:15 PM

Sensitivity of treatment-free survival (TFS), a novel outcome, to subgroup analyses of patients (pts) with advanced melanoma (MEL) treated with immune checkpoint inhibitors (ICI). First Author: Charlene Mantia, Beth Israel Deaconess Medical Center, Boston, MA

Background: Many pts treated with ICIs can discontinue treatment and experience ongoing disease control and toxicity. We previously proposed a novel outcome, TFS, as the time between ICI therapy cessation and subsequent therapy initiation or death, with integrated graphical analysis to better characterize the unique effects of ICIs (ASCO 2018 #111). In the CheckMate 067 and 069 trials of ipilimumab (IPI) and nivolumab (NIVO) alone or in combination (NIVO+IPI) in pts with MEL, the 36-month restricted mean TFS was 8.7, 4.6 and 11.1 mo, respectively. We explored the sensitivity of TFS to be informative of overall survival (OS) differences through subgroup analysis. Methods: Data from MEL pts in the CheckMate 067 and 069 trials were pooled and analyzed. TFS was defined as the area between the Kaplan-Meier curves for two endpoints, from randomization: (A) time to ICI therapy cessation; and (B) time to subsequent therapy initiation or death. TFS was estimated by restricted mean survival time until 36 mo since randomization. Differences in restricted mean TFS between subgroups of pts (such as PD-L1 status, lactate dehydrogenase [LDH], performance status [PS], gender) were calculated with bootstrapped 95% CIs. OS from randomization was also estimated. Results: Among 407 pts treated with NIVO+IPI, restricted mean TFS ranged from 8-13 mo across subgroups (Table). Subgroup differences in mean TFS were larger for prognostic factors LDH and PS and smaller in non-prognostic PD-L1 status and gender subgroups. Conclusions: Clinically meaningful TFS differences were seen across all subgroups. TFS was sensitive to prognostic subgroup differences. These results provide further support for TFS as a relevant clinical endpoint. Additional subgroups and comparisons with single agent NIVO and IPI arms will be presented at the meeting.

9551 Poster Session (Board #122), Mon, 1:15 PM-4:15 PM

Patient-reported quality of life (QoL) of advanced melanoma patients in a Phase III study of the novel BRAFV600E inhibitor Vemurafenib (VEMO). First Author: Dirk Schadendorf, Universitätsklinikum Essen & German Cancer Consortium, Essen, Germany

Background: Early CheckMate 067 data showed maintenance of QoL in patients with advanced melanoma treated with NIVO with or without IPI based on 1-year data; however, the long-term QoL of these patients has not been evaluated previously. The patient-reported outcomes (PRO) analyses presented here for CheckMate 067 is the first time QoL results have been evaluated in this melanoma population over a 4-year period. Methods: In CheckMate 067, 945 patients were randomized 1:1:1 to receive NIVO (3mg/kg Q2W) + placebo (PBO), NIVO+IPI (1mg/kg +3mg/kg Q3W X 4) followed by NIVO (3mg/kg Q2W, or IPI) (3mg/kg Q3W X 4) + PBO. PRO data were collected using the EORTC QLQ-C30 (5 functional domains, 9 symptoms, global health status) and EQ-5D-3L (utility index, VAS) at baseline, weeks 1 and 5 of each 6-week tx cycle, and off-tx follow-up (FU) visits. Mean changes in PRO scores from baseline (randomization) were evaluated descriptively for the PRO analysis population, with conclusions drawn from time points with ≥30 patients completing assessments per tx arm. Least square mean changes from baseline were assessed using a longitudinal mixed model analysis adjusting for repeated measures, including all on-tx data for patients. Results: Completion rates at baseline ranged from 89-92% across tx arms. Of 813 patients included in the PRO analysis population (278 NIVO, 274 NIVO+IPI, 261 IPI), >200 receiving tx remained for the first year, >100 receiving tx remained after 2 years, and >50 receiving tx remained after 3 years. QoL, including assessment of functioning and symptom burden, was maintained for the duration of tx and in FU, with no sustained clinically meaningful deterioration in any tx arm. Global health status (EQ-5D-3L utility index, VAS) also remained during prolonged tx. Overall, results from the mixed model analysis support the long-term maintenance of QoL over the course of tx.

Conclusions: Patient-reported QoL and symptoms in patients with advanced melanoma were maintained from baseline during extended tx with NIVO with or without IPI. Clinical trial information: NCT01844505.
9552 Poster Session (Board #123), Mon, 1:15 PM-4:15 PM
Organ site-specific radiological responses in anti-PD-1 monotherapy treated advanced melanoma patients. First Author: Xue Bai, Massachusetts General Hospital Cancer Center/Peking University Cancer Hospital, Boston, MA

Background: Melanoma is notorious for its high degree of heterogeneity with the implication that metastases in different sites react differently to immunotherapy. We aimed to explore the site-specific response pattern in anti-PD-1 monotherapy treated advanced melanoma patients. Methods: Clinical data was collected retrospectively from 61 advanced melanoma patients treated with anti-PD-1 monotherapy at Massachusetts General Hospital (MGH) from Sept 2009 to Dec 2017. Radiological evaluations were carried out by radiologists from the MGH Tumor Imaging Metrics Core using iRECIST 1.1. Statistical analysis was carried out using ANOVA test. Results: Among 61 evaluated patients, 56 (91.8%) had at least one measurable target lesion(s) at baseline, including 35 (57.4%) patients with measurable lymph nodes (LN)/subcutaneous lesion(s), 25 (40.0%) with lung lesion(s), and 21 (34.4%) with liver lesion(s). At week-12 radiological evaluation after anti-PD-1 monotherapy initiation, lesions at different sites responded differently at marginal statistical significance (P = 0.071), namely mean percent changes compared with baseline were 3.75%, 5.12%, and -30.95% for LN/subcutaneous, liver, and lung lesions, respectively. Among patients who had disease under control (CR/PR/SD) (n = 37, 60.7%) by week-12 evaluation, the mean tumor percentage change at week-24 compared with week-12 was -8.94%, -12.18%, and -5.91% for LN/subcutaneous, liver, and lung lesions, respectively. Among patients who had prior anti-PD-1 therapy and were enrolled, 2 DLTs (rash and acute kidney injury) occurred in first cohort, a lower dose of VEM 720 mg COB and COB 40 mg, with the same XL888 cohorts was investigated. 3 DLTs (rash) in 12 pts were observed in the XL888 60 mg cohort, which was determined as the maximum tolerated dose. Most common grade 3 toxicities included diarrhea (8), hypotension (6), rash (5), and pneumonitis (2). No immune-related AEs were reported. 2 non-protocol dose reductions of VEM and/or COB were observed in 18 of 25 pts (72%; 95% CI: 51-88%). Median PFS was 8.1 months (4.7 – NA); median overall survival was not reached, with 1-year OS of 71% (45-86%). Single cell RNA-Seq (10X genomics) was performed on baseline and on-treatment biopsies. 8 days of treatment was associated with an increase in immune cell influx (CD4+ and CD8+) and a decrease in number of melanoma cells. At day 8, one patient (now without progression for nearly 2 years) had no tumor cells remaining with only immune cells and stromal fibroblasts left. Further analyses will be presented. Conclusions: The combination of ipi and ABI in this small study demonstrates acceptable safety, tolerability and preliminary activity. Median PFS was 8.1 months (4.7 – NA), median OS was not reached. 3 DLTs (rash, constipation, pneumonitis) were observed but no immune-related AEs were reported. 2 non-protocol dose reductions were reported. 2 non-protocol dose reductions of VEM and/or COB were observed in 18 of 25 pts (72%; 95% CI: 51-88%). First Author: Kaysia Ludford, MD Anderson, Houston, TX

9554 Poster Session (Board #125), Mon, 1:15 PM-4:15 PM
Phase II trial of nab-paclitaxel (ABI) and ipilimumab (ipi) in patients with treatment naïve metastatic melanoma. First Author: Kay sia Ludford, MD Anderson, Houston, TX

Background: Conventional chemotherapies possess intrinsic immune-regulatory properties. Some taxanes for instance, stimulate antigen presentation and impair regulatory T-cells while leaving effector T cells intact. Combining chemotherapies with anti-PD-1/PD-L1 therapies has the potential to overcome resistance. Methods: This is a single center, phase II trial, ABI was administered to treatment naïve metastatic patients at 150mg/m2 on days 1,8 and 15 every 3 weeks limited to 4 cycles until disease progression or unacceptable toxicity. Endpoints included ORR, OS and safety. Results: 18 of 21 enrollees between 6/2013 and 6/2015 with Stage IV melanoma (M1a: 56%, M1b: 33%, M1a: 11%) were included in the analysis. The median age was 57 years old (33-69) and 67% were men. 44% harbored BRAF mutations. Median duration of treatment was 9 weeks (5 to 17). Median follow-up time for OS analysis was 22.5 months (2 to 52 months). 12 and 24 month OS were 77.8% and 60.6% respectively. Among patients who had disease under control (CR/PR/SD) (n = 37, 60.7%) by week-12 evaluation, the mean tumor percentage change at week-24 compared with week-12 was -8.94%, -12.18%, and -5.91% for LN/subcutaneous, liver, and lung lesions, respectively. Among patients who had disease under control (CR/PR/SD) (n = 37, 60.7%) by week-12 evaluation, the mean tumor percentage change at week-24 compared with week-12 was -8.94%, -12.18%, and -5.91% for LN/subcutaneous, liver, and lung lesions, respectively. Among patients who had disease under control (CR/PR/SD) (n = 37, 60.7%) by week-12 evaluation, the mean tumor percentage change at week-24 compared with week-12 was -8.94%, -12.18%, and -5.91% for LN/subcutaneous, liver, and lung lesions, respectively. Among patients who had version of the combination of BRAF+MEKi (Eroglu, CCR, 2018). Results: 18 of 21 enrollees (86%) had stable disease at first and second follow-up CT scans, will be presented at the meeting. Clinical trial information: NCT02521870.
Characterization of the genetics of mucosal melanoma in patients treated with immunotherapy. First Author: Elizabeth Iannotti Buchbinder, Beth Israel Deaconess Medical Center, Boston, MA

Background: Mucosal melanomas can be effectively treated with checkpoint inhibitors, although the response rates are lower than those observed for melanomas arising in cutaneous sites. The mechanistic basis for the lower efficacy of immunotherapies in mucosal melanoma has been suggested to be related to their lower mutational burden. However, there has been limited characterization of the genetics in this melanoma subtype. Methods: Tumor genotyping was performed on all mucosal melanoma patients seen within the Dana Farber Cancer Institute from 2011 until the present by Oncopanel analysis. Results: We identified a total of 57 mucosal melanoma patients whose tumors had been genotyped. Of these 42 received immunotherapy and had response data available. Within the cohort of mucosal melanoma patients, 42.3% had a clinical benefit (CR/PR/SD) at 6 cycles. Patients with KIT alterations had a higher rate of response compared with wildtype KIT (73 vs. 33%). In addition, there were several genetic differences observed based upon the site of origin of the mucosal melanoma. A higher rate of SF3B1 mutations was observed in patients with melanoma of anal/rectal origin while patients with vulvar/vaginal melanoma had higher rates of ATRX mutations, which frequently correlated with p53 TP53 mutations. Conclusions: This analysis is one of the first to look at genetic patterns in a large cohort of a relatively rare type of melanoma and correlate with response. Our findings confirm the low mutational burden observed in mucosal melanoma despite the high response rate observed in these patients. In addition, this study uncovered a higher rate of response to immunotherapy in mucosal melanoma patients with a KIT mutation.

Use of immunotherapy for stage-III and IV melanoma and likelihood of regional and distant lymph node resection and surgical resection for distant metastasis. First Author: George Molina, Massachusetts General Hospital, Boston, MA

Background: Immunotherapy (IMT) for stages-III and IV melanoma has been demonstrated to improve overall survival. Mesothelioma and lung cancer patients benefitting from chemotherapy and immunotherapy may have improved outcomes. Methods: This is a single institution retrospective analysis of patients with stage-III and IV melanoma who received chemotherapy and/or immunotherapy from 2011 to 2016. Results: We identified a total of 70 stage-III and 58 stage-IV melanoma patients who were treated with chemotherapy and/or immunotherapy. The most common chemotherapy regimens were: Bevacizumab (n=18), ipilimumab (n=15), and Ipilimumab+Bevacizumab (n=11). The most common immunotherapy regimen was ipilimumab (n=15). Conclusions: Stage-III melanoma patients who received a check-point inhibitor had a higher likelihood of regional lymph node resection when compared to those who did not receive a check-point inhibitor (75% vs. 31%, p=0.0005). Stage-IV melanoma patients who received a check-point inhibitor had a higher likelihood of distant lymph node resection when compared to those who did not receive a check-point inhibitor (82% vs. 50%, p=0.001). Stage-III melanoma patients who received a check-point inhibitor had a higher likelihood of surgical resection for distant metastasis when compared to those who did not receive a check-point inhibitor (50% vs. 19%, p=0.001). Stage-IV melanoma patients who received a check-point inhibitor had a higher likelihood of surgical resection for distant metastasis when compared to those who did not receive a check-point inhibitor (66% vs. 42%, p=0.02). Conclusions: The Findings: Our analysis of patients with stage-III and IV melanoma who received chemotherapy and/or immunotherapy demonstrate that patients who received check-point inhibitors had improved regional and distant lymph node resection rates when compared to those who did not receive a check-point inhibitor. Further analysis is needed to determine if these differences are due to disease burden and are not due to chance.

Stereotactic radiotherapy combined with immunotherapy is safe and effective: Results from a phase I clinical trial. First Author: Gishan Ratnayake, Alfred Health, Melbourne, VIC, Australia

Background: There is growing evidence to suggest synergism between stereotactic ablative radiotherapy (SABR) and immunotherapy (IO) against metastatic melanoma. The optimal timing and dosing of SABR for this purpose has not been established. Here, we report results from a Phase I trial, finding the best outcomes with low dose SABR delivered late. Methods: Metastatic melanoma pts with at least two metastases received SABR to a single metastasis. All pts had standard dose IO with anti-PD-1 and/or anti-CTLA4. Following a standard 3+3 design, pts were escalated through three SABR doses (10Gy, 15Gy and 20Gy) delivered at three different time points (Cycle 1, 2, or 3 of IO). Dose limiting toxicity (DLT) were defined as Grade 3 or higher toxicity within 3 months of first treatment and assessed by an independent data safety monitoring committee (IDSMC). Logistic or Cox regressions were used to assess the impact of SABR dose, timing and use of combination IO on toxicity, progression-free (PFS) and overall survival (OS) while controlling age, gender and baseline performance status. Results: Between April 2016 and August 2018, 24 pts were enrolled. The median age was 66 years and most were ECOG 0-1 (92%). The median follow-up was 10 months. Three pts (12.5%) developed DLTs (enterocolitis, hepatitis and liver function derangement). None occurred at SABR treated sites and all were in pts receiving 15Gy. DLTs were not associated with SABR timing (p = 0.44) or use of combination IO (p = 0.72). On this basis the IDSMC recommended stopping the trial and maximum tolerated SABR dose was defined at 10 Gy. The median PFS and OS were respectively 5.4m (95% CI 2.1m-NR) and 16.9m (95% CI 7.1m-NR). The median PFS for those receiving 10Gy was numerically higher than those receiving 15Gy (11.8m vs 2.6 m, p = 0.42). The only treatment related factor associated with improved PFS (HR = 0.14, p = 0.02) and OS (HR = 0.09, p = 0.04) was receiving SABR with Cycle 3. SABR dose (PFS p = 0.70, OS p = 0.67) and IO type (PFS p = 0.13, OS p = 0.06) were not significant. Conclusions: SABR combined with IO is generally safe overall. We found the optimal therapeutic index may be achieved with 10Gy delivered with the third cycle of IO; a strategy that warrants further testing. Clinical trial information: ACTRN12616001064493.
Background: Immune checkpoint blockade (ICB) have improved survival for many pts with MM, offering durable responses in up to 35% of pts, but many are PD-1 naive and reverse resistance to ICB in pts refractory/resistant to PD-1. Methods: This study (NCT02816021) evaluated the safety and efficacy of CC-486 (300 mg PO QD on days 1-14/21 cycle) + PEMBRO (200mg IV Q 21 days) defined by Objective Response Rate (ORR) by RECIST 1.1 in pts with MM. PD-1 naive pts were assigned to Arm A and pts with progression on prior PD-1 therapy to Arm B. Unlimited prior systemic therapies were allowed on Arm B. Continuous monitoring for toxicity and futility was performed and assumes an ORR of 35% (Arm A) and >15% (Arm B) at 95% power. Tumor biopsies at baseline and post treatment were acquired from all pts from each arm, have been treated. The most common AEs were nausea, vomiting, diarrhea, fatigue, and anemia. The most common gr 3/4 toxicities were neutropenia (3), diarrhea (2), dehydration (2), and rectal hemorrhage (1). 5 of 9 evaluable pts in Arm A achieved a PR (55% ORR); 0 of 9 evaluable pts in Arm B have responded. Conclusions: Although this regimen was tolerated in both arms, Arm B met futility stopping rules and was closed. The initial response rate in Arm A (55%) is promising, and accrual to this Arm continues. Analyses of longitudinally collected tumor biopsies are underway to interrogate the effects of HMA on the immune response to both arms. Clinical trial information: NCT02816021.
9564  Poster Session (Board #135), Mon, 1:15 PM-4:15 PM
Clinical features and response to immune checkpoint inhibitors (ICIs) in pregnancy-associated melanoma (PAM). First Author: Daniel Ying Wang, Baylor College of Medicine, Houston, TX.

Background: Melanoma is one of the most common malignancies diagnosed during pregnancy. Little is known about the clinical outcomes of PAM, in particular, response to ICIs. We performed a retrospective study to assess this issue. Methods: A multicenter retrospective study was performed at 4 large melanoma centers. Patients (pts) with PAM treated with ICIs were identified and examined. Clinical data and molecular data (RNA sequencing, IHC) were explored. PAM was defined as development of advanced melanoma during pregnancy or within 2 years post-partum. Results: 19 pts with PAM were treated with ICIs. Median follow-up was 11.7 months (range 1.4 - 41.9 months). Median age was 29 years (range 16-36). Most pts had a cutaneous primary (N = 17, 89%) including the extremity (N = 8) or trunk (N = 7), and 5% were occult. 11 (58%) had a BRAF V600E (range 6-32%) pts received BRAF/MEK targeted therapy. Most pts had prior primary melanoma (N = 12, 63%) and presented with advanced melanoma in the part-purtum setting (N = 11, 58%). At advanced presentation, 6 (32%) pts were stage III/II; and 13 (68%) pts were stage M1b/c; 7 (41%) pts had elevated LDH and 13 (68%) had visceral involvement. Among 11 patients treated with combination (ipilimumab + anti-PD-1) therapy, 7 (64%) had objective responses (OR) with a 1-year progression free survival (PFS) of 40% and 1-year overall survival (OS) of 100%. By contrast, ICI monotherapy (3 with anti-PD-1/L1 and 4 with ipilimumab) was associated with poorer outcomes (OR in 25% and 33% for ipilimumab and anti-PD-1/L1, respectively). Molecular features (RNA sequencing, immunohistochemistry) will be presented. Conclusions: Patients with PAM represent a unique population and may particularly benefit with combination ICI therapy compared with ICI monotherapy (in a limited sample size). Molecular underpinnings of PAM biology are still being elucidated.

9565 poster Session (Board #136), Mon, 1:15 PM-4:15 PM
Molecular profiling of melanoma brain metastases (MBM) compared to primary cutaneous melanoma (CM). First Author: Gina Kim In, USC Norris Comprehensive Cancer Center, Los Angeles, CA.

Background: Nearly 50% of metastatic melanoma patients develop brain metastases, warranting further investigation into the biology of this event. Methods: We analyzed 132 MBM and 745 CM submitted to Caris Life Sciences from 2015-2018, using next generation sequencing of a 44 or 592 cancer-related gene panel, tumor mutational burden (TMB), and PD-L1 expression by IHC. Genomic alterations (GA), including somatic mutations or CNA, were reported. High TMB (TMB-H) was defined as >17 mut/Mb. Comparison of molecular profiles, including cancer-related genes and recurrently altered pathways, between tumor sites and by genomic subgroup (BRAF, NRAS, KIT, NF1), was performed using Fisher’s exact test. Results: Among 132 MBM, 72.7% were male, with median age 62 yo (range 25-83). The most common GAs among MBM were: BRAF (52.4%), NRAS (26.6%), CDKN2A (23.3%), NF1 (18.9%), TP53 (18%), ARID2 (13.8%), SETD2 (11.9%), and PBRM1 (7.5%). Compared to CM, MBM were more often TMB-H (53.7% vs. 38%, p = 0.025), with higher PD-L1 expression, using both a 1% (54.4% vs. 35.6%, p = .002) and ≥5% cut-off (32.9% vs. 15.9%, p = .0006). MBM showed higher rates of GAs among: SETD2 (11.9% vs. 9.9%, p = .008), BRAF (52.4% vs. 35.6%, p = .017), PBRM1 (7.5% vs. 1.6%, p = .018), KRAS (4% vs. 1%, p = .026), CDC20 (2.9% vs. 0%, p = .03), and DICE1 (4.4% vs. 0.4%, p = .04), compared to CM. Alterations of the MAPK (87.9% vs. 77.8%, p = .015) and SWI/SNF (22.1% vs. 11.6%, p = .036) pathway were more frequent in MBM, than CM. No significant associations were seen between BRAF, PD-L1, or other GAs among MBM. Conclusions: In this cross-sectional study, MBM demonstrated higher PD-L1 expression and were more often TMB-H, compared to CM. MBM also featured more GAs involving BRAF and the MAPK pathway. We identified two novel genes, PBRM1 and SETD2, as well as recurrent alterations of the SWI/SNF pathway, supporting future studies of chromatin remodeling pathways in MBM.

9566 poster Session (Board #137), Mon, 1:15 PM-4:15 PM
Anal melanoma: A comparative comprehensive genomic profiling study. First Author: Jeffrey S. Ross, SUNY Upstate Medical University, Syracuse, NY.

Background: We performed a comprehensive genomic profiling (CGP) study of AM and CM to learn of potential genomic alterations (GA) linked to targeted and immune checkpoint inhibitor (ICI) therapies. Methods: 90 AM and 1,804 CM FFPE tissues from late stage underwent hybrid-capture based CGP to evaluate all classes of genomic alterations (GA). Tumor mutational burden (TMB) was determined on unpaired DNA and microsatellite instability (MSI) was determined on 114 loci. PD-L1 expression was determined by IHC. Results: AM and CM had a similar age, but AM females and CM males were significantly more common (P < 0.0001). A GaTumor was significantly higher in CM (UV light exposure) as were the median TMB and frequency of TMB > 10 and 20 mutations/Mb (P < 0.0001 for all comparisons). PD-L1 expression was higher in AM than CM (P = 0.0023). AM and CM were all MS-stable. The contrast in SF3B1 mutations in AM and TERTGA in CM were significant (P < 0.0001). Of potentially targetable GA, AM featured significantly more KIT GA than CM (P < 0.0001), whereas CM featured significantly more BRAF/AGA (P < 0.0001). Only 11% of AM BRAF/AGA were V600E whereas 74% of CM BRAF/AGA were V600E (P < 0.0001). ATO pathway mutations were common in both tumor types. Additional potentially targetable alterations in PDGFRα and ERBB2 kinases were seen in AM but not in CM. Conclusions: AM is distinct from FM using different GA tumor, higher TMB and frequent BRAF V600E GA that predict benefit from ICPI and anti-BRAF therapies. Although both AM and CM feature MTD tumor targets, AM does have higher PD-L1 expression than CM and is characterized by an array of potentially targetable kinase genes including KIT, PDGFRα, ERBB2 and to a lesser extent than CM, BRAF.

9567 poster Session (Board #138), Mon, 1:15 PM-4:15 PM
 Pretreatment steroid use and completion of immunotherapy: A population-based study. First Author: Grace L. Lu-Yao, Sidney Kimmel Cancer Center at Jefferson, Philadelphia, PA.

Background: The relationship between immunosuppressants and immunotherapy (IO) is an active area of research. Here we study the impact of pretreatment steroid use on the completion of immunotherapy (ipi) therapy. Methods: This population-based study identified patients diagnosed with melanoma and treated with ipi (brand name Yervoy) in 2010-2014 from the linked Surveillance, Epidemiology and End Result-Medicare files. "Completion of IO on time" was defined as receiving 4 cycles of IO within 90 days. Otherwise, the patients were considered to have delayed or incomplete IO. The frequencies of patients completing each dose, up to 4 doses were tabulated. Exact Clopper-Pearson 95% confidence intervals (CI) were computed for prevalence estimates. A crude relative risk (RR) for completing IO was calculated. Results: We identified 1,205 melanoma patients treated with ipi with a median age of 71 years. Among 709 patients with no pre-treatment steroids, 35.7% had completed 4th dose of IO, compared to 20.3% of patients who received pre-treatment steroids within 1 month of IO (Table). In these patients, having no exposure to steroids in the year prior to initiating IO was associated with a 28% increased probability of completing the 10 regimen (RR=1.28, 95% CI: 1.07-1.53). Conclusions: This large scale real-world study demonstrated both the overall completion rate of ipi in melanoma patients as well as the negative impact of pre-treatment steroids on rate of treatment completion. Further studies on treatment outcomes associated with pre-IO steroids use are warranted.

Completion of Immunotherapy Doses by Pre-treatment Exposure to Steroids.

Exposure to Steroids before IO Had 2nd dose of IO Had 3rd dose of IO Had 4th dose of IO % (95% CI) % (95% CI) % (95% CI) No Steroids within 12 months, N = 709 77.6 55.9 35.7 ≤1-month, N=158 74.3 (80.6) (52.1, 59.6) (32.2, 39.3) 63.7 (79.2) (52.6, 74.3) 20.3 (26.9) (13.4, 27.4) 1-3 months, N=210 75.2 (82.6) (46.9, 53.2) 23.8 (28.5) 3-6 months, N=194 74.2 (79.6) (52.5, 64.4) 28.4 (32.9) 6-12 months, N=258 74.0 (79.6) (53.8, 64.4) 40.8 (45.3) 32.9 (37.5) (23.3, 42.1) 30.2 (34.7) (20.5, 40.4) 24.7 (29.3) (14.3, 34.7) 27.4 (31.9) (17.0, 32.4) 36.4 (40.8) (24.3, 52.4) 40.4 (44.1) (25.7, 55.3)
Quality of life (QoL) and symptom burden in patients (pts) with advanced melanoma during the treatment-free interval (TFI) after discontinuation of nivolumab (NIVO) or NIVO plus ipilimumab (IPI). First Author: Fiona Taylor, Adelphi Values, Boston, MA

Background: The TFI after discontinuation of study therapy has been reported to be longer with NIVO+IPI compared to NIVO or IPI alone, but QoL during the TFI has not been reported in advanced melanoma (MEL) studies. 1-y data from CheckMate (CM) 067 showed maintenance of QoL after treatment (tx) discontinuation with NIVO or NIVO+IPI. Here, we present long-term QoL results from CM 067 during the TFI (period off study tx and free of subsequent therapy), based on an updated 4-y dataset. Methods: In CM 067, 945 pts were randomized 1:1:1 to receive NIVO 3 mg/kg + placebo; NIVO 1 mg/kg + IPI 3 mg/kg × 4, then NIVO 3 mg/kg; or IPI 3 mg/kg × 4 + placebo. Patient-reported outcomes (PRO) were collected using the EORTC QLQ-C30 (5 functional domains, 3 symptoms, global health status) and EQ-SD-3L (utility index, visual analog scale) at baseline, on-tx visits, and follow-up (FU) visits 1 (FU1; 30 d after last dose) and 2 (FU2; 84 d after FU1). EQ-SD-3L was also collected at survival FU visits every 3 mo after FU2 in the first year and every 6 mo thereafter. Within the PRO analysis population, 480 of 764 pts who discontinued protocol tx (for any reason, including drug toxicity; n = 155) had PRO scores, collected prior to initiation of subsequent anticancer therapy, evaluated. Mean changes in PRO scores from last on-tx visit were reported for each FU visit. Results: Across tx arms, PRO scores were maintained from last on-tx visit to FU1 or FU2 for pts who discontinued for any reason. EORTC QLQ-C30 functional and symptom scores remained stable during the TFI. Among pts who discontinued due to toxicity, clinically meaningful deterioration in QoL was observed in a few subscales at FU1, but QoL was restored to the same level as the last on-tx visit in all except one subscale by FU2. PRO scores remained stable beyond FU2 for the EQ-SD-3L, regardless of reason for discontinuation. Data interpretation at later FU visits was limited due to small sample sizes. Sensitivity analyses for mean change in PRO scores from randomization to FU visits will be presented. Conclusions: QoL was maintained during the TFI, compared to last on-tx visit, in pts with MEL treated with NIVO or NIVO+IPI.

The clinical utility of neuron-specific enolase serum levels as a biomarker for dominization to FU visits will be presented.

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Background: Retrospective studies suggest that various med could dichotomous effects in regards to immunotherapy. These include adverse (antibiotics) and positive (aspirin, beta-blockers) influences. To evaluate potential additive or detrimental effects of various med in patients (pts) receiving PD-1 immunotherapy, we performed a retrospective evaluation of med intake in 172 pts with stage IV cutaneous MEL focusing on aspirin (asp), beta-blockers, antibi-otics (abx), metformin (met) and statin (stat). Med intake was documented based on chart review in all pts. Intake was confirmed by analyzing at least one other note from a non-oncological provider. Descriptive statistics were created for all covariates. Kaplan Meier and Cox proportional hazard regression were performed to assess how categorical variables related to response (ORR), overall survival (OS) and progression free survival (PFS) measured in months (mths). Results: 172 pts with advanced MEL were evaluated. Asp, ant, bisp, met and stat use was documented in 62, 82, 29, 4, and 57 pts respectively. ORR was not significantly related to intake of asp, ant, bisp, met and stat use; although ORR was lower in pts who received abx (p = 0.3238). There were no significant differences in PFS and OS in pts who received asp, ant, bisp, met and stat. In patients who received abx compared to those who did not, median PFS (16.6 mths vs. 19.8 mths) and median OS (23.8 mths vs. 35.4) were both lower. Abx use did not interact with other meds. Conclusions: In this retrospective series of advanced MEL pts treated with PD-1 blockade, abx use was associated with poorer PFS and OS. Conversely, neither a positive nor negative association with ORR, PFS and/or OS was seen with asp, ant, bisp, met and stat use. These results validate prior studies suggesting that abx use is associated with worse outcomes in pts receiving PD-1 blockade possibly by mediating intestinal dysbiosis.

9574 Poster Session (#145), Mon, 1:15 PM-4:15 PM
Plasma proteomic analyses and treatment predictive biomarker candidates in melanoma patients receiving immune checkpoint blockade or targeted therapy. First Author: Hanna Eriksson, Department of Oncology and Pathology, Karolinska Institutet and Department of Oncology, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden

Background: The introduction of immune checkpoint inhibitors (ICIs) or therapies targeting the MAPK-pathway (MAPKis) has significantly improved clinical outcomes in metastatic melanoma patients. Still, a large proportion of the patients become resistant to therapy and there is a need for treatment predictive biomarkers. The aim of this study was to analyze the treatment predictive biomarkers based on the plasma proteome of patients with metastatic melanoma treated with ICIs or MAPKis. Methods: We analyzed serial plasma samples from 48 patients with metastatic melanoma collected; 24 patients were treated with ICIs and 24 patients with MAPKis, respectively. A non-biased, high-resolution isoelectric focusing of peptides-liquid chromatography-mass spectrometry (HiRIEFLC-MS/MS)-based method, and with proximity ligation assays (PEA) targeting 92 immuno-oncology-related proteins were used. We analyzed the change in protein levels during treatment with a paired t-test, and their association with progression free survival (PFS) with Cox proportional hazards models. Results: HiRIEFLC-MS/MS detected 1,835 proteins. We detected statistically-significant log2-fold-changes in 109 protein levels out of 40 patients with MM treated with immunotherapy from 2013 to 2018 in the patients become resistant to therapy and there is a need for treatment predictive biomarkers. The aim of this study was to analyze the treatment predictive biomarkers based on the plasma proteome of patients with metastatic melanoma treated with ICIs or MAPKis.

9575 Poster Session (#146), Mon, 1:15 PM-4:15 PM
Delta-radiomics for prediction of pseudoprogression in malignant melanoma treated with immune checkpoint inhibition. First Author: Lucas Basler, University Hospital Zurich, Zurich, Switzerland

Background: Distinguishing progressive disease (PD) from pseudoprogression (PP) in patients treated with immune-checkpoint inhibition (ICI) is challenging and usually requires confirmation follow-up imaging or invasive diagnostic techniques. This project aimed to identify predictive radiomic signatures for PP from CT imaging. Methods: The response to ICI of 105 metastatic melanoma patients with 645 measurable lesions was retrospectively correlated with radiomic signatures (172 total features). All metastatic lesions were delineated at 3 time points: prior to ICI (t0), at 3 (t1) and 6 months (t2). Response was defined individually for each metastasis using RECIST 1.1, comparing baseline t0 to t2. Three prediction models for PP were built: CT radiomics at t0 and t1, as well as the relative difference between both t0 and t1 (delta-radiomics).

Results: Median follow-up was 18 months and 2-year OS and PFS were 72% and 25%, respectively. Median OS: not reached, median PFS: 6 months. Response per lesion at t1: 13% complete remission (CR), 19% partial remission (PR), 52% stable disease (SD) and 19% PD. At t2: 16% CR, 31% PR, 38% SD and 15% PD. 106 progressive lesions were identified at t1, of which, 26 changed to SD, 1 to CR and 3 to PR at t2, resulting in 30 PPs (4.7%). Metastasis location significantly influenced response rates but was not associated with PP (p = 0.4). Lung metastases had significantly higher response rates than soft tissue (p < 0.001), liver (p < 0.001) and bone metastases (p = 0.008). Univariate analysis followed by removal of correlated features revealed no significant radiomic features associated with PP at t0. One independent feature was identified at t1 (AUC 0.74), while delta-radiomics was the best performing approach, identifying four independent features (AUC 0.72 to 0.81). A final multivariate delta radiomics logistic regression model was generated and internally validated, achieving an AUC of 0.81 (± 0.11, 10-fold cross-validation). Conclusions: Metastasis location significantly influenced response rates and CT-based delta-radiomics is a promising biomarker for early differentiation between pseudoprogession and true progression in metastatic melanoma patients treated with ICI.
Comprehensive genomic profiling reveals distinct patterns of driver mutations and chromosomal alterations in acral and mucosal melanomas. First Author: Nguyen Zou, The Comprehensive Cancer Center of Drum-Tower Hospital, Nanjing, China

Background: The incidence of melanoma subtypes differs significantly among ethnicities. Ultraviolet (UV) radiation-driven melanomas are common in Caucasians, while non-cutaneous melanomas including acral and mucosal melanomas are more frequent in Asians. It will be of great interest and clinical relevance to decipher the molecular pathogenesis of different melanoma subtypes.

Methods: We retrospectively studied a cohort of 89 Chinese melanoma patients who underwent surgical resection of their primary tumors followed by chemotherapy. Genomic profiling of primary melanomas was performed using next generation sequencing by targeting 422 cancer-relevant genes. The Kaplan-Meier method and logrank test were used for survival analysis, and a cox model was used for multivariate survival analysis.

Results: Acral melanomas (54/89, 60%) were the most common subtype of this cohort, while cutaneous and mucosal subtypes accounted for 25% and 15%, respectively. Mutation profiling revealed that BRAF was most frequently mutated in cutaneous melanomas, but aberrant BRAF, RAS, KIT, and NFI were almost evenly represented in acral and mucosal melanomas. Of note, cutaneous melanomas had a propensity for concurrent driver mutations. Chromosomal alterations were detected across all subtypes, and chr7p amplification significantly correlated with poor prognosis while independently of cutaneous melanomas. Cohort 1 (Yale Medical Center), had n = 86 patients, of which 43 were alive or had no evidence of disease at death (no DMR) and 37 died from melanoma. The second set, Cohort 2 (Geisinger Health Systems), had n = 29 patients, 15 without DMR and 14 with DMR. Prediction scores correlated with DMR status in both sets (AUC = 0.94 and 0.77 for Cohorts 1 and 2, respectively). A multivariate Cox proportional hazard model showed DMR recurrence prediction to be an independent prognostic factor for both Cohort 1 (HR = 2.54, 95% CI: 1.54-4.19, p = 0.004**) and Cohort 2 (HR = 8.43, 95% CI: 2.58-27.51, p = 0.001**).

Conclusions: We designed a DNN for quantitative prediction of melanoma recurrence from a H&E stained tissue. This prediction score will provide a further study in larger patient cohorts and may constitute a novel digital pathology tool for the selection of melanoma patients for adjuvant immunotherapy.

Melanoma/Skin Cancers

Comprehensive genomic profiling reveals distinct patterns of driver mutations and chromosomal alterations in acral and mucosal melanomas. First Author: Shirin Bajaj, The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, NY

Background: The recently revised (AJCC) Staging Manual, 8th edition, introduced changes including removal of mitotic index and addition of the IIID substage. There is active debate on the utility of this revision, especially, without the inclusion of a novel prognostic biomarker, during an era of major therapeutic shifts and amidst accrual of adjuvant clinical trials for high-risk resected primary melanoma. We examined whether re-staging primary melanoma patients using the new AJCC 8 system yielded improved prognostication as compared to AJCC 7. Methods: We compared the impact of changes in staging criteria in stage I-III melanoma patients who were prospectively enrolled in a NYU clinicopathological database between January 2010 and December 2016 with active protocol-driven follow-up (FU). We assessed primary tumor category (T) and nodal status (N) according to both AJCC 7 and 8. Progression free survival (PFS) and overall survival (OS) curves were generated for both editions and then stratified by substage. We analyzed discordance using Cox Regression Models. Results: 1,379 patients (56% male, mean thickness 1.6, median FU 34.8 months) were included in the analyses. All but one patient remained in the same ‘major’ stage using AJCC 7 and 8 (stage I- 998; II- 224, 225; III- 157, 156) whereas 44% of stage III substage classifications were discordant comparing AJCC 7 to 8. Despite removing mitoses as a criterion for Stage I, there was no significant change between three substages in PFS/OS when evaluating major and substages of stage I. Stage IIC patients had worse PFS/OS than stage IIIA patients in AJCC 8 (PFS p = 0.04, OS p = 0.20). AJCC 8, which implemented four rather than three substages, had improved PFS prognostication (c-index = 0.59 vs 0.66, p = 0.05 for AJCC 7 vs 8). Conclusions: Our results reinforce the added value of AJCC 8 compared to 7, as removing an operator dependent variable is more practical for stage I, and increased influence of thickness/ulceration and the addition of a new substage is more prognostically informative for stage III. Nevertheless, the poor prognosis of stage IIC patients, despite nodal negative disease, continues to be an unaddressed gap within our current staging framework.

Association of baseline body mass index (BMI) with response and survival in patients (Pts) with advanced melanoma (MEL) receiving PD-1 inhibitors. First Author: Amit Hemadri, UPMC Passavant Hospital, Pittsburgh, PA

Background: Obesity promotes PD-1-mediated T cell dysfunction but also improves tumor response to PD-1 blockade. Obesity has been linked with positive outcomes in pts treated with PD-1 blockade. To evaluate the prognostic utility of BMI, we performed a retrospective evaluation of BMI and other covariates in 172 pts with stage IV cutaneous MEL. Methods: Pts with stage IV cutaneous MEL who received anti-PD-1 therapy at the University of Pittsburgh between 2014-2018 were included in this analysis. PD-1 blockade was continued until progression or intolerable toxicity. Tumor assessment was performed at baseline and every 12 weeks and response classified per RECIST v1.1. Clinical and demographic data were obtained. BMI was defined based on values at the first treatment date and dichotomized into two groups: >30 vs. <30. Fisher exact test was used to evaluate the correlation between BMI group and ORR. Kaplan Meier method and Cox proportional hazard models were performed to analyze the time-to-event outcomes (OS and PFS). Results: 172 pts with advanced MEL were evaluated. Greater BMI was associated with greater ORR, PFS and OS across various BMI cutoffs (BMI>28, BMI>30 and BMI>35) although this effect was most obvious at BMI>30. Pts with BMI>30 achieved higher ORR than those with BMI <30 (74% vs. 58%, p-value = 0.04). Concordantly, pts with BMI=30 had improved PFS and OS: median PFS (BMI=30:21.1 mos vs BMI <30: 10.7 mos) and median OS (BMI=30: 35.4 mos vs BMI <30: 22.8 mos). Higher BMI was independently associated with improved OS (p = 0.018) and PFS (p = 0.047) adjusting for age, Breslow thickness and sex. No significant interaction was observed between the effects of BMI and that of age, sex, or Breslow thickness. Conclusions: Increased BMI was associated with greater ORR in addition to previously reported associations with PFS/OS in a large retrospective series of advanced MEL pts treated with PD-1 blockade. This data was independent of other prognostic factors and underscores the “inflammaging” effects of obesity and age in relation to anti PD-1 therapy in advanced cancer.
Disparities in the occurrence of late effects following treatment among adolescent and young adult melanoma survivors. First Author: Alicia Gingrich, Comprehensive Cancer Center, University of California Davis, Sacramento, CA

Background: Melanoma is the third most common cancer in the adolescent and young adult (AYA) population and the incidence worldwide is increasing. However, no studies have addressed the occurrence of late effect medical conditions following melanoma treatment in these young survivors.

Methods: All patients ages 15-39 diagnosed with cutaneous melanoma from the 1996-2012 and surviving >2 years were obtained from the California Cancer Registry and linked to statewide hospitalization data. The influence of age at diagnosis, sex, race/ethnicity, neighborhood socioeconomic status (SES), and health insurance on the development of late effects by system was evaluated using multivariable Cox proportional hazards regression models.

Results: Of 8,524 patients, 35.6% were male, 83.1% non-Hispanic white, 82.1% had private health insurance, 60.3% were considered high SES, and 70.7% had no documented co-morbidities at diagnosis. After controlling for competing factors, males had an increased risk of developing late effects across all systems, including cardiac (HR: 2.13, 95% CI 1.87-2.42), neurologic (HR: 2.24, CI 1.92-2.63), lymphedema (HR: 2.22, CI 1.89-2.62), bland events (HR: 2.35, CI 2.00-2.77), major infection/sepsis (HR: 2.3, CI 1.95-2.56), and second cancers (HR: 1.66, CI 1.47-1.89). In addition, patients with public or no insurance (vs. private) had a greater risk of developing all studied late effects, including lymphedema (HR: 2.48, CI 2.04-3.01), respiratory illness (HR: 2.21, CI 1.85-2.64) renal dysfunction (HR: 2.31, CI 1.95-2.71), and subsequent cancers (HR: 2.62, CI 1.94-3.42). AYA patients residing in low SES neighborhoods had a similar increased risk of developing late effects. However, neither age nor race/ethnicity had an impact on the occurrence of late effects. Conclusions: Of AYA melanoma survivors, males, those with public or no health insurance, and those living in low SES neighborhoods had a much greater likelihood of developing late effects. Strategies to improve surveillance and secondary prevention of these late effects is needed among AYA melanoma survivors, particularly for this demographic.

Association between baseline disease characteristics and relapse-free survival (RFS) in patients (pts) with BRAF V600-mutant stage III melanoma treated with adjuvant dabrafenib (D) + trametinib (T) or placebo (PBO). First Author: Dirk Schadendorf, Department of Dermatology, University Hospital Essen, Essen, Germany

Background: In the COMBI-AD trial (NCT01682083), 12 mo of adjuvant D+T led to significant improvement of RFS vs PBO (hazard ratio [HR], 0.47; P < .001) in pts with resected BRAF V600-mutant stage III melanoma; 3- and 4-year RFS rates were 59% and 54%, respectively. Previous results demonstrated consistent treatment benefit across baseline disease stage according to AJCC edition 7 or 8. Here, we further explore the association between baseline disease characteristics and RFS to identify pt subgroups likely to benefit from adjuvant treatment. Methods: Randomized pts with completely resected BRAF V600E/K-mutant stage III melanoma received 12 mo of adjuvant D (150 mg BID) + T (2 mg QD) or PBO. Within each subgroup, predictive value was explored using Kaplan-Meier analysis, and HRs were calculated using a Pike estimator. Results: Minimum follow-up was 40 mo for 870 enrolled pts (D+T, 438; PBO, 432). Kaplan-Meier analysis demonstrated treatment benefit across all subgroups analyzed. Assessment of RFS by extent of primary tumor (T stage) showed consistent benefit favoring D+T vs PBO (HR 95% CI: T1, 0.42 [0.25-0.70]; T2, 0.51 [0.34-0.76]; T3, 0.55 [0.39-0.77]; T4, 0.42 [0.29-0.60]). HRs by nodal burden (N stage) also showed consistent treatment benefit (N1, 0.52 [95% CI, 0.37-0.72]; N2, 0.38 [95% CI, 0.28-0.53]; N3, 0.58 [95% CI, 0.41-0.83]). Substantial treatment benefit was observed in pts with baseline in-transit metastases (HR, 0.45 [95% CI, 0.24-0.82]) and those with no in-transit metastases detected at baseline (HR, 0.49 [95% CI, 0.40-0.60]). When RFS was assessed according to melanoma presentation, treatment benefit favoring D+T vs PBO was observed in pts with superficial spreading melanoma (HR, 0.48 [95% CI, 0.35-0.70]) and those with nodular melanoma (HR, 0.53 [95% CI, 0.37-0.75]). Conclusions: These results confirm earlier findings showing that treatment benefit with adjuvant D+T vs PBO is independent of baseline factors. Clinical trial information: NCT01682083.

Efficacy of immune checkpoint inhibitors (ICIs) for in-transit melanoma. First Author: Emilia Nan Tie, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: The efficacy of ICIs in metastatic melanoma is well-established. However, there is limited data regarding their efficacy in in-transit melanoma (ITM). This study assessed the efficacy of IC in patients with ITM. Methods: A multisite, retrospective review of patients with ITM treated with IC from 2004-2018. Demographic and clinicopathological factors (age, sex, primary site, AJCC version 8 stage, BRAF status, prior locoregional therapies) were collected. Objective response rate (ORR) based on a clinician-assessed best overall response, progression free survival (PFS) and overall survival (OS) were analyzed by the Kaplan-Meier method. Results: Fifty-four patients were included: 27 (50%) female; median age 69 (range 19-89); 12 (22%) stage IIB, 40 (74%) stage IIC and 2 (4%) stage III; 10 (19%) BRAF mutant. Forty (74%) received single agent PD-1 inhibitor (pembrolizumab or nivolumab), 8 (15%) single agent anti-CTLA-4 (ipilimumab), 5 (9%) combination anti-PD-1/anti-CTLA-4 (ipilimumab and nivolumab or pembrolizumab) and 1 (2%) combination anti-PDL-1/MEK inhibitor (atezolizumab and cobimetinib). ORR to IC was 54%: 14 (26%) complete responses; 15 (28%) partial responses; 9 (17%) stable disease; 16 (30%) progressive disease. Seventeen (46%) responders had only one ITM lesion. ORR was 58% for single agent anti-PD-1, 38% for single agent anti-CTLA-4, and 40% for anti-PD-1/anti-CTLA-4 (Table). The median follow-up was 15 months (2-46). The median PFS was 11.7 months (6.6-NA). At 1 and 2 years OS were 85% and 63%; the median OS was not reached. No clinicopathological features were associated with ORR. Conclusions: IC induces objective responses in ITM and should be considered in patients with unresectable ITM or disease recurrence despite locoregional therapies.

Clinician assessed best overall response

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<th>Response</th>
<th>Single agent PD-1 (%)</th>
<th>Single agent anti-CTLA-4 (%)</th>
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Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
An analysis of nivolumab-mediated adverse events and association with clinical efficacy in resected stage III or IV melanoma (CheckMate 238). First Author: Mario Mandal, Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy

Background: In both previous 18- and 24-month follow-up reports from CheckMate 238, NIVO demonstrated significantly longer recurrence-free survival (RFS) than ipilimumab (IPI) in patients (pts) with resected stage IIIB/C or stage IV melanoma. Here we provide a more comprehensive analysis of treatment-related adverse events (TRAES) for NIVO over discrete follow-up intervals and an investigation of the association of these AEs with efficacy (RFS).

Methods: Eligible pts were aged ≥15 years and underwent complete resection of stage IIIB/C or IV melanoma. A total of 453 pts were treated with NIVO 3 mg/kg Q2W for up to 1 year. The primary endpoint was RFS. Pts were followed for safety for up to 100 days following their last dose; as of the previous 18-month database lock, all pts had been off study drug for > 100 days. Here safety data were analyzed within discrete time intervals: months 0–3 of treatment (0–3), months 3–12 of treatment (3–12), and from last dose to 100 days after last dose (+100). In addition, the association of TRAES with RFS was investigated using the 24-month efficacy dataset, accounting for time-delay bias within the first 12 weeks after randomization.

Results: The incidence of the first onset of TRAES reported in ≥5% of pts was highest in the 0–3 time frame; the most common TRAES with NIVO were fatigue (28% for 0–3 vs 6% for 3–12 vs 2% for +100), pruritus (16% vs 7% vs 1%), and diarrhea (15% vs 7% vs 2%). Most TRAES with NIVO resolved within 3 months of occurrence, except for endocrine AEs, which could have required hormone supplementation, and skin AEs (median overall resolution time of 48 and 22 weeks, respectively). Similar results were observed in an analysis taking into account repeat occurrences of TRAES over time. Analyses investigating the association of TRAES with RFS are ongoing and will be presented.

Conclusions: These results in pts with resected stage IIIB/C or IV melanoma are consistent with the established safety profile of NIVO. Based on the time periods analyzed, the majority of TRAES with adjuvant NIVO occurred early during treatment, and patients had a reduced frequency of TRAES after the treatment course. The majority of select TRAES resolved within 3 months. Clinical trial information: NCT02389906.

A sequential dual cohort II clinical trial on adjuvant low-dose nivolumab with or without low-dose ipilimumab as adjuvant therapy following the resection of melanoma macrometastases (REDUCTOR trial). First Author: Julia Katharina Schwarze, Universitair Ziekenhuis Brussel, Brussels, Belgium

Background: Optimal dosing and duration of adjuvant treatment with anti- PD-1 checkpoint inhibitors, e.g., nivolumab (NIVO), following complete resection of melanoma (MEL) lymph node metastases has not been established. We investigated a regimen of low-dose NIVO with/without low-dose ipilimumab (IPI) as adjuvant therapy in MEL pts. Methods: After complete resection of MM, pts were treated with IPI 50mg (fixed dose, 1x) plus NIVO 10mg (fixed dose, Q2w x4) (Cohort-A), or NIVO 10mg (Q2w x9, Q8w x4) (Cohort-B). One-year relapse-free survival (RFS) rate served as primary endpoint. Sample size (34 pts) was calculated according to a Fleming one-stage clinical trial design. Recruitment to Cohort-B was closed prematurely following registration of NIVO in the adjuvant setting by EMA. Secondary endpoints were safety, distant metastasis-free survival (DMFS) and overall survival (OS). Quantitative measurement of BRAF/V600S/M354 mutant circulating tumor DNA (ctDNA), as well as tumor gene expression profiling were performed. Results: 34 pts (15M/19F, 31 stage II/III/IV stage II) and 22 pts (12M/10F, 21 stage II/III stage II) were enrolled in Cohort-A and -B, respectively. After a median follow-up of 86 months for Cohort-A and 36 months for Cohort-B, estimated 12 months (m) RFS-rate was respectively 55% (95% CI, 39–72%) and 78% (95% CI, 73–82%), 12m OS-rate was 97% (95% CI, 94–100%) and 100%, and 12m DMFS-rate was 79% (95% CI, 92–65), no distant metastases occurred in Cohort-B. Median RFS for Cohort-A was 84w (95% CI, 69-124) vs 78w (95% CI, 28-139), not reached for Cohort-B. Median DMFS and OS had not been reached at time of analysis in either cohort. All grade treatment-related adverse events were observed in 21 (61%)/17 (77%) with 3 (8%)/4 (4%) grade 3 AEs in Cohort-A/B, respectively. One patient in Cohort-A had a detectable level of ctDNA at baseline and relapsed 3w after initiating treatment. Tumor profiling is ongoing for cohort-B. Conclusions: The investigated adjuvant low- dose regimens have an acceptable safety profile. Survival rates resemble those of standard regimens. These regimens could be economically advantageous alternatives for pts without access to standard regimens. Clinical trial information: NCT02941744.

A phase I study of neoadjuvant combination immunotherapy in locally/regionally advanced melanoma. First Author: Yana Najjar, University of Pittsburgh, Pittsburgh, PA

Background: A trial of neoadjuvant pembrolizumab (P) in combination with high dose interferon-α (HDI) in high-risk patients (pts) with locoregionally advanced melanoma (mel) has completed enrollment. Methods: Primary endpoint: safety of combination P-HDI. Pts were treated with P x 2 doses followed by definitive surgery, then x1. HDI was given concurrently, and both agents were per standard regimen. Tumor and blood samples were obtained at baseline and at surgery (wk 6-8), blood at 6 wks, 3,6,12 months (mos).

Results: 30 pts were treated (22 male, 8 female, age 26-83). 16 had cutaneous primary, 3 mucosal, 11 unknown. At enrollment, 16 had recurrent disease, 6 received prior adjuvant therapy with ipilimumab (4) or HDI (2). 16 had AJCC 7 stage IIIB, 9 IIIC, 5 IV. 332 P cycles have been delivered (median 13), 496 doses of HDI induction (median 17), 1329 doses of HDI maintenance (median 44). HDI dose was reduced in 20 pts, discontinued in 27, P discontinued in 8. Radiologic preoperative RR was 77% (95% CI, 59-88) (6 CR, 17 PR), 20% (6) had SD and 1 had PD. All pts underwent definitive surgery. The pathologic complete response (pCR) of 26 pts was 32% (95% CI, 18-51). 6 pts recurred and 3 died. No pt with pCR has recurred. Median f/u time is 17.4 mos, median PFS/OS not reached. Most common grade (Gr) 3 toxicities: hypophosphatemia (10; 33%), fatigue (10; 33%), 1TCPK (6%; 20%), lipase (4; 13%). 3 Gr 4 events (1CPK, hyperglycemia, lymphocyte count decreased). 1 suspected grade 5 event occurred 6 months after completion of therapy, PD-L1 expression at baseline did not correlate with clinical outcomes. In 8 pts with pre and post treatment tumor samples, IHC expression of PD-1, PD-L1, CD11b, CD8, FoxP3 and CD25 increased post-treatment (p < 0.05).

Conclusions: Neoadjuvant P-HDI has promising clinical activity, although treatment is limited by HDI toxicity. Treatment increases the immune cell infiltrate, and outcomes do not correlate with baseline expression of PD-L1. Longer follow up and further mechanistic studies are underway. Clinical trial information: NCT02339324.

Neoadjuvant cytoreductive treatment with BRAF/MEK inhibition of prior unresectable regionally advanced melanoma to allow complete surgical resection. REDUCTOR trial. First Author: Stephanie A. Blankensteijn, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

Background: The aim of this study is to evaluate the potency of short-term neoadjuvant cytoreductive therapy with dabrafenib and trametinib (BRAF and MEK inhibitor respectively) to allow radical surgical resection in patients with unresectable BRAF-mutated, locally advanced stage III or oligometastatic stage IV melanoma. Methods: A total of 25 pts with BRAF-mutated, unresectable locally advanced stage III or oligometastatic stage IV (>3 metastases) melanoma will be treated with dabrafenib and trametinib for 8 weeks. Response evaluation by positron emission tomographycomputed tomography (PET/CT) will occur at 2 and 8 weeks. If sufficient downsizing occurs, surgical resection will be performed. Biopsies for translational research will be taken at baseline and 2 weeks. The dissection specimen will be stored at 8 weeks. Results: Currently 20 patients have been included. Of these, 2 patients showed PD upon treatment and did not proceed to surgery. In 17/18 (94%) patients resection was possible after neoadjuvant treatment, of which 16 (94%) were R0 resections. Median follow-up time is 28 months with a median recurrence-free survival of 9 months in patients undergoing surgery. The 1-year overall survival (OS) was 94% and 2-year OS 82%. Median OS was not reached. Metabolic response rates (RR) on PET/CT at 8 weeks were: 4 (20%) CR, 14 (70%) PR, 0 (0%) SD, 2 (10%) PD. Pathologic RR differed: 7 (35%) CR, 7 (35%) PR, 3 (15%) SD, 0 (0%) PD and in 3 patients (15%) no pathologic response was measured, since no resection was performed. Most patients (85%) experienced any toxicity, of which 50% was grade 1, 20% grade 2 and 3 patients (15%) experienced grade 3 toxicity. The most common reported toxicity was fever. Conclusions: Neoadjuvant dabrafenib and trametinib shows to be a potent cytoreductive treatment, allowing radical resection of metastases in 16/20 (80%) patients with prior unresectable locally advanced melanoma. Patients with no recurrence remained disease-free for a prolonged period of time. If there was recurrent disease, this usually occurred within months after surgery and this may present an opportunity for further tailored adjuvant therapy. Clinical trial information: NTR4654.

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Background: Results from the phase 1b (OpACIN) study comparing neo-
adapter to adjutant ipilimumab (3mg/kg) plus nivolumab (1mg/kg) demonstrated a high clinical activity of neoadjutant treatment in high-risk melanoma. However, the toxicity was high, with 90% grade 3 to 4 toxicity. These findings raise questions about long-term quality of life (QoL) in these patients who were treated with curative intent. Here we present the first analysis of patient-reported outcomes of patients treated with (neo)adjutant immune checkpoint combination therapy. Methods: Sixteen of 20 pts had completed study treatment and were currently in follow-up (FU). Pts were asked to fill in The European Organisation for Research and Treatment of Cancer QoL questionnaire-C30 (QLQ-C30). The QLQ-C30 was used to assess health-related QoL and is composed of functional, symptomatic dimensions and a dimension of global health/QoL. A reference population (controls without a diagnosis of cancer) was obtained from the ‘Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship’ study. Pts were individually matched on age, gender, node-negative status with up to 9 controls. Pts and controls were compared on QLQ-C30 scores using univariable linear regression analyses. Results: Thirteen out of 16 invited pts (81% response) returned a completed questionnaire. Median FU was 30 months after randomization. Pts scored significantly lower in emotional (std coef. = -1.0, p = 0.071), role (std coef. = -0.8, p = 0.018) and social (std coef. = -1.0, p = 0.014) functioning and higher in symptom burden of fatigue (std coef. = 9, p = 0.024) compared to controls, which were all clinically relevant. The physical functioning and global QoL score did not differ between pts and controls. Conclusion: (neo)adjutant immune checkpoint combination therapy showed significantly lower emotional, role, cognitive and social functioning scores than controls. Pts reported higher levels of fatigue, however, there was no difference on physical functioning and global QoL between pts and controls.

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Resensitization of uveal melanoma (UM) to immune checkpoint inhibition (ICI) by IMCgp100 (IMC). First Author: Jessica Yang, Columbia University Medical Center, New York, NY

Background: ICI responses in UM are rare (~5% with anti-CTLA4/PD1 monotherapy, 10-12% with combination ICI). IMC is a bispecific agent composed of a high affinity T cell receptor targeting the gp100 melanoma antigen fused to an anti-CD3 scFv that increases intratumoral CD8+ T cell infiltration and PD1/PDL1 expression, and may enhance response to pre- and post-IMC ICI.

Methods: We previously reported on 19 UM pts treated in the phase I dose escalation cohort of IMC (IMCgp100-102). We performed a retrospective analysis of clinical features and response to pre- and post-IMC ICI for the 12 pts in this cohort as well as 17 other pts (n = 29) treated with post-IMC ICI at 7 centers from 8/2016 to 1/2019. 21/29 pts (including 10/12 pts from IMCgp100-102) are evaluable for response and/or survival and are included in the analysis.

Results: Baseline characteristics (n = 21): median age 56 (range 45-69); 57% female; median number of prior therapies 2 (range 1-4). Pre- and post-IMC ICI included: IPI+NIVO (3 pts; 8 post), anti-PD1 monotherapy (7 pre; 8 post), and anti-CTLA4 monotherapy (4 pre; 5 post). 20 pts were evaluable for post-IMC ICI response (1 died before restaging; 3/20 (15%) had partial responses (53.7-87% regression); 9/20 (45%) had stable disease (SD); 2/20 (10%) had progressive disease (PD). 1/20 had SD of unknown duration. Median PFS and OS from the initiation of post-IMC ICI were 4.9 (95% CI 2.7-10.7) and 10.1 (95% CI 5.7-7.9) months, respectively. 15 pts received pre-IMC ICI, all with eventual disease progression. 3 pts had treatment duration or SD lasting >6 months. Of these 3 pts, 2 had clinical benefit (defined by SD >16 weeks) with post-IMC ICI. There was no clear association between rates of Gr ≥ 2 IRAE with pre- or post-IMC ICI and response. For the 10 evaluable pts treated on IMCgp100-102, no marked difference in prior response to IMC (3 SD vs 10 IR) was observed.

Conclusions: Survival outcomes with post-IMC ICI compare favorably to historical figures in pretreated UM pts. IMC may re-sensitize pts who had prior clinical benefit with ICI to subsequent ICI.

Lenvatinib (len) plus pembrolizumab (pembro) in patients (pts) with advanced melanoma previously treated with OX37 KEYNOTE-146 trial. The efficacy and safety of len plus pembro combination therapy will be evaluated in an open-label, phase 2 trial of pts with advanced melanoma that progressed on OX37 KEYNOTE-146.

Methods: Key inclusion criteria: age ≥18 years, histologically/cytologically confirmed unresectable stage III-IV melanoma that progressed (per RECIST) within 12 weeks of last dose of an approved PD-1/PD-L1 inhibitor therapy (≥2 doses as monotherapy or combined with other therapies), measurable disease, ECOG PS 0/1, no active autoimmune disease, and adequate organ function. Pts must provide a baseline tumor sample. Pts will receive len 20 mg/day orally plus pembro 200 mg IV Q3W for approximately 2 years (35 doses of pembro), after which they may receive len alone until PD or unacceptable toxicity. Response will be assessed per RECIST v1.1 based on blinded independent central review (BICR) Q9W until week 54, Q12W until week 102, and Q24W thereafter. Pts with CR may discontinue treatment after ≥24 weeks of therapy; eligible pts may continue treatment beyond initial RECIST- or RECIST-defined PD. AE will be assessed throughout treatment and for 90 days (120 days for serious AEs) after last dose and graded per NCI CTCAE v4.0. Pts will be followed-up for survival status Q12W. The primary efficacy end point is ORR per modified RECIST v1.1 (BICR). Key secondary end points are PFS and DOR per modified RECIST v1.1 (BICR), OS, and safety; an exploratory biomarker analysis is planned. Clinical trial: NCT03776136.
Pembrolizumab versus placebo as adjuvant therapy in resected high-risk stage II melanoma: Phase 3 KEYNOTE-716 study. First Author: Matteo S. Carrino, Westmead and Blacktown Hospitals, Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia

Background: Adjuvant pembrolizumab showed significantly longer recurrence-free survival than placebo in patients with resected stage III melanoma in the KEYNOTE-054 study. KEYNOTE-716 (NCT03553836) is a randomized, placebo-controlled, double-blind, multicenter phase 3 study of adjuvant pembrolizumab in patients with surgically resected high-risk stage II melanoma. Methods: Key eligibility criteria are age ≥12 years with newly diagnosed, completely resected stage IIB/IIIC cutaneous melanoma, defined by the AJCC Cancer Staging Manual, 8th edition (wide excision and negative sentinel lymph node biopsy with no evidence of distant metastasis). Patients will be enrolled. Clinical trial information: NCT03553836.

TPS9596 Poster Session (Board #166a), Mon, 1:15 PM-4:15 PM

Pembrolizumab versus placebo as adjuvant therapy in resected high-risk stage II melanoma: Phase 3 KEYNOTE-716 study. First Author: Matteo S. Carrino, Westmead and Blacktown Hospitals, Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia

Background: Adjuvant pembrolizumab showed significantly longer recurrence-free survival than placebo in patients with resected stage III melanoma in the KEYNOTE-054 study. KEYNOTE-716 (NCT03553836) is a randomized, placebo-controlled, double-blind, multicenter phase 3 study of adjuvant pembrolizumab in patients with surgically resected high-risk stage II melanoma. Methods: Key eligibility criteria are age ≥12 years with newly diagnosed, completely resected stage IIB/IIIC cutaneous melanoma, defined by the AJCC Cancer Staging Manual, 8th edition (wide excision and negative sentinel lymph node biopsy with no evidence of distant metastasis). Patients will be enrolled. Clinical trial information: NCT03553836.

TPS9597 Poster Session (Board #166b), Mon, 1:15 PM-4:15 PM

KEYNOTE-630: Phase 3 study of adjuvant pembrolizumab versus placebo in patients with high-risk, locally advanced cutaneous squamous cell carcinoma. First Author: Jessy Hand, Cleveland Clinic, Cleveland, OH

Background: Among patients with high-risk, locally advanced (LA) cutaneous squamous cell carcinoma (cSCC) who receive current standard-of-care surgical resection and adjuvant radiotherapy, ~40-50% develop local recurrence and regional metastasis (J Clin Oncol, 2018;36:1275-1283). Recent data suggest that programmed death 1 inhibitors such as pembrolizumab may provide a well-tolerated, effective, and durable response in patients with LA or metastatic cSCC. To evaluate the efficacy and safety of adjuvant pembrolizumab in patients with high-risk LA cSCC, the randomized, double-blind, placebo-controlled phase 3 KEYNOTE-630 trial (NCT03833167) will be conducted. Methods: After surgical resection and radiotherapy for high-risk LA cSCC, eligible patients will be randomly assigned 1:1 to intravenous pembrolizumab (400 mg Q6W) or placebo for up to 18 cycles. Adverse events will be monitored throughout the study and graded according to the NCI CTCAE, version 4.0. The primary efficacy end point will be investigator-assessed and biopsy-confirmed recurrence free survival. Secondary end points will be overall survival, health-related quality of life, and safety. Recruitment is ongoing in 19 countries and will continue until approximately 570 patients are enrolled. Clinical trial information: NCT03833167.

TPS9598 Poster Session (Board #17a), Mon, 1:15 PM-4:15 PM

KEYNOTE-629: Phase 2 study of pembrolizumab for recurrent/metastatic or locally advanced, unresectable cutaneous squamous cell carcinoma (cSCC). First Author: Jean Jacques Grob, AIX-Marseille University, Marseille, France

Background: Findings from phase 1 and 2 studies suggest that targeting programmed death 1 (PD-1)-PD-L1 pathway can provide durable antitumor activity in patients with local/regionally advanced or metastatic cSCC and may be a promising treatment option. The open-label, single-arm, phase 2 KEYNOTE-629 trial (NCT03284424) will be conducted to test the clinical activity of the PD-1 inhibitor pembrolizumab in locally advanced, unresectable, and recurrent or metastatic cSCC. Methods: Patients will receive intravenous pembrolizumab 200 mg every 3 weeks for up to 35 infusions (≤24 months) or until protocol-specified treatment discontinuation. Treatment will not be stratified in this study. Eligibility criteria include age ≥18 years; locally advanced cSCC for which the patient is ineligible for resection or radiotherapy (RT) or for which the patient previously underwent RT to the index site or systemic therapy for curative intent; presence of measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; Eastern Cooperative Oncology Group performance status 0 or 1. Treatment will be discontinued for progressive disease, unacceptable toxicity, intercurrent illness preventing administration, investigator’s decision, patient withdrawal of consent, pregnancy, or cessation for administrative reasons. Response will be assessed by imaging 6 weeks after treatment initiation, every 6 weeks through year 1, and every 9 weeks thereafter or more frequently if clinically indicated. After disease progression or the start of new anticancer therapy, the patient will be followed up every 12 weeks until death, consent withdrawal, or study end, whichever occurs first. Safety will be monitored throughout the study and for 30 days after treatment end or 90 days if the patient experiences serious adverse events. The primary end point is objective response rate (RECIST v1.1). Secondary end points include response duration, disease-free control rate, progression-free survival, overall survival, and safety. Recruitment is ongoing in 10 countries and will continue until approximately 50 additional patients with locally advanced, unresectable cSCC are enrolled. Clinical trial information: NCT03284424.

TPS9599 Poster Session (Board #167b), Mon, 1:15 PM-4:15 PM

ILLUMINATE 301: A randomized phase 3 study of itilisolimod in combination with ipilimumab compared with ipilimumab alone in patients with advanced melanoma following progression on or after anti-PD-1 therapy. First Author: Marcus O. Butler, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

Background: Itilisolimod (IMO-2125) is a Toll-like receptor (TLR) 9 agonist with potent immunostimulating activity. In an ongoing Phase 1/2 clinical study in patients with advanced melanoma who progressed on or after anti-PD-1 therapy (NCT02644967), intratumoral (IT) itilisolimod with ipilimumab was well-tolerated, demonstrating durable responses (including complete response > 21 months), dendritic cell activation, type I interferon response, CD8+ T-cell proliferation in responders, and an abscopal effect. Methods: ILLUMINATE 301 (NCT03445533) is a randomized phase 3 global, multi-center, open-label study of IT itilisolimod (8 mg) in combination with ipilimumab (3 mg/kg) versus ipilimumab monotherapy in patients with advanced melanoma and progression on or after anti-PD-1 therapy. Eligible patients are ≥18 years with histologically confirmed unresectable Stage III or Stage IV melanoma, ≤1 measurable lesion accessible for injection (superficial or visceral, the latter with image guidance), ECOG PS ≤1, and adequate organ function. Exclusion criteria include prior TLR agonists, prior ipilimumab (except adjuvant ≥12 weeks before progression), and CNS disease other than stable brain metastases. Patients are randomized 1:1 and stratified by duration of prior anti-PD-1 (≥12 weeks vs <12 weeks), stage (M1c vs other), and BRAF status/prior targeted therapy (TT) (BRAF wildtype vs BRAF mutation+ with TT vs BRAF mutation+ without TT). Primary endpoints are overall survival rate (RECIST v1.1) by independent central review and overall survival. Secondary endpoints include durable response rate, time to response, progression-free survival, patient-reported outcomes, and safety. Patients are enrolling at sites in the United States, Europe, Australia, and Canada. References: (1) Haymaker C. Society for Immunotherapy of Cancer Annual Meeting, November 2017, National Harbor, MD; (2) Diab A, et al. European Society of Molecular Oncology Annual Meeting, October 2018, Munich, Germany. Clinical trial information: NCT03445533.
Nivolumab combined with ipilimumab is active in melanoma metastases, with intracranial response rates > 45% and durable survival in treatment-naïve patients (pts) (Long GV et al Lancet Onc 2018; Taiwbi H et al NEJM 2018). We seek to determine if the addition of stereotactic radiotherapy (SRS) results in improved intracranial outcomes. Methods: This is a multisite, open-label, phase 2 trial in systemic treatment-naïve pts with melanoma brain metastases. Pts must have ≥ 1 asymptomatic brain metastases that are ≥ 5mm and ≤ 40mm as per modified RECIST 1.1, on gadolinium-enhanced MRI, and no history of previous treatment with SRS. Eligible pts are randomly assigned to either receive nivolumab plus ipilimumab with SRS or nivolumab plus ipilimumab alone. Nivolumab (1mg/kg) and ipilimumab (3mg/kg) are given every 3 weeks for 4 doses. Following induction, 480mg nivolumab is given every 4 weeks until progression, unacceptable toxicity, or a maximum of 2 years. SRS is administered as single fraction of 16-22Gy, or hypofractionated for larger lesions (24-27Gy in 3 fractions), within 7 days of immunotherapy commencement. Pts will be evaluated for intracranial and extracranial response, and overall response, every 6 weeks to week 24 and 12 weeks thereafter until overall disease progression or death. The primary endpoint is neurologic specific survival (NSS) at 12 months. Secondary endpoints include intracranial response rate, intracranial PFS, overall PFS, overall survival, neurocognitive function and incidence of radiation necrosis. 109 patients in each cohort (218 total) will achieve > 80% power at the significance level (alpha) of 0.10 to detect a minimum absolute increase of 9% in the NSS rate at 12 months. Clinical trial information: NCT03340129.

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Phase II single-arm multicenter study of adjuvant ipilimumab in combination with nivolumab in subjects with high-risk ocular melanoma. First Author: Suthee Rapisuwon, Georgetown University, Lombardi Comprehensive Cancer Center, Washington, DC

Background: Treatment of primary ocular melanoma is often very effective, with local recurrence rates of < 5%. However, distant recurrence is as high as 50% depending on features of the primary tumor. These data emphasize the need for effective adjuvant therapy for patients with locally treated ocular melanoma. Several adjuvant treatments have been developed for patients with high-risk cutaneous melanoma, including ipilimumab and nivolumab monotherapies and an ongoing trial is exploring the nivolumab/ipilimumab combination (CA209-915), but patients with high-risk ocular melanomas have been excluded from these trials. As yet there is no approved adjuvant treatment for high-risk ocular melanoma patients. Methods: We are conducting a Phase II single-arm multi-center study of adjuvant ipilimumab in combination with nivolumab in subjects with high-risk ocular melanoma. This study aims to generate efficacy and safety data for adjuvant this regimen in patients with locally treated high-risk ocular melanoma with 3-year risk of relapse > 50%. The primary endpoint is 3-year relapse-free survival rate. Secondary endpoints are median relapse-free survival, median overall survival, 3-year overall survival rate and safety. All patients will receive nivolumab 240mg IV every 2 weeks plus ipilimumab 1mg/kg IV every 6 weeks. Subjects may receive up to 25 doses of nivolumab and 8 doses of ipilimumab. The accrual goal is 50 patients across all participating institutions. Subjects treated in this study will be matched with controls selected from a contemporaneously collected OM registry, “contemporaneous control” in order to better assess efficacy. Control subjects will be from institutions not participating in this trial, will otherwise meet the trial eligibility criteria and will be further matched with trial participants for various demographic and risk factors to the extent possible. The study is enrolling in 6 comprehensive cancer centers in the US. Clinical trial information: NCT03528408.

Personalized response-driven adjuvant therapy after combination ipilimumab and nivolumab in high-risk resectable stage III melanoma: PRADO trial. First Author: Irene Reijers, Netherlands Cancer Institute, Amsterdam, Netherlands

Background: Adjuvant (adj) immune checkpoint inhibition (ICI) improves relapse free survival (RFS) in stage III melanoma patients (pts). However, preclinical and translational data suggest that neo-adjuvant (neoadj) treatment might be favorable due to broader immune activation. The phase 1b OpACIN study comparing neoadj to adj IPI plus NIVO demonstrated a high pathological response rate (pRR) of 78% complicated by 90% gr 3-4 immune-related adverse events (irAEs). The phase 2 OpACIN-neo trial tested safety and efficacy of three different schemes of neoadj IPI+NIVO and identified two cycles of IPI 1mg/kg + NIVO 3mg/kg as well tolerated (20% gr 3-4 irAEs), with a high pRR of 77%. In both trials, none of the pts with a pathologic response have relapsed after a median follow-up of 30 and 8.3 months. In stage IV melanoma, long-term benefit is observed in patients achieving CR with ICI, even after cessation of therapy. This raises the question of whether a therapeutic lymph node dissection (TLND) can be omitted when a deep pathologic response with neoadj IPI+NIVO is achieved. Methods: The aim of this international multi-center investigator-initiated phase 2 PRADO extension study is to confirm the pRR and toxicity of 2 cycles of neoadj IPI 1mg/kg + NIVO 3mg/kg (the preferred OPACIN-neo regimen) and to test response-driven subsequent therapy i.e. omitting surgery and adjuvant ICI based on the pathological response. 100-110 pts with stage IIIB/C melanoma and a measurable lymph node ($\geq$15mm according to RECIST 1.1) will receive two cycles of IPI 1mg/kg + NIVO 3mg/kg after marker placement into the largest lymph node metastasis. After six weeks, pts will undergo resection of the index lymph node. For pCR/near pCR, pts will not undergo TLND; For pPR, pts will undergo TLND; and for pNR, pts will undergo TLND and start adjuvant NIVO or targeted therapy +/- radiotherapy for 52 weeks. Primary endpoints are pRR of marked lymph node and RFS at 24 months. Baseline biopsies, blood samples (week 0, 6, 12) and faeces (week 0, 6) will be collected for translational research analyses. The first patient in this trial was included in October 2018; 22 patients have been enrolled. Clinical trial information: NCT02977052.
Background: Vincristine with irinotecan (VI) is effective in patients with relapsed RMS but outcomes remain poor. The addition of temozolomide to VI (VIT) is attractive owing to different resistance mechanisms and distinct toxicity profiles. Methods: The VIT-0910 trial, an EpSSG-ITCC randomized phase 2 trial, evaluated efficacy and safety of VI and VIT in patients (pts) aged 0.5-50 years with relapsed/refractory RMS. Pts received Vincristine 1.5 mg/m2 d1, d8, Irinotecan 50mg/m2 d1-d5 +/- Temozolomide 125 mg/m2 d1-d5 (150 mg/m2 from cycle 2 if no toxicity > grade 2); 21-day cycles were given until progression/unacceptable toxicity. The primary endpoint was centrally reviewed objective response rate (ORR) after 2 cycles (primary lesion, WHO criteria, RECIST 1.1). Secondary endpoints included progression-free survival (PFS), overall survival (OS) and adverse events (NCI-CTCAE v4). Initially a Simon 2-stage design was used to analyze separately 40 pts/arm. After amendment, the trial sample size was increased to 120, and a comparison between arms, adjusted for confounding factors, was added to the statistical plan. Results: 120 pts (60VI, 60VIT) were recruited in 37 European centers from 03/2012-04/2018. Median age was 11 years (0.75-46), 89% pts relapsed RMS. ORR was 24/55 (44%) for VIT vs 18/58 (31%) for VI; adjusted odds ratio = 0.50, 95% CI, 0.22-1.12, p=0.09. The VIT arm achieved significantly better PFS (adjusted Hazard Ratio (HR)=0.65, 95% CI, 0.43-0.97, p=0.036) and OS (HR=0.33-0.83, p=0.018) compared to VI. PFS and OS results were similar when only relapsed patients were included. Adverse events ≥ grade 3 were more frequent in VIT compared to VI, but only hematological toxicity was significantly increased (81% for VIT, vs 59% for VI, odds ratio=1.36, 95% CI, 1.06-1.76, P=0.02). Conclusions: The addition of temozolomide to VI improves PFS and OS of pts with relapsed/refractory RMS. VIT is now standard treatment for relapsed RMS in Europe. Clinical trial information: NCT01354545.

Effect of intensification of induction II chemotherapy and liberalization of stem cell donor source on outcome for children with high risk acute myeloid leukemia: A report from the Children’s Oncology Group. First Author: Richard Apilenc, Children’s Hospital of Philadelphia, Philadelphia, PA

Background: Patients with residual acute myeloid leukemia (AML) after induction fared poorly. The recently completed AAML1031 Phase III clinical trial intensified Induction II chemotherapy, altered the stem cell transplant (SCT) conditioning regimen, and liberalized SCT donor source criteria. We sought to test whether these practice changes improved clinical outcomes. Methods: Patients on AAML0531 and AAML1031, sequential Phase III trials for AML with shared high risk features of both > 15% residual blasts by morphology and ≥ 0.1% minimal residual disease (MRD) by flow cytometry with uninformative cytogenetics or high risk cytogenetic features (-7 or -5/5q-) were included. Gemtuzumab exposed and patients with high allelic ratio FLT3/ITD were excluded. Patients were observed from the start of Induction II through last available follow up. Induction II chemotherapy (ADE or AraC/Mito) was the exposure of interest. Disease free and overall survival (DFS, OS) were the primary outcomes. Standard descriptive statistics were used to compare patient characteristics and secondary outcomes; Kaplan Meier analyses were used to evaluate DFS/OS. Results: A total of 47 patients from AAML0531 (ADE) and 95 patients from AAML1031 (AraC/Mito) were included and did not differ in baseline characteristics. Five year DFS ±2SE was 17.5 ± 11.4 for ADE and 23.9 ± 8.8 for AraC/Mito, p = 0.528. Five year OS was 38.1 ± 14.2 for ADE and 33.3 ± 10.7 for AraC/Mito, p = 0.364. End of Induction II disease response and MRD did not differ between ADE and AraC/Mito. Patients receiving ADE had a higher probability of neutrophil recovery (74% vs 53%, p = 0.019) and recovered neutrophils a median of 7 days more quickly (27 vs 34 days), p < 0.001. ADE patients also had fewer inpatient hospital days (28 days versus 32 days, p = 0.002). Ten patients after patients receiving SCT did not differ 34% vs 44%, p = 0.253 and post-SCT outcomes did not differ. Conclusions: The intensification of Induction II chemotherapy, change in SCT conditioning regimen, and liberalization of SCT donor source was not associated with improved clinical outcomes. Intensification of Induction II was associated with higher G1W and longer time to neutrophil recovery. Further study is needed to support the intensification of Induction II chemotherapy with AraC/Mitoaxtane. Clinical trial information: NCT01371981.

Temozolomide versus irinotecan-temozolomide for children with relapsed and refractory high risk neuroblastoma (RR-HRNB): Results of the BEACON-Neuroblastoma randomized phase 2 trial—A European Innovative Therapies for Children with Cancer (ITCC) - International Society of Pediatric Oncology Europe Neuroblastoma Group (SIOPEN) trial. First Author: Lucas Moreno, Hospital Universitario Nito Jesús, Madrid, Spain

Background: BEACON-Neuroblastoma is a randomized Phase II trial to assess the activity of backbone chemotherapy regimens for children with RR-HRNB and to determine if patients with refractory RR-HRNB and with unfavorable cytogenetics have an increased benefit from adding temozolomide to backbone chemotherapy. Methods: Patients aged 1-21 years with RR-HRNB with adequate organ function and performance status were randomized in a 2x2 factorial design to: temozolomide (T) versus irinotecan-temozolomide (IT), with or without bev-acizumab. Here we report the results of the irinotecan randomization (T vs. IT), which had a probability-based Bayesian design. Primary endpoint was best overall response (complete or partial) during the first 6 courses, by RECIST for measurable disease patients and International Neuroblastoma Response Criteria for evaluable disease patients for which overall response rate (ORR) was calculated. Results: From 2013 to 2018, 61 patients were randomized to treatment with T and 60 to IT. Median age was 5.8 years, 85 and 36 had measurable and evaluable disease respectively; 55 and 66 had refractory and relapsed disease; 22 had MYCN amplification. Baseline characteristics were balanced between the arms. Response data was not yet available for 2 patients on T. Response was not assessable for 17 patients (did not have treatment or stopped early) who were considered non-responders. The ORR was 24% for T and 17% for IT (risk ratio (RR) = 0.70, 95% credible interval 0.32 to 1.44). The probability that the RR for ORR was > 1.0 was 17%, meaning that IT did not show greater activity than T. There was no interaction between treatment with/without bev-acizumab (heterogeneity test, p=0.7). 27 (44%) T and 35 (58%) IT patients had grade ≥ 3 toxicities as per CTCAE v4.0. Diarrhea occurred in no patients on T (0%) vs 9% (12%) on IT and myelosuppression (WHO grade 3 neutropenia (T 14, IT 22), and thrombocytopenia (14, T 11, IT 11)). Conclusions: Irritomazolide does not improve the response rate when added to temozolomide in RR-HRNB, but does increase diarrhea. Longer follow-up is needed before assessing whether it impacts progression-free or overall survival. Number of responses by treatment arm. Clinical trial information: NCT02308527.
Safety and activity of venoclax in combination with high-dose cytarabine in children with relapsed or refractory acute myeloid leukemia

Background: Venoclax is an orally available BCL-2 antagonist with demonstrated activity in adults with newly diagnosed or relapsed acute myeloid leukemia (AML). Here, we describe the first use of venoclax 1 in combination with high-dose cytarabine and idarubicin 2 in patients aged 2-22 years old with relapsed AML. Methods: Patients with relapsed AML or AML refractory to at least two courses of induction therapy were enrolled in this Phase 1 study with a rolling 2 design. All patients received venoclax 240 or 360 mg/m^2 ID days 1-28 and low-dose (LD: 100 mg/m^2 every 12 hours x 20 doses) or high-dose (HD: 1000 mg/m^2 every 12 hours x 8 doses) cytarabine beginning on day 8 (Table). Patients who had previously received < 270 mg/m^2 of doxorubicin equivalents also received idarubicin 12 mg/m^2 on day 8 in dose level 3; other patients were enrolled on the expansion cohort at dose level 3. Non-hematologic CTCAE grade 3 or higher toxicities were intensity limiting (ILT), excluding those anticipated with HD cytarabine. Results: Among 18 evaluable patients, a single ILT (prolonged hematopoietic suppression beyond day 50) was observed (Table). Toxicities were consistent with the underlying cytotoxic chemotherapy, with 4 patients experiencing a total of 40 grade 3 toxicities including 6 documented infections and 23 episodes of febrile neutropenia. There was 1 grade 4 fungal sepsis. The recommended phase 2 dose of venoclax was 360 mg/m^2 (max 600 mg) when combined with HD cytarabine or HD cytarabine/idarubicin. Of the 12 patients with > 50% reduction in blasts following the 7-day venoclax window these patients proceeded to day 28 and included 7 CR/CRI and 3 PR. Minimal residual disease negative remissions occurred in 4 patients. BH3 profiling of samples and a phase 2 expansion of both dose levels 3 and 4 to further characterize the promising activity of these combinations are underway. Conclusions: Venoclax combined with cytarabine or cytarabine/idarubicin is active and well tolerated in pediatric patients with relapsed/refractory AML. Clinical trial information: NCT03194932.

Efficacy and toxicity of pegaspargase and calaspargase pegol in pediatric acute lymphoblastic leukemia/lymphoma: Results of DFCI 11-001

Background: Asparaginase (ASP) is an important component of acute lymphoblastic leukemia (ALL) treatment, but is often discontinued due to toxicity. For allergic reactions, but not other toxicities, Erwinia Asparaginase (EA) is often substituted. The majority of treatment protocols use discrete, discontinuous periods of asparaginase depletion. In the context of such protocols, the impact of EA substitution or complete ASP discontinuation is unknown. Methods: Patients age 1-30.99 years enrolled on frontline COG trials for B-ALL [standard risk (NCI SR): AALL0331; high risk (NCI HR) AALL0232] were included. The number of prescribed pegaspargase (PEG) doses varied by trial, risk strata, and randomization (Table). Maintenance therapy did not contain ASP. Landmark analyses starting at Maintenance compared event free survival (EFS) between those receiving all prescribed doses of PEG vs those switched to EA but receiving all doses vs those not receiving all ASP doses. Results: This study included 5,195 AALL0331 and 3,001 AALL0232 patients. The cumulative incidence of PEG discontinuation was 12.2±4.6% on AALL0331 and 25.4±0.8% on AALL0232. In multivariable analyses adjusted for patient and disease variables, NCI HR patients who did not receive all prescribed ASP doses had inferior EFS (hazard ratio (HR) 1.5, 95% confidence interval (95CI) 1.2-1.9; p=0.002) compared to those receiving all prescribed PEG doses. Patients with EA substitution who completed their courses were not at increased risk (HR 1.1, 95CI 0.7-1.6; p=0.69). Sensitivity analyses excluding patients discontinuing ASP due to pancreatic toxicity yielded similar results. NCI SR patients who discontinued ASP were not at elevated risk (HR 1.2, 95CI 0.9-1.6; p=0.23) except when analyses were restricted to NCI SR patients with slow early response (HR 1.7, 95CI 1.1-2.7; p=0.03). Conclusions: Discontinuation of ASP doses is associated with significantly inferior EFS and must be balanced against the risks of ASP re-challenge. Our results also illustrate the potentially severe consequences of EA shortages. Prescribed pegaspargase doses.

Impact of asparaginase discontinuation on outcome in childhood ALL: A report from the Children’s Oncology Group (COG)

Background: Asparaginase (ASP) is an important component of acute lymphoblastic leukemia (ALL) treatment, but is often discontinued due to toxicity. For allergic reactions, but not other toxicities, Erwinia Asparaginase (EA) is often substituted. The majority of treatment protocols use discrete, discontinuous periods of asparaginase depletion. In the context of such protocols, the impact of EA substitution or complete ASP discontinuation is unknown. Methods: Patients age 1-30.99 years enrolled on frontline COG trials for B-ALL [standard risk (NCI SR): AALL0331; high risk (NCI HR) AALL0232] were included. The number of prescribed pegaspargase (PEG) doses varied by trial, risk strata, and randomization (Table). Maintenance therapy did not contain ASP. Landmark analyses starting at Maintenance compared event free survival (EFS) between those receiving all prescribed doses of PEG vs those switched to EA but receiving all doses vs those not receiving all ASP doses. Results: This study included 5,195 AALL0331 and 3,001 AALL0232 patients. The cumulative incidence of PEG discontinuation was 12.2±4.6% on AALL0331 and 25.4±0.8% on AALL0232. In multivariable analyses adjusted for patient and disease variables, NCI HR patients who did not receive all prescribed ASP doses had inferior EFS (hazard ratio (HR) 1.5, 95% confidence interval (95CI) 1.2-1.9; p=0.002) compared to those receiving all prescribed PEG doses. Patients with EA substitution who completed their courses were not at increased risk (HR 1.1, 95CI 0.7-1.6; p=0.69). Sensitivity analyses excluding patients discontinuing ASP due to pancreatic toxicity yielded similar results. NCI SR patients who discontinued ASP were not at elevated risk (HR 1.2, 95CI 0.9-1.6; p=0.23) except when analyses were restricted to NCI SR patients with slow early response (HR 1.7, 95CI 1.1-2.7; p=0.03). Conclusions: Discontinuation of ASP doses is associated with significantly inferior EFS and must be balanced against the risks of ASP re-challenge. Our results also illustrate the potentially severe consequences of EA shortages. Prescribed pegaspargase doses.

10007 A randomized trial of a sacubitril/valsartan (6MP) adherence-enhancing intervention in children with acute lymphoblastic leukemia (ALL): A COG AALL1033 study

Background: We previously reported that > 40% of children with ALL are non-adherent to 6MP, and >52% of ALL relapses are attributable to 6MP non-adherence. The most common barrier is forgetting to take 6MP; the most common facilitator is parental vigilance. These observations informed a randomized trial to enhance 6MP adherence (COG-ACCL1033, NCT01503632; 89 COG sites). Results are described here. Methods: The Intervention Package (IP) consisted of: i) Education; ii) 6MP schedules; iii) daily personalized text message reminders from physician to patient and caregiver, to prompt iv) directly supervised therapy (DST), with text back response by patient/caregiver. Baseline adherence was measured for 4 weeks, followed by intervention for 16 weeks to examine the impact of IP vs Edu (education) on 6MP adherence (measured electronically by MEMs Cap) in all patients, ≥12yo, <12yo. Longitudinal binomial logistic regression using generalized estimating equations was used. Missing data were handled by multiple imputation. Results: 444 patients were randomly assigned to IP (n = 230) or Edu (n = 214). Baseline characteristics (age at study: 6.8 vs 7.5; years; males: 67% vs 69%; non-Hispanic whites: 40% vs 42%) and adherence rates (92% vs 94%) were comparable (except paternal education: 49% vs 38%; p = 0.04). No study arm*time interaction was found; thus, the 16-week overall mean fitted adherence rates were compared between IP and Edu, adjusting for baseline adherence, time on study, patient education. All patients: Adherence rates were marginally higher on IP (94% vs 92.5%, p = 0.09). On IP, for times with a record of text response, adherence rates were higher (94%) when compared with times with no response (89%); p = 0.02. <12yo: Adherence rates were comparable (IP: 94.4% vs Edu: 93.7%, p = 0.5). >12yo: Adherence rates were significantly higher on IP (93.1% vs 90.0%, p = 0.037). >12yo with baseline adherence < 90%: IP had the highest impact for this subgroup (83.4% vs 74.6%, p = 0.008). Conclusions: A 16-week comprehensive intervention resulted in higher 6MP adherence rates in children with ALL who were 12y or older at study. IP was most impactful in adolescents with baseline non-adherence. Clinical trial information: NCT01503632.
Prognostic factors for survival after relapsed acute lymphoblastic leukemia (ALL): A Children’s Oncology Group (COG) study. First Author: Susan R. Rheingold, Children’s Hospital Los Angeles, CA

Background: Survival of pediatric ALL patients (pts) now approaches 90% but is historically poor for those who relapse. Methods: In the largest cohort assembled to date we analyzed overall survival (OS) rate post relapse, defined as duration between date of relapse and death, among pts diagnosed from 1996-2014 treated on 10 contemporary COG frontline trials. Comparisons of post-relapse OS were based on logrank tests, with two-sided p values reported. Results: Of 15,874 pts enrolled on frontline trials, 1,967 (12%) relapsed. Relapse rates ranged from 35% in infant ALL to 9.7% in pts with NCI standard risk B-ALL. Rates were similar for T and B-ALL, 11% vs. 12%. Relapse patterns differed by phenotype: almost half of non-infant B-ALL relapses occurred late (>36 mos), and at all time periods bone marrow (BM) relapse predominated. Conversely 65% of T-ALL relapses were early (<18 mos) with similar number of isolated CNS (iCNS) and isolated BM (iBM) relapses. Median time to relapse was shorter for infant ALL and T-ALL (both 13.8 mos) compared to B-ALL (34.4 mos). The 5yr OS rates (>3E) after relapse for B, T, and infant ALL were 52 ± 1%, 33 ± 3% and 19 ± 4%, respectively, with greater variability in OS by site in T vs. B-ALL. 5yr OS rates for pts with early BM relapse was similar for both B and T-ALL (28%), but pts with B-ALL who relapsed between 18-36 mos fared better than pts with T-ALL (OS 50 ± 2% vs 34 ± 8%, p = 0.014). The 5yr OS rates for pts with late relapses were 65 ± 2% for B-ALL and 50 ± 12% for T-ALL. In multivariate analysis, time to relapse, sex of relapse, initial B/WC > 100K, and T-cell phenotype were associated with worse outcomes post relapse (all < .01). Sex, CNS status at diagnosis, or prior therapy on POG versus CCG/COG backbone did not influence OS. Compared to pts treated from 1988-2002 (Nguyen et al. Leukemia 2008), 5yr OS rates reported.

Results: p values reported.

Methods: (ALL): A Children’s Oncology Group (COG) study. First Author: Susan R. Rheingold, Children’s Hospital Los Angeles, CA

Background: TRK fusions involving NTRK1, NTRK2, and NTRK3 genes have been identified in a broad range of pediatric and adult malignancies. Larotrectinib, a highly-selective oral TRK inhibitor, was well tolerated and showed encouraging antitumor activity in 17 pediatric patients (pts) with TRK fusion-positive tumors (Lee et al. JCO 2019). Treatment was pursued with the goal of clinical efficacy and safety of larotrectinib in 38 pediatric pts with TRK fusion cancer from an expanded dataset. Methods: Pediatric pts enrolled in two larotrectinib clinical trials (NCT02637687, NCT02576431) with TRK fusion cancer detected by local testing were included; pts with primary CNS tumors were excluded from this report. Larotrectinib was administered until complete surgical resection, disease progression, withdrawal, or unacceptable toxicity. Disease status was investigator-assessed using RECIST v1.1. Data cutoff: July 30, 2018. Results: As of July 30, 2018, 38 children and adolescents <18 yrs with TRK fusion cancer were enrolled. Median age was 2.3 yrs (range 0.1-14.0); 14 (37%) were < 1 yr. 18 (47%) had infantile fibrosarcoma, 15 (39%) other soft tissue sarcoma, 2 (5%) thyroid cancer and 1 (3%) each had gastrointestinal stromal tumor, melanoma, or mesoblastic nephroma. TRK fusions involved NTRK1, 2, and 3 in 18 (47%), 2 (5%), and 18 (47%) pts, respectively. Half of the pts had metastatic disease and half locally advanced disease at entry, 26 pts (68%) had received prior systemic therapy (median lines: 1 [range 0-4] and 4 pts were treatment-naïve. In 34 evaluable pts, the overall response rate was 94%; 12 CRs, 18 confirmed PRs, and 2 PRs pending confirmation; 2 had stable disease. Median duration of response had not been reached (range 1.6+ to 26.7+ months); 84% > 1 y. At data cutoff, 28 pts (74%) remained on treatment; 4 pts discontinued due to complete surgical resection and 4 due to disease progression while on therapy, 2 of whom initially responded (PR). Adverse events were mostly grade 1-2. Conclusions: Larotrectinib treatment resulted in a high and durable response rate in pediatric pts with TRK fusion cancer together with a favorable safety profile. Routine testing for NTRK gene fusions in pediatric cancer pts is recommended in all clinical contexts. Clinical trial identifications: NCT02637687 and NCT02576431.

Phase 1/1b trial to assess the activity of entrectinib in children and adolescents with recurrent or refractory solid tumors including central nervous system (CNS) tumors. First Author: Giles W. Robinson, St. Jude Children’s Research Hospital, Memphis, TN

Background: Entrectinib is a CNS-penetrant oral inhibitor of TrkA/B/C, ROS1 and ALK tyrosine kinases. We report the efficacy of entrectinib in children with recurrent/refractory solid or CNS tumors. Methods: Patients ≤ 20 old with recurrent/refractory solid tumors were eligible. After determination of the recommended dose in all-comers, disease-specific expansion cohorts of CNS and solid tumors harboring targetable alterations in NTRK1/2/3, ROS1 and ALK, and neuroblastoma (NBL), regardless of mutation spectrum, were enrolled. Response, assessed by Investigator, was classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) using RANO for CNS tumors, RECIST for solid tumors, and Curie score for NBL. Results: Between May 2016 and October 2018, 29 patients aged 4.9–20y (median 7y) were enrolled and 28 were evaluated for response. Entrectinib was well tolerated. Dose limiting toxicities were elevated creatinine, dysgeusia, fatigue and pulmonary edema. The recommended dose was 550 mg/m² daily. All responses occurred at doses ≥ 400 mg/m². In CNS tumors (n = 6), all high-grade with gene fusions: 1 achieved a CR (ETV6-NTRK3); 3 achieved a PR (TPR-NTRK1, EEF1G-ROS1, EML1-NTRK2); 1 achieved an unconfirmed PR (GOPC-ROS1); and 1 has yet to be evaluated (KANK1-NTRK2). In extracranial solid tumors (n = 8), 6 had a fusion of whom 1 achieved a CR (DCTN1-ALK) and 5 achieved a PR (TFG1-ROS1, EML1-NTRK2, EML1-NTRK3, ROS1, EML1-NTRK2, ETV6-NTRK3). In NBL (n = 15): 1 achieved a CR (ALK F1174L). Median duration of therapy was 85d (6–592d) for all patients; 56d (6–338d) for non-responders; and 281d (56–592d) for responders. Median time to response was 57d (30–58d). Conclusions: Entrectinib produced striking, rapid and durable antitumor responses in children harboring NTRK1/2/3, ROS1 or ALK fusions (11 out of 11) as well as an ALK-mutated NBL. No responses were seen in tumors lacking aberrations in target kinases. These results support the continued evaluation of entrectinib as a targeted therapeutic in solid tumors with NTRK1/2/3, ROS1 and ALK fusions, especially in high-grade CNS neoplasms. Clinical trial identification: NCT02655041.
Background: The COG risk classification system previously used the International Neuroblastoma Staging System (INSS). The pre-treatment INRG staging system (INRGSS) has been adopted internationally, requiring integration of INRGSS with known prognostic biological and clinical characteristics to evaluate outcomes and assess whether this incorporation will require revision to the existing COG risk classifier. Methods: High-risk INRGSS patients (< 18mo HR) < patients were enrolled on COG ANBL00B1 between 2006-2014. Staging per the INSS and INRGSS was determined. Tumor biology and histologic features, including MYCN status (amplified (A) versus not amplified (NA)), ploidy, histology, and segmental chromosome aberrations (SCA) including 1p and 1q LOH, were assessed centrally. Survival analyses were performed to identify independent prognostic factors and to calculate event-free and overall survival (EFS, OS) for combinations of variables used to determine risk group according to COG and INRG classification templates. Results: Using the original COG risk classifier 1,309 low (LR), 992 intermediate (IR) and 1,736 high-risk (HR) patients were identified with 5-year EFS of 91.4±2.1%, 84.3±2.9%, 45.2±3.1%, and OS of 98.1±1.0%, 94.0±1.9%, 54.1±3.0%, respectively. Outcomes based on combinations of clinical and biological prognostic factors were determined and compared for subsets of patients according to the COG (version 1.) and INRG risk classification systems to develop a revised COG risk classifier that incorporates the INRGSS (version 2, subset shown in Table). Conclusions: Use of INRGSS requires a revision to the COG risk classifier. By combining INRGSS and presence of SCA together with age, MYCN status, ploidy, and histology to determine outcome of patients treated with modern era therapies, we developed a revised risk classification that incorporates information from biology and COG clinical trial eligibility. Clinical trial information: NCT00904241.

10012 Oral Abstract Session, Sun, 8:00 AM-11:00 AM
A revised Children’s Oncology Group (COG) neuroblastoma risk classification system: Report from the COG biology study ANBL00B1.
First Author: Meredith Irwin, The Hospital for Sick Children, Toronto, ON, Canada
Background: The COG risk classification system previously used the International Neuroblastoma Staging System (INSS). The pre-treatment INRG staging system (INRGSS) has been adopted internationally, requiring integration of INRGSS with known prognostic biological and clinical characteristics to evaluate outcomes and assess whether this incorporation will require revision to the existing COG risk classifier. Methods: High-risk INRGSS patients (< 18mo HR) < patients were enrolled on COG ANBL00B1 between 2006-2014. Staging per the INSS and INRGSS was determined. Tumor biology and histologic features, including MYCN status (amplified (A) versus not amplified (NA)), ploidy, histology, and segmental chromosome aberrations (SCA) including 1p and 1q LOH, were assessed centrally. Survival analyses were performed to identify independent prognostic factors and to calculate event-free and overall survival (EFS, OS) for combinations of variables used to determine risk group according to COG and INRG classification templates. Results: Using the original COG risk classifier 1,309 low (LR), 992 intermediate (IR) and 1,736 high-risk (HR) patients were identified with 5-year EFS of 91.4±2.1%, 84.3±2.9%, 45.2±3.1%, and OS of 98.1±1.0%, 94.0±1.9%, 54.1±3.0%, respectively. Outcomes based on combinations of clinical and biological prognostic factors were determined and compared for subsets of patients according to the COG (version 1.) and INRG risk classification systems to develop a revised COG risk classifier that incorporates the INRGSS (version 2, subset shown in table). Conclusions: Use of INRGSS requires a revision to the COG risk classifier. By combining INRGSS and presence of SCA together with age, MYCN status, ploidy, and histology to determine outcome of patients treated with modern era therapies, we developed a revised risk classification that incorporates information from biology and COG clinical trial eligibility. Clinical trial information: NCT00904241.

10013 Oral Abstract Session, Sun, 8:00 AM-11:00 AM
Randomization of dose-reduced subcutaneous interleukin-2 (sIL2) in maintenance immunotherapy (IT) with anti-GD2 antibody dinutuximab beta (DB) bone-tumor-infiltrating lymphocytes (BTL) in front-line high-risk neuroblastoma patients: Early results from the HR-NBL1/SIOPEN trial.
First Author: Ruth Lydia Ladenstein, St. Anna Children’s Hospital and Department of Paediatrics, Medical University Vienna, Vienna, Austria
Background: We tested dose-reduced sIL2 in combination with DB-LTI and oral isotretinoin and evaluated toxicity and efficacy in high-risk neuroblastoma patients (EudraCT:2006-001489-17). Efficacy results on risk group assignment and full treatment response rates are previously reported. Here, we report on the first-line high-risk risk group assignment in HR patients, the impact of the sIL2 dose reduction on toxicity, and the combination’s impact on survival. Methods: For this phase I/II trial (HR-NBL1/SIOPEN), 490 patients from 18 countries were randomized. Median follow-up is 18 years. Stage, age, MYCN, induction treatment and remission status were well balanced between randomized arms. The 2yrs-EFS and -OS for DB-LTI (205 pts) vs. DB-LTI&sIL2 (203 pts) was 64%±4% vs63%±5% (p = 0.844) and 83%±3% vs74%±4% (p = 0.337). For patients in CR the 2yrs-EFS was 69%±5% for DB and 66%±5% for DB&sIL2. Patients with evaluable disease prior DB or DB&sIL2, the end of treatment response rate was 57% (26% CR, 31% PR) vs 52% (27% CR, 25% PR) for 2yrs-EFS of 58%±7% and 64%±8%, respectively. Grade 3&4 toxicity was lower in the group with DB vs DB&sIL2 for fever (14%vs31%, p < 0.001) and pain (7%vs16%, p = 0.005), and no significant difference was seen for general condition (17% vs22%, ns), allergy (3%vs3%, ns), capillary leak (4%vs8%, ns), liver enzyme elevation (20%vs27%, ns) and neurological toxicities (2%vs2%, ns). Conclusions: We previously reported grade 3&4 toxicity to DB short-term infusion (STI) = 60x10^9/10^9 uml* for general condition (16%vs41%, p = 0.000), fever (14%vs40%, p = 0.000), allergic reaction (10%vs20%, p = 0.006), capillary leak (4%vs15%, p = 0.004), liver enzyme elevation (17%vs23%, ns), central neurotoxicity (3%vs6%, p = 0.034) and pain (15%vs26%, p = 0.048). Our results indicate that DB-LTI and dose-reduced sIL2 clearly reduced the toxicity profile, but showed absence of benefits of sIL2. DB-LTI achieved 2yrs-EFS in line with DB-STI (Ladenstein, Lancet Oncology 2018; Yu, NEJM, 2010) and a benefit. Clinical trial information: EudraCT:2006-001489-17.
Chronic health conditions (CHC) and late mortality in survivors of acute lymphoblastic leukemia (ALL) in the Childhood Cancer Survivor Study. First Author: Stephanie Dixon, St. Jude Children’s Research Hospital, Memphis, TN

Background: The impact of evolving risk-stratified therapy on long-term morbidity and mortality in survivors of childhood ALL remains largely unknown. Methods: All-cause and health-related late mortality (HRM; captures death from late-effects occurring > 5 yrs from diagnosis), subsequent (malignant) neoplasm (SMN), CTCAE graded CHC and neurocognitive outcomes were assessed in 5-yr survivors of ALL diagnosed < 21 yrs of age from 1970-99. Therapy combinations defined 6 groups: 1970s-like (70s), standard and high risk 1980s- and 1990s-like (80sSR, 80sHR, 90sSR, 90sHR), relapse/transplant (R/BM). Cumulative incidence and standardized mortality ratios (SMR) were calculated. Piecewise exponential and log-binomial models estimated relative rate ratios (RR) with 95% confidence intervals (CI). Results: Among 6148 survivors (median age 31.5 yrs), 15-yr cumulative incidence of all-cause mortality was 5.8% (CI 5.3-6.2) and HRM was 1.5% (1.2-1.7). Compared to 70s, HRM was lower for 90sSR and 90sHR (RR 0.1, CI 0.0-0.3; 0.2, 0.1-0.7), similar to that in the US population (SMR; CI: 90sSR 1.1; 0.6-1.9, 90sHR 1.9; 0.8-3.7). 20-yr cumulative incidence of SN was 3.5% (CI 3.1-3.9). Compared to 70s, 90sHR had lower risk of benign meningioma (RR 0.1, CI 0.0-0.3) and SMN (0.3, 0.1-0.6) with no absolute excess risk compared to the US population. 90sSR was associated with a lower risk of CHCs (Table). Conclusions: More recent risk-stratified therapy has succeeded in reducing risk of late mortality and CHCs among long-term survivors of ALL.

10018 Poster Discussion Session; Displayed in Poster Session (Board #400), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM

Can pediatric and adolescent patients with recurrent tumors benefit from a precision medicine approach? The European MAPPYACTS experience. First Author: Pablo Berlanga, Gustave Roussy Cancer Campus, Villejuif, France

Background: The international prospective precision medicine trial MAPPYACTS (NCT02613962) aims to define the molecular profile in recurrent/refractory malignancies in order to suggest the most adapted salvage treatment. Methods: Patients < 18 years-old at the time of initial diagnosis underwent on-purpose tumor biopsy/surgery of their recurrent/refractory malignancy for molecular characterization by WES and whole RNA sequencing. Results were reviewed in a dedicated weekly molecular tumor board (MTB), followed by discussion with the treating physician in a clinical MTB. Patients with possible positive results were enrolled in clinical trials based on CMTB recommendations. Results: From February 2016 to October 2018, 500 patients have been included in 17 centers in France, Italy and Ireland. Median age at inclusion was 13 years, 38% had sarcomas, 28% brain tumors, 22% other solid tumors, 12% hematological malignancies with a median of one prior relapse/progression. Eleven patients did not undergo intervention procedure (10 screening failures, 1 consent withdrawal). Molecular profiling was performed on samples for 433 patients and was contributive for 390 patients. For 271/390 patients (70%), there was at least one genetic alteration that could represent a potential therapeutic target and 8% had alterations considered as “ready for use” for treatment at relapse. Among them, 19 (7%) died before the CMTB. With follow-up censored in January 2019, 72 patients (27%) were treated with at least one matched targeted agent, 57 of them in a clinical trial, mostly the proof-of-concept AcSé-ESMART trial (NCT02813135). Of the 166 patients (61%) that did not receive the matched treatment recommended by CMTB (50 still on follow-up), main reasons were: no available drug or disease on previous therapy (50), another treatment (48), rapid disease progression/death (30) and legal representative refusal (12). Conclusions: MAPPYACTS profiling allowed tailored treatment, mainly through early clinical trials, in patients with recurrent pediatric cancer. Since most detected molecular findings (50%) were lacking tumor material and it is likely that additional clinically-relevant mutations can be uncovered. Conclusions: These data demonstrate the value of incorporating comprehensive sequencing into clinical diagnostics and patient care. We endeavor to make this large and richly annotated dataset available to others in real time rather than holding it back for months or years until publication. We are incorporating additional applications with 500 and 1000 patients at regular intervals, and as the resource grows, expect users to identify new targetable alterations that may be incorporated into patient care.

10019 Poster Discussion Session; Displayed in Poster Session (Board #401), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM

Real-time sharing of comprehensive clinical genomics sequencing data in St. Jude Cloud. First Author: Scott Newman, St. Jude Children’s Research Hospital, Memphis, TN

Background: As tumor and germline genomic data from pediatric cancer patients is scarce in existing genomic databases, there is an urgent need for more comprehensive datasets. Such data will allow us to fully assess the androgen receptor pathway, facilitate novel disease discoveries, and identify new clinical associations. Methods: We sequenced 1002 tumor/normal pairs as part of a real-time clinical genomics service including whole genome, exome and transcriptome for 775 and exome/transcriptome for 227 samples. Tumor types were representative of the common and rare diseases treated at our institution (37% hematological, 31% brain and 32% solid tumors). A multidisciplinary team assessed every case, and after clinical reporting was complete, genomics data and basic clinical information (primary diagnosis, age, sex, ethnicity, primary/relapse/metastasis status), was made securely available online through St. Jude Cloud (www.stjudecloud.com). Results: Based on analysis of 253 initial cases from the Genomes for Kids study, our multi-platform sequencing approach uncovered diagnostic, prognostic and/or therapeutically relevant findings in 78% of patients. We estimate 11-16% of clinically-relevant gene mutations could be missed by less comprehensive sequencing approaches. One quarter of patients had a potentially druggable mutation. This surprising high proportion was driven, in part, by BRAF fused low-grade gliomas and diverse JAK/STAT pathway alterations in B-Cell acute lymphoblastic leukemias. Whole genome/transcriptome sequencing allowed us to detect rare and novel gene fusions in 8% of cases and facilitated discovery of a new recurrent fusion gene in pediatric melanoma. All data is available online for other investigators and facilitates the potential for drug development. We continue to evolve our manuscript offering this resource to others in real-time, including clinical sequencing, quality control, and associated clinical data back to our users. We have reviewed 775 patients and 227 tumor/normal samples. The majority of patients (49%) had a potentially druggable mutation. Conclusion: These findings suggest that the St. Jude Cloud will continue to be an essential tool for researchers, clinicians, and patients to access and use high-quality, real-time genomic data to enhance clinical care and research.
Population-based cancer predisposition testing as a component of newborn screening: A cost-effectiveness analysis. First Author: Jennifer Yeh, Boston Children’s Hospital and Harvard Medical School, Boston, MA

Background: The role of population-based newborn genetic testing to identify infants at high risk of childhood-onset cancers has not been studied, despite the availability of cancer surveillance guidelines for early detection in high-risk infants and children. Methods: We developed the Precision Medicine Prevention and Treatment (PreEMPT) Model to estimate the value of targeted population-based newborn genomic sequencing (tNBS) for a select panel of genes associated with early onset pediatric malignancy. Cohorts of US newborns were simulated under tNBS screening vs. usual care, from birth to death. Six pediatric cancer predisposition syndromes were included in the model with mutations in RET, RBL1, TP53, DICER1, SUFU or SMARC1 assigned at birth, using mutation prevalence and disease risks drawn from the published literature, as well as SEER, ClinVar and gnomAD databases. Newborns with mutations underwent cancer surveillance based on established guidelines for each gene-related pediatric malignancy. Survival benefit was modeled as a reduction in proportion of advanced disease, cancer deaths, and treatment-related late mortality risks. Costs were based on published literature and national databases. Results: In a typical US birth cohort of 4 million newborns, we estimated 1280 cancer cases in the malignancies associated with this gene panel would be detected before age 20 under usual care, resulting in 457 cancer survivors at age 90 living with radiation exposure risks. tNBS would prevent 8 cancers (in RET mutation carriers), averting 34 deaths through surveillance, result in 3190 life-years (LY) gained and a 13% relative reduction in proportion of adult survivors at risk for radiation-associated late mortality. Given a sequencing cost of $330 per genotype, the incremental cost-effectiveness ratio (ICER) for tNBS was $235,500 per LY saved; if no additional cost was incurred beyond standard newborn screening, the ICER decreased to $101,100/LY. Conclusions: Population-based genetic testing of newborns can reduce mortality associated with pediatric cancers and could potentially be cost-effective as sequencing costs decline. Further work will include modeling a broader panel of predisposition genes.

Outcome of children with malignant germ cell tumors by response status at the end of induction chemotherapy. First Author: Adriana Fonseca, The Hospital for Sick Children, Toronto, ON, Canada

Background: The management of pediatric malignant germ cell tumors (MGCTs) includes induction therapy with 3-4 cycles cisplatin, etoposide, bleomycin (PEb) as chemotherapy. The current practice recommends 2-3 cycles of PEb (total 6-9 cycles) as consolidation therapy if response is complete at the end of induction, a significantly different approach that than used in adults who receive a standard number of cycles. Furthermore, there is no evidence supporting the addition of a consolidation phase with PEb in pediatric patients with MGCTs. Methods: We retrospectively reviewed all patients enrolled in a phase III, single-arm trial for low-risk and intermediate-risk MGCTs (AGCT0132). All patients received 3 cycles of PEb and underwent response assessment at the end of induction. Complete Response (CR) was defined as negative tumor markers and no viable residual lesion. Patients in CR were not to receive any further chemotherapy. Patients not in CR were prescribed 3 additional cycles of PEb as consolidation. Event-free survival (EFS) and Overall survival (OS) was calculated using the Kaplan-Meier method. Results: Among 210 patients enrolled, 193 patients had CR after 3 cycles of induction chemotherapy, and their post-induction 4yr-EFS and OS was 93% and 99%. Fifteen patients were not in CR at the end of the first 3 cycles and received additional chemotherapy, and their 4yr-EFS and OS was 51% and 60%. Conclusions: Children with MGCTs who have a partial response after the first 3 cycles of chemotherapy had an inferior outcome compared to those with a CR, despite receiving additional cycles of PEb chemotherapy. Thus, we conclude that consolidation is of unclear benefit. Although our results are limited by small sample size and lack of comparator, we propose that pediatric MGCT patients who fail to achieve a CR after standard induction chemotherapy should receive a salvage regimen with different agents rather than consolidation with more cycles of the same chemotherapy.
High-dose naxitamab plus stepped-up dosing of GM-CSF for high-risk neuroblastoma (HR-NB): Efficacy against histologically-evident primary refractory metastases in bone marrow (BM). First Author: Brian H. Kushner, Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Cure of HR-NB often requires ablating BM metastases that are chemoresistant and survive 1,47 (1.26-1.73) 1.35 (1.14-1.58)

Thoracotomy 1.36 (1.13-1.63) 1.17 (0.92-1.47)

Pelvic radiation dose

Abdominal radiation dose

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First Author: Brian H. Kushner, Memorial Sloan-Kettering Cancer Center, New York, NY

Methods: We evaluated HR-NB patients with histologically-evident chemoresistant disease in BM, but no soft tissue or prior progressive disease, for response to naxitamab+GM-CSF on protocol (NCT01757626). Cycles comprised naxitamab infused intravenously (30 minutes) x3 (Mon-Wee-Fri) and subcutaneously-administered GM-CSF starting 5 days pre-naxitamab in priming doses of 250μg/m²/day, then stepped-up to 500μg/m²/day beginning with antibody. Naxitamab was dose-escalated in the phase I portion and 9mg/kg/cycle (−270mg/m²/cycle, i.e., −2.5x dosage of ch14.18) in the phase II/I expansion. BM was assessed post-cycle 2 in aspirates-biopiles from bilateral posterior and anterior iliac crests. Cycles were monthly but were deferred if human anti-human antibody (HAHA) developed.

Results: The 19 patients enrolled through 5/2018 were 5m-to-19m (median 7.5m) post-diagnosis and 65 years (9.0%). Radiation, platinum, am-

Cures of HR-NB patients with histologically-evident chemo-

exerts a dose-response effect in antibody-dependent cellular cytotoxicity and significantly improves outcome with murine-3F8 (I/T) therapy was permitted. Each cycle comprised of irinotecan 50 mg/m²/day intravenously (IV) plus tomozolomide 150 mg/m²/day IV or orally (days 1-5); naxitamab 2.25 mg/kg/day IV over 30 minutes, days 2, 4, and 8 (total 9 mg/kg or 270 mg/m² per cycle), and GM-CSF 250 mg/m² subcutaneously, days 6-10. Toxicity was measured by CTCAE v4.0 and responses by modified International Neuroblastoma Response Criteria. Results: Forty-six (23 enrolled on protocol and 23 on compassionate-use basis) heavily prior-

adjusted for sex, race and age at assessment. Aims: Estimate the prevalence of frailty among survivors, and examine direct and indirect effects of treatment, lifestyle, and chronic disease factors on frailty. Direct and indirect effects of treatment, lifestyle factors, these associations were attenuated. Findings: The prevalence of frailty among survivors was higher compared to siblings (5.8%, 3.5-8.1%) and Hodgkin lymphoma (7.5%, 4.9-10.1%). In models adjusted for chronic diseases (I/T) therapy was permitted. Each cycle comprised of irinotecan 50 mg/m²/day intravenously (IV) plus tomozolomide (150 mg/m²/day) and/or anti-GD2 MoAb (14/36;39%), and in soft tissue (6/22; 27%) MBG-avid skeletal sites (20/36;39%) and on bone marrow histology (9/12;75%). Conclusions: High-dose naxitamab-based chemoinmunotherapy is safe and effective against chemoresistant HR-NB. This ongoing phase II/I study may define a broader role for naxitamab which was recently granted breakthrough designation by the FDA. Clinical trial information: NCT03189706.

Impact of protein supplementation on lean muscle mass in adult survivors of childhood cancer engaged in resistance training. First Author: Matthew R Krull, St. Jude Children’s Research Hospital, Memphis, TN

Methods: This double-blind placebo-controlled trial enrolled survivors aged ≥18 to < 45 years. Participants were randomized to resistance training with daily protein supplement (21g protein/day, 90kcal) (RT+S) or resistance training with placebo (sucrose, 90kcal) (RT+P). Both groups received educational materials, access to a local fitness center and a tailored resistance training program with tapered supervision. Lean muscle mass and muscle strength were assessed at baseline and 24 weeks, using dual x-ray absorptiometry and dynamometer testing respectively. Change means were compared within and between groups. Results: Of 93 participants randomized, 57 completed the 24-week intervention (24 in RT+S, 33 in RT+P). The mean age was 33.1 (SD 7.0), 67% were white and 47% female. The RT+S group had a significant increase in lean body mass (1.05 kg (SD 2.34), p = 0.04), whereas the RT+P group did not (0.13 kg (SD 2.19), p = 0.74). Mean change in handgrip strength also improved in the RT+S group (1.98 (SD 4.30), p = 0.03); change approached significance in the RT+P group (1.49 (SD 4.60), p = 0.07). All survivors significantly improved their strength over time (Table) as measured by one max repetition test at baseline and follow-up.

Conclusions: Preliminary findings indicate that a supervised resistance training program among adult survivors of childhood cancer that includes protein supplementation is feasible and may increase total lean body mass and muscle strength. Clinical trial information: NCT02501460.
10028 Poster Discussion Session; Displayed in Poster Session (Board #410), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM

Subsequent neoplasm risk associated with rare variants in DNA repair and clinical radiation sensitivity syndrome genes: A report from the Childhood Cancer Survivor Study. First Author: Lindsay M. Morton, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD.

Radiotherapy for childhood cancer is associated with strikingly elevated risk for developing subsequent neoplasms (SNs). Whether mutations in DNA repair and radiation sensitivity genes modulate SN risks is largely unknown. Methods: We conducted whole-exome sequencing in 5105 long-term childhood cancer survivors of European descent (mean follow-up = 32.7 years). SnpEff and ClinVar identified potentially damaging rare variants in 476 DNA repair or radiation sensitivity genes. Conditional logistic regression assessed SN risk associated with these variants aggregated by gene or pathway (N = 155 with ≥5 carriers). Controls were matched on sex, childhood cancer type and diagnosis age, radiation dose to the SN site, and survival. Exact p-values were calculated by permutation. Analyses used all survivors or subgroups stratified on radiation dose. Results: A total of 1108 (21.7%) survivors developed at least one SN type known to be related to ionizing radiation exposure (e.g., breast cancer, basal cell carcinoma, meningioma, thyroid cancer, sarcoma). Radiation-related SN risk was associated with homologous recombination (HR) gene variants for SN sites that received ≥ 0 < 10 Gy (20.9% cases, 11.0% controls; odds ratio [OR] = 2.20, 95% confidence interval [CI]: 1.52-3.18; median follow-up = 11.7 years), a modestly increased risk for SNs with ≥10 Gy (5.5% cases, 2.0% controls; OR = 2.57, 95%CI 1.01-6.51; P = 0.52x10^-2). For radiation-related SNs at sites with higher doses (≥10 Gy), associations were not observed for the HR pathway (14.4% cases, 12.4% controls, P = 0.17) but were observed for two individual genes implicated in double-strand DNA break repair (XRCC5, 0.5% cases; 0.2% controls; OR = 3.50, 95%CI 1.3-9.4; P = 7.85x10^-3). For radiation-related SNs at sites with higher doses (≥10 Gy), associations were not observed for the HR pathway (14.4% cases, 12.4% controls, P = 0.17) but were observed for two individual genes implicated in double-strand DNA break repair (XRCC5, 0.5% cases; 0.2% controls; OR = 3.50, 95%CI 1.3-9.4; P = 7.85x10^-3). For radiation-related SNs at sites with higher doses (≥10 Gy), associations were not observed for the HR pathway (14.4% cases, 12.4% controls, P = 0.17) but were observed for two individual genes implicated in double-strand DNA break repair (XRCC5, 0.5% cases; 0.2% controls; OR = 3.50, 95%CI 1.3-9.4; P = 7.85x10^-3).

Conclusions: In this discovery study, we identified dose-specific novel associations between SN risk after radiotherapy for childhood cancer and potentially damaging rare variants in genes involved in double-strand break repair, particularly for genes implicated in DNA repair. If replicated, these results could impact long-term screening of childhood cancer survivors and risk-benefit assessments of treatment approaches.

10030 Poster Session (Board #412), Sat, 8:00 AM-11:00 AM

A novel association between GSTM1 null variant and anthracycline-induced cardiac dysfunction (ACD) in childhood cancer survivors (CCS): A COG ALTE03N1 report. First Author: Purnima Singh, University of Alabama at Birmingham, Birmingham, AL.

Background: ACD is a leading cause of mortality in CCS. Previous studies have identified genomic variants that moderate the ACD risk. An agnostic evaluation of differential gene expression between those with and without ACD has not been explored, and could provide insights into the mechanism of cardiotoxicity in CCS. Methods: Gene expression profiles in human iPSC-derived cardiomyocytes (hiPSC-CMs) were obtained from anthracycline-exposed NHW CCS (65 cases; 76 controls) and matched NHWs (32 cases; 46 controls) untreated for ACD. hiPSC-CMs were treated with doxorubicin or vehicle for 24 h, used RNA-seq. Results: 109522 probes were analyzed in 36 hiPSC-CMs. ACD-exposed hiPSC-CMs (20.9% cases, 11.0% controls; odds ratio [OR] = 2.20, 95% confidence interval [CI]: 1.01-4.73; median follow-up = 11.7 years), a modestly increased (OR=2.20, 95%CI 1.01-4.73, P=0.04) risk for SNs with ≥10 Gy (5.5% cases, 2.0% controls; OR = 2.57, 95%CI 1.01-6.51; P = 0.52x10^-2). For radiation-related SNs at sites with higher doses (≥10 Gy), associations were not observed for the HR pathway (14.4% cases, 12.4% controls, P = 0.17) but were observed for two individual genes implicated in double-strand DNA break repair (XRCC5, 0.5% cases; 0.2% controls; OR = 3.50, 95%CI 1.3-9.4; P = 7.85x10^-3). For radiation-related SNs at sites with higher doses (≥10 Gy), associations were not observed for the HR pathway (14.4% cases, 12.4% controls, P = 0.17) but were observed for two individual genes implicated in double-strand DNA break repair (XRCC5, 0.5% cases; 0.2% controls; OR = 3.50, 95%CI 1.3-9.4; P = 7.85x10^-3). For radiation-related SNs at sites with higher doses (≥10 Gy), associations were not observed for the HR pathway (14.4% cases, 12.4% controls, P = 0.17) but were observed for two individual genes implicated in double-strand DNA break repair (XRCC5, 0.5% cases; 0.2% controls; OR = 3.50, 95%CI 1.3-9.4; P = 7.85x10^-3).

Conclusions: In this discovery study, we identified dose-specific novel associations between SN risk after radiotherapy for childhood cancer and potentially damaging rare variants in genes involved in double-strand break repair, particularly for genes implicated in DNA repair. If replicated, these results could impact long-term screening of childhood cancer survivors and risk-benefit assessments of treatment approaches.

10031 Poster Session (Board #413), Sat, 8:00 AM-11:00 AM

Upfront azacitidine (AZA) in juvenile myelomonocytic leukemia (JMML): Integration analysis of the phase 3 prospective AZA-JMML-001 study. First Author: Charlotte M. Niemeyer, Department of Pediatrics and Adolescent Medicine, Division of Pediatric Hematology and Oncology, Medical Center, University of Freiburg, Freiburg, Germany.

Background: Hematopoietic stem cell transplantation (HSCT) is the only curative therapy for JMML patients (pts). Novel therapies controlling the disorder prior to HSCT are urgently needed. A phase 2, multicenter, open-label, prospective, single-arm safety study (SCOPE-1) evaluated the safety of AZA monotherapy prior to HSCT in pts with newly diagnosed (ND) JMML. Methods: AZA (75 mg/m² IV) was administered once daily on days 1–7 of each 28-day cycle (C). Primary endpoint was number of pts with clinical complete remission or clinical partial remission (cPR) at C3 day (D) 28 (C3D28). Results: 18 JMML pts (13 PTPN11-, 3 NRAS-, 1 KRAS-, 1 NFI- mutated) were enrolled from 09/2015 to 11/2017. Median (range) white blood cell and platelet (Pt) counts were 19.7 (4.3–59.0) ×10⁹/L and 28 (7.8–85) ×10⁹/L, respectively. DNA methylation class (MC) was high, intermediate (int), or low in 11, 5, and 2, respectively. 16 pts completed C3 and 5 pts C6. 2 pts discontinued treatment (Tx) pre-C3D28 due to disease progression (PD). 6 pts (33%) had ≥1 grade (Gr) 3–4 manageable adverse event (AE) related to AZA. Most common Gr 3–4 AEs related to AZA were neutropenia (2) and anemia (2). 11 pts (61%) were in cPR at C3D28; 7 had PtD at C3D28 or prior. All 7 pts of the int/low MC and 4/11 in high MC achieved cPR. 17 pts received HSCT at median of 58 days (37–518) from last AZA dose; 14 were leukemia-free at a median follow-up of 15.7 months (0.1–31.7) after HSCT. 2 pts (high MC) given HSCT relapsed after allograft. 16/18 pts were alive at a median follow-up of 19.8 months (2.6–37.3) from diagnosis. 1 pt discontinuing Tx prior to C3 died from PD; 1 non-responder did not meet transplant-related causes. Pit response in pts with cPR prompted retrospective comparison of Pit counts at time of HSCT with a historical registry control cohort. Pts with NFI1-mutated JMML with higher Pit counts versus other genetic subtypes were excluded. While 7/16 (44%) study pts had Pit counts ≥ 100 ×10⁹/L at HSCT, only 10/58 (17%) historical cohort pts reached this cutoff. Conclusions: In this phase 3 prospective trial, upfront AZA monotherapy was well tolerated in pts with ND JMML. Although the long-term adverse effects of AZA Tx remains to be fully assessed, responses show it was effective in JMML and provided clinical benefit to pts in this study. Clinical trial information: NCT02447666.

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A phase II trial testing interventions to shorten time to diagnosis and reduce abandonment of treatment of children with Burkitt lymphoma in Kenya. First Author: Sandra Langat, Moi University School of Medicine, Eldoret, Kenya

Background: Burkitt Lymphoma (BL) is a common pediatric cancer in sub-Saharan Africa. Despite advances in care, prognosis is poor. The BL treatment protocol at our center in Kenya used since 2010, had a one-year survival of 29% (Martijn et al. BMJ Paed Open 2017). We hypothesized that financial burdens and delays in start of therapy impact outcomes. Methods: Our trial tested interventions aimed to: 1) Shorten time from presentation to start of treatment to improve survival; and 2) Support families during therapy to reduce abandonment. Initial eligibility included clinical suspicion of BL in a child 0-13 years of age. Patients with confirmed diagnosis of a mature B-cell lymphoma received support to complete therapy. Children with prior treatment of cancer were excluded. The trial was approved by human protection boards in Kenya and Indiana and consent was obtained prior to study entry. We enrolled 96 children with possible BL. Study personnel expedited routing of tissue samples by pathologists. Fresh tissue from all sources was used for flow cytometry.

Conclusions: Simple interventions to improve efficiency of diagnosis and reducing abandonment leads to improved outcomes for children with BL in Kenya.

Pretreatment poverty exposure was significantly associated with in vitro dexamethasone resistance and post-induction minimal residual disease in pediatric T-cell acute lymphoblastic leukemia. First Author: Lauren K. Meyer, University of California, San Francisco, San Francisco, CA

Background: T-cell acute lymphoblastic leukemia (T-ALL) is a genetically heterogeneous disease, which has largely precluded the use of genetic mutations for risk stratification. We hypothesized that despite this heterogeneity, diverse T-ALLs may have functional similarities that underlie patterns of chemotherapy sensitivity. Methods: We used flow cytometry to evaluate in vitro dexamethasone (DEX) sensitivity and baseline expression of signal transduction effectors and BCL2-family proteins in 68 fresh diagnostic T-ALL samples from patients enrolled on the Children’s Oncology Group (COG) trial AALL1231. We also performed RNA-sequencing (RNA-seq) on 40 AALL1231 samples and used hierarchical clustering and linear regression to analyze these and published T-ALL RNA-seq data from COG AALL0434. Comparisons between groups were made using t-tests and Fisher’s exact tests.

Results: Of the proteins analyzed, only high BCL2 expression was significantly associated with increased in vitro DEX resistance (p=0.002). Hierarchical clustering of the AALL1231 RNA-seq data identified two distinct clusters. Cluster 1 was associated with significantly higher BCL2 transcript expression (p=0.0002) and in vitro DEX resistance (p=0.04) relative to cluster 2. We defined a gene set consisting of the top 210 differentially expressed genes between these clusters and applied this gene set to the COG AALL0434 cohort. In this analysis, the early T-cell precursor (ETP) and near-ETP samples clustered together (p<0.0001) in cluster 1 along with all non-ETP samples. Not only did these cluster 1 non-ETP samples have significantly higher BCL2 transcript expression relative to the non-ETP samples in cluster 2 (p<0.0001), but 54% of these non-ETP samples were minimal residual disease (MRD) positive (≥0.01%) at the end of induction, as opposed to only 16% of near-ETP and non-ETP samples in cluster 2 (p<0.0001). Conclusions: Gene expression profiling identifies non-ETP T-ALLs that cluster with near-ETP T-ALLs and have significantly higher BCL2 expression and increased rates of post-induction MRD.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: There are several studies describing the correlation between unsatisfactory tumor marker decline and poor prognosis in adult patients treated for germ cell tumors. In pediatric patients the data is limited. We therefore retrospectively analyzed data collected from pediatric patients treated at the Children’s Oncology Group (COG) Protocol AGCT0132 to determine whether a relationship exists between AFP decline and outcome.

Methods: One hundred and thirty-one patients with germ cell tumors enrolled on Children’s Oncology Group Protocol AGCT0132 were eligible for analysis of AFP decline. Serum AFP half-life was calculated from levels collected post-operatively and after the start of chemotherapy, excluding values in the first 7 days of chemotherapy to accommodate unpredictable increases in the initial days of treatment. AFP decline was defined as automatically satisfactory (AFP normalized within the first two AFP measures following the start of chemotherapy), calculated satisfactory (AFP half-life ≤ 7 days following the start of chemotherapy), and unsatisfactory.

Results: The 3-year event-free survival (EFS) was 87% (95% confidence interval CI: 79-92%) for patients with a satisfactory decline and 62% (95% CI: 31-82%) for patients with an unsatisfactory decline (p = 0.006). In stratified analyses, this effect was limited to patients ≥11 years of age and with standard risk (SR2) disease (p = 0.002 and p = 0.004, respectively).

Conclusions: This study is the first to show an association between AFP decline and EFS in pediatric patients. Although there is no statistically significant association between tumor marker decline and overall survival, recognition of patients at high-risk of relapse may allow for early intensification of therapy and impact the rationale for future clinical trial design.

10038 Poster Session (Board #420), Sat, 8:00 AM-11:00 AM
Evaluation of the multi-kinase inhibitor regorafenib in the Pediatric Preclinical Testing Consortium osteosarcoma, rhabdomyosarcoma, and Ewing sarcoma xenograft models. First Author: Douglas James Harrison, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Regorafenib is a multi-kinase inhibitor, developed by adding a fluorine atom to the phenyl ring of sorafenib. Regorafenib inhibits multiple kinases including BRAF, FGFR1, KIT, PDGFRB, RAF, RET, and VEGFR1-3, many at a higher potency than sorafenib. Prior studies within the Pediatric Preclinical Testing Consortium (PPTC) demonstrated sorafenib exhibited intermediate activity for tumor growth inhibition in more than 50% of the sarcoma models tested at a dose of 60mg/kg by oral gavage daily (5 days/week for 6 consecutive weeks). The in vivo effects of regorafenib were studied in the PPTC osteosarcoma (OS), rhabdomyosarcoma (RM) and Ewing (EW) sarcoma xenograft models. Methods: The in vivo anticancer effects of regorafenib were assessed in a panel of 6 osteosarcoma models (OS2, OS9, OS31, OS33, OS36, OS60), two rhabdomyosarcoma models (Rh30, Rh41), and one Ewing sarcoma model (EWS). Regorafenib was administrated by oral gavage at a dose of 30 mg/kg/day given daily for 21 consecutive days. Time to event and tumor volume responses were defined and analyzed utilizing standard PPTC statistical methods. Results: Regorafenib induced significant improvements in event-free survival (EFS) compared to control in 100% (9/9) of sarcoma models tested. Most models showed pronounced slowing of tumor growth compared to control during the 21 days of regorafenib treatment, with tumor growth generally approximating control rates soon after completion of regorafenib treatment. Three out of 8 sarcoma models demonstrated EFS T/C values > 2 (1/6 OS, 2/2 Rh, 0/1 EW). Minimum relative tumor volumes ranged from 0.74 to 1.60, with no models meeting criteria for objective response.

Conclusions: Regorafenib induced modest inhibition of tumor growth in the PPTC sarcoma models evaluated. The overall pattern of response to the multi-kinase inhibitor regorafenib against the PPTC sarcoma models appears similar to that of the kinase inhibitor sorafenib, with pronounced slowing of tumor growth in some models that is limited to the period of agent administration being the primary treatment effect.

10037 Poster Session (Board #419), Sat, 8:00 AM-11:00 AM
Impact of low-income public insurance on survival for children and young adults with bone and soft tissue sarcomas. First Author: Neela Lakshmi Penumarthy, University of California San Francisco, San Francisco, CA

Background: Racial and ethnic survival disparities have been described for many pediatric malignancies, but the impact of income has not been extensively explored. To assess whether socioeconomic status affects outcomes, we evaluated low-income public health insurance as a proxy. We analyzed how low-income public health insurance influences overall survival in children, adolescents, and young adults diagnosed with bone and soft tissue sarcomas. Methods: The University of California San Francisco Cancer Registry was used to identify patients age 0-39 diagnosed with bone or soft tissue sarcomas between 2000-2015. Low-income patients were defined as those with Medicaid, which is only available under state law to eligible low-income individuals or families, or those with no insurance. The comparison group included all other patients with private insurance, Medicare, or Tricare. Survival curves were computed using the Kaplan-Meier method and compared using log-rank tests and Cox models. Logistic regression was used to investigate the association of low-income public insurance and presence of metastatic disease at diagnosis. Results: A total of 1,106 patients were included in the analysis. 444 (40%) were considered low-income; of these, 428 (39%) had public insurance and 16 (1%) had no insurance. Low-income patients were more likely to be both racial/ethnic minorities and present with metastatic disease on multivariable analysis. Low-income patients had significantly worse 5-year OS (61% vs 71%, p = 0.0003). When stratified by location of origin, median survival of patients who had Medicaid consistently had significantly worse 5-year OS (localized: 78% vs 84%, regional: 64% vs 73%, metastatic: 23% vs 30% respectively, p < 0.0001). Age and race/ethnicity did not significantly impact OS in this study population. Conclusions: Low-income patients with bone and soft tissue sarcomas had decreased survival. Whether they were more likely to have metastatic disease, disparities in survival were noted even within the localized and regional disease groups. The means by which insurance status impacts survival requires additional investigation, but may be through reduced access to care.
Background: Adjunct therapy in patients with localized grossly resected synovial sarcoma (SS) still is a matter of debate. This analysis was performed to contribute to the clarification. Methods: SS patients of all ages with initially gross tumor resection registered in the prospective international CWS-trials 1981–2013 were evaluated. CWS-protocols currently recommend chemotherapy for all SS patients. Results: 185 patients with median age of 13.9 years (range 0.1–56.9) and median follow-up of 7.2 years (0.2–31.1) had 5-year event-free (EFS) and overall survival (OS) of 82.9%±5.7 (95%CI) and 92.5%±3.9, respectively. All but six patients received adjuvant chemotherapy. Best surgical treatment consisted of R0-resection in 107 and R1-resection in 70; no information in 7. 135 (73%) were irradiated. In the univariate analysis factors associated with EFS are tumor size and the application of chemotherapy; factors associated with OS are tumor site, size and invasiveness. In the multivariate analysis independent factors for adverse EFS are large tumor size and the application of chemotherapy, for OS tumor site and size. In the group of 58 patients with tumors < 3 cm one patient suffered metastatic recurrence (2%), in those 59 patients with tumors 3–5 cm 3 suffered metastatic recurrence (5%). In 42 patients with tumors 5–10 cm, 4 metastatic and 2 combined recurrences were reported (14%), and in those 13 patients with tumors > 10 cm 4 suffered metastatic and 1 combined relapse (38%). Conclusions: Patients with grossly resected SS treated according to the CWS recommendations have an excellent prognosis. A subgroup with very low metastatic potential probably does not need chemotherapy. Whether tumor size and surgery are sufficient criteria has still to be proven by long term results. Biological studies are needed.
Background: ONC201 is the first DRD2 antagonist for clinical oncology. The recommended 2 dose (RP2D) of 625mg ONC201 orally once a week has been established in adult patients. ONC201 efficacy has been shown in high-grade glioma preclinical models and radiographic regressions with single agent ONC201 have been reported in adult recurrent H3 K27M-mutant glioma patients. We report results from the first Phase I pediatric clinical trial of ONC201. This multicenter, open-label, dose-escalation and dose-expansion clinical trial (NCT03416530) determined the RP2D of ONC201 in pediatric H3 K27M-mutant glioma patients as a single agent. ONC201 was orally administered once a week and scaled by body weight. Dose escalation was performed by a 3+3 design beginning with one 125mg capsule less than the adult RP2D equivalent. Three patients were treated at the starting dose and 19 were treated at the adult RP2D equivalent.

Results: The primary endpoint was achieved by establishing the safety of the adult RP2D scaled by body weight to pediatric patients. Twenty-two patients with a median age of 9 (range 3-18) years old who received at least one cycle radiation have been treated with ONC201: 15 with diffuse intrinsic pontine glioma (DIPG) (4 recurrent; 11 not recurrent) and 7 without DIPG H3 K27M-mutant glioma (all not recurrent). As of February 5, 2019, patients have received a median of 18 ONC201 doses (range 3-41) without instance of dose-limiting toxicity. Pharmacokinetic profiles were comparable to those observed in adults (Cmax ~2 ug/mL; AUC ~2.3hr*ug/mL) with no appreciable change in renal function for patients who received a median of 3 cycles (1-10 cycles). Plasma for pharmacokinetics (PK) was available from 129 patients, mean 4 cycles (range 1-10). PK analysis to establish appropriate dose escalation recommended phase 2 dose (RP2D) of 625mg ONC201 orally once a week. ONC201 was well tolerated and achieved therapeutic exposure in pediatric H3 K27M-mutant glioma patients at the adult RP2D. Dose escalation was performed by body weight. Further investigation of first-line ONC201 to treat H3 K27M-mutant glioma and/or DIPG is ongoing. Clinical trial information: NCT03416530.

Conclusions: ONC201 is safe and tolerable at the recommended phase 2 dose (RP2D) of 625mg ONC201 orally once a week. A randomized phase 2 study comparing single agent ONC201 to high dose carboplatinum (per 100 mg/m 2) is ongoing. Day 1-5 dose (1.04 (1.02 to 1.06) BMI) was significantly higher in non-cancer controls compared to cancer survivors. On a median 10 years (years) post-diagnosis, age ≥ 18 years. Renal function was graded per the Kidney Disease International Global Outcomes 2012 Clinical Practice Guideline for the Evaluation and Management of Renal Dysfunction (KDQI). COMET was used to estimate associations between demographics, treatment exposures, and CKD (grades 1-5) risk. Radiation treatment was expressed as percentage of total kidney volume treated with V5 (5), V10 (V10), V15 (V15) and V20 (V20) Gray.

Results: Among 2753 survivors, 48.7% were female and 82.5% non-Hispanic white. Median age at diagnosis - 7.3 years (interquartile range [IQR]=3.3-13.2), time from diagnosis to evaluation - 31.4 years (IQR=25.8-37.8), and median time from diagnosis to evaluation - 23.2 years (IQR=17.6-29.7). Prevalence of grades 1-5 and 3-5 CKD was 7.4% and 2.1%, respectively, (grade 1-3 = 113, grade 2 = 30, grade 3 = 44, grade 4 = 5, and grade 5 = 8). Individual and cumulative amino-glycoside doses and treatment with high-dose methotrexate were not associated with CKD (data not shown). Cumulative number of doses of ambomouss/abelcet and of amphotericin B were significant risk factors for grades 1-5 and grades 3-5 CKD models for V10 and V20 (data not shown). The multivariable results for V10 are shown in the Table. Conclusions: In addition to nephrotic anti-neoplastic and supportive care therapy, race, ethnicity, and body composition contributed to risk of CKD in long-term survivors. These novel results inform late effects reduction strategies for future treatment protocols and identify survivors at highest risk for CKD.

<table>
<thead>
<tr>
<th>Grades 1 – 5 CKD</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI 30 ≤ age 13 ≤ 25</td>
<td>1.02 (1.02 to 1.03)</td>
<td>0.001</td>
</tr>
<tr>
<td>Neutrophils (≥ 5000 cells/µL)</td>
<td>1.03 (1.01 to 1.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hemoglobin (≥ 15 g/dL)</td>
<td>1.03 (1.01 to 1.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>C-reactive protein (≥ 1 mg/L)</td>
<td>1.03 (1.01 to 1.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>D-dimer (≥ 0.5 µg/mL)</td>
<td>1.03 (1.01 to 1.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>Other vs Non-Hispanic white</td>
<td>1.02 (1.01 to 1.03)</td>
<td>0.001</td>
</tr>
<tr>
<td>Neutrophils (≥ 5000 cells/µL)</td>
<td>1.03 (1.01 to 1.05)</td>
<td>0.001</td>
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<tr>
<td>Hemoglobin (≥ 15 g/dL)</td>
<td>1.03 (1.01 to 1.05)</td>
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<tr>
<td>C-reactive protein (≥ 1 mg/L)</td>
<td>1.03 (1.01 to 1.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>D-dimer (≥ 0.5 µg/mL)</td>
<td>1.03 (1.01 to 1.05)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusions: Prevalence of symptoms and impaired QOL in HCT survivors is comparable to survivors treated with conventional therapy, but higher than non-cancer controls. PROs may have a role in facilitating identification of adverse events in survivors.
Conclusions: Under an IRB protocol and 6 (4%) as a clinical service. Confidence interval [CI] 1.2-9.3), and the presence of a FP navigator/team [OR 3.3 95% CI 1.4-7.8]. Seventeen sites (12%) offered TCC by referring elsewhere, 14 (10%) under an IRB protocol and 6 (4%) as a clinical service.

Methods: A REDcap survey was emailed to one individual previously identified as knowledgeable about FP or the Principal Investigator at each COG site. Site specific factors associated with outcomes were determined using logistic regression. All study procedures were IRB-approved. Results: Responses were received from 144 of 220 institutions (65%). Discussions about fertility were reported as routinely held with all post-pubertal males, all males “at risk” of infertility, and all males at 108 (75%), 100 (69%), and 55 (38%) institutions, respectively. SB was available at 135 (94%) sites; 105 (73%) offer SB inpatient and outpatient, 88 (64%) offer SB to all post-pubertal males, and 39 (28%) offer SB after chemotherapy has started. TCC was accessible at 37 (27%) sites and was independently associated with large (>120 new patients/year) size (odds ratio [OR] 3.3 95% CI 1.2-9.3), and the presence of a FP navigator/team (OR 3.3 CI 1.4-7.8). Seventeen sites (12%) offered TCC by referring elsewhere, 14 (10%) under an IRB protocol and 6 (4%) as a clinical service.

Conclusions: SB is widely available across participating COG sites, however only 2/3 of sites offer SB to all pubertal males. The availability of SB across COG institutions is quite limited. This access may be modifiable given the association of an established FP navigator/team with the ability to offer and/or refer patients to outside institutions for TCC. There are practices, such as SB after the start of treatment and offering TCC as a clinical service, that do not align with guideline recommendations. These survey results suggest FP services remain inadequate in this patient population and highlight opportunities for research leading to interventions.

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Long-term health status of high-risk neuroblastoma survivors treated with high-dose chemotherapy and hematopoietic stem cell transplantation. First Author: Sandrine Haghir, Children and Adolescent Oncology Department, Gustave Roussy, Villejuif, France

Background: Current treatment strategies including high-dose chemotherapy with stem cell transplantation rescue (HDC-SCT) have improved 5-year event-free survival for high-risk neuroblastoma (HRNB) patients, but with an increased risk of late treatment-related toxicities. Methods: Between 1980 and 2012, 439 children were treated for HRNB with HDC-SCT in Gustave Roussy (GR), among which 145 were alive and disease-free at 5-year post-SCT. Long-term health data have been collected for those 145 patients, prospectively within the long-term follow-up clinic in GR or retrospectively from pediatric consultations. Results: With a median follow-up post-SCT of 15 years (range 5-34), we observed 6 late relapses, 11 second cancers (including 3 papillary thyroid carcinomas; median delay = 20 years post-SCT [18-22]) and 9 deaths. Event-free and overall survival at 20-year post-SCT were 82% (95% CI = 70-90) and 89% (95% CI = 78-95), respectively. A second health event was observed in 135 patients (median = 3 patient), including 103 patients with at least 1 severe event (median = 1 patient). Cumulative incidence at 15-year post-SCT for second cancers is 4%, cardiac diseases 8%, renal 7%, hepatic focal nodular hyperplasia 14%, dental mal-development 70%, and severe hearing loss 20%. Height-for-age z-score was ≤-2 for 30 patients (21%) and ≤-3 for 12 patients (8%). After Busulphan-Melphalan conditioning regimen, 40/43 females and 33/35 males had a gonadal insufficiency. Conclusions: Long-term consequences of HRNB treatment including HDC are frequent and disabling, mainly due to hearing loss and gonadal insufficiency.

Incidence and predictors of significant hearing loss requiring hearing assistive devices among childhood cancer survivors: A population-based study. First Author: Summit Gupta, Hospital for Sick Children, Toronto, ON, Canada

Background: Though hearing loss is a significant late effect among childhood cancer survivors, recent guidelines note insufficient evidence to quantify natural history or risk associated with specific exposures. We examined the long-term incidence and predictors of hearing loss requiring hearing amplification devices (HAD) using population-based healthcare data. Methods: In Ontario, Canada, HAD costs are subsidized by the provincial Assistive Devices Program (ADP). Ontario children age <18 years at cancer diagnosis between 1987-2016 were identified using a pediatric cancer registry and linked to ADP claims. The cumulative incidence of HAD use was compared between cases and matched controls. Conclusions: We identified 11,842 cases and 59,210 matched controls. Cases were at higher risk of HAD (hazard ratio (HR) 12.8, 95% confidence interval (95CI) 9.8-16.7; p < 0.001). The cumulative incidence of HAD among survivors was 2.1% (95CI 1.7-2.5%) at 20-years and 6.4% (95CI 2.8-12.1%) at 30-years. 30-year incidence was highest in survivors of neuroblastoma (10.7%, 95CI 3.8-21.7%) and hepatoblastoma (16.2%, 95CI 8.6-26.0%). Predictors of HAD in multivariable analyses included age 0-4 years at diagnosis (v < 5-years, HR 2.2, 95CI 1.4-3.3; p < 0.001). Relative to no cisplatin exposure, patients receiving 1-200mg/m2 were not at greater risk, unlike those receiving higher cumulative doses (Table). Relative to no radiation, those receiving >320Gy were at no higher risk, unlike while those receiving >320Gy. Carboplatin exposure was not associated with HAD. Conclusions: Childhood cancer survivors are at elevated risk of requiring HAD which continues to rise between 20 and 30 years from diagnosis. Thresholds of cisplatin and radiation exposure exist above which risk substantially increases. Prolonged monitoring and trials of otoprotective agents are warranted in high-risk populations.

Table: HR (95CI) p

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HR (95CI) p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin exposure (mg/m2)</td>
<td>Ref (Ref)</td>
</tr>
<tr>
<td>&lt;200</td>
<td>1.8 (0.7-4.9) 0.24</td>
</tr>
<tr>
<td>200-999</td>
<td>3.1 (1.1-9.0) &lt;0.001</td>
</tr>
<tr>
<td>≥400mg</td>
<td>4.7 (3.0-7.4) &lt;0.001</td>
</tr>
<tr>
<td>Radiation exposure (Gy)</td>
<td>Ref (Ref)</td>
</tr>
<tr>
<td>≤32</td>
<td>0.9 (0.4-1.9) 0.81</td>
</tr>
<tr>
<td>&gt;32</td>
<td>2.4 (1.6-3.7) &lt;0.001</td>
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Progression of frailty in young adult survivors of childhood cancer: St. Jude Lifetime Cohort. First Author: Kirsten K. Ness, St. Jude Children’s Research Hospital, Memphis, TN

Background: Childhood cancer survivors are at risk for premature aging; over 8% (ages 18-60 years) meet Fried Frailty Criteria (≥3 of low lean muscle mass, muscle weakness, slow walking speed, exhaustion, low energy expenditure). Longitudinal changes and new onset frailty has not been studied. Methods: Childhood cancer survivors (N = 1,001, 51% female, 14.9% black, median age at diagnosis 7-10 years), were evaluated clinically to ascertain frailty at baseline (median age 30-45 years) and five years later. Risk factors for incident frailty and impact of baseline frailty on mortality were evaluated in proportional hazard models. Results: Frailty increased from 6.0% (95% CI 1.8-8.9) to 11.7% (95% CI 6.7-16.7) overall, and for all diagnoses (Table). Risk factors for new onset frailty among those not frail at baseline were amputation (HR 5.1, 95% CI 1.1-14.4), anthracyclines (HR 1.2, 95% CI 1.1-1.4 per 100 mg/m2), and carboplatin (HR 1.3, 95% CI 1.1-1.5 per 2000 mg/m2). Severe, disabling or life threatening chronic conditions (HR 1.2, 95% CI 1.1-1.4 per organ system) and inactivity (HR 2.0, 95% CI 1.2-3.2) also predicted new onset frailty. Sixty-nine participants died from baseline to follow-up. Accounting for age, sex and chronic conditions, frailty baseline was associated with a 2.9 (95% CI 1.6-5.2) increased hazard of death. Conclusions: Prevalent frailty nearly doubled in five years and was associated with increased risk for death. Given that previous treatment exposures cannot be altered, interventions to remediate chronic disease and promote activity may impact function and longevity for childhood cancer survivors.
Cardiac events in survivors of childhood cancer treated in more recent eras: A report from the Childhood Cancer Survivor Study. First Author: Daniel A. Mulrooney, St. Jude Children’s Research Hospital, Memphis, TN

**Background:** Contemporary cancer protocols have incorporated modifications to minimize cardiotoxic exposures and preserve long-term health. We investigated the impact of these changes on late cardiac outcomes in a large cohort of adult survivors of childhood cancer. **Methods:** Congestive heart failure (CHF), myocardial infarction (MI), valvular disease, pericardial disease, and arrhythmias were graded by the National Cancer Institute’s Common Terminology Criteria for Adverse Events among 23,452 five-year cancer survivors [6,193 (26%) treated in the 1970s, 9,363 (40%) in the 1980s, and 7,906 (34%) in the 1990s] and 5,057 siblings. Cumulative incidence and 95% confidence intervals (CI) were estimated by piecewise exponential models, associations of STC rates with PRS were assessed, both overall and stratified by neck RT exposure. Models were adjusted for sex, age at primary diagnosis, attained age, neck RT dose, epipodophyllotoxin therapy, and eigenvectors within survivors of European ancestry from SJLIFE with whole-genome sequencing data and CCS with SNP data imputed to HaploType Reference Consortium. **Results:** Among 2,324 SJLIFE survivors, 61 (43 with, 18 without neck RT) developed STC. The rate of STC was increased by 5.3-fold (95% CI 1.8-13.7) and 3.1-fold (CI 1.3-7.7) for survivors in the third and second PRS tertiles, respectively, compared to those in the first tertile, with corresponding cumulative incidence at age of 40 years of 5.3% (CI, 3.3-7.3%), 2.5% (CI, 1.1-3.9%), and 1.0% (CI, 0.005-2.0%), respectively. Stratified by neck RT, the corresponding rate increases were 7.6 (CI, 2.3-25.3) and 4.8-fold (CI, 1.1-13.6) respectively, among survivors exposed to neck RT; however, no association was observed among survivors without neck RT (only 18 STC cases). Replication was performed among 4,302 CCS survivors, 100 (61 with, 39 without neck RT) developed STC. The rates of STC were increased by 2.3-fold (CI, 1.4-3.9) and 1.7-fold (CI, 1.0-2.9) for survivors in the third and the second PRS tertiles, respectively, compared to those in the first tertile. Significant associations were observed in survivors with and without neck RT (PR external = 0.04 and 0.02, respectively). **Conclusions:** High PRS conferring STC risk can inform screening practices and help personalize and improve survivorship care.

**Results:** After a mean follow-up of 30 years, 199 cases of severe ototoxicity were identified. Cumulative incidences at 30 and 50 years of age (30,50y-CumInc) were 2.8% (95% CI 2.4-3.3) and 5.5% (4.6-6.5), respectively. Mean RT dose at inner ear (Hazard Ratio HR = 1.6) was 1.02-2.5. 4.5 (2.7-7.2), 5.7 (3.0-10.8) and 14.0 (9.2-21.2) for 0- < 5, 5- < 30, 30- < 40 and >40 Gy), as well as cisplatin (HR = 2.8, 95% CI 1.9-4.0), melphalan (HR = 3.3, 95% CI 1.9-5.7) and busulfan exposure (HR = 2.6, 95% CI 1.6-4.4) were significantly associated with severe ototoxicity. Concerning melphalan (n = 199/5243 exposed), almost all cases were identified in neuroblastoma patients (NBL), who also received cisplatin 200mg/m2cycle (26/92 NBL, 30y-CumInc = 36.4% (95% CI = 25.9-48.4), vs. 3/107 non-NBL, 30y-CumInc = 1.6% (0.4-5.6). Concerning busulfan (n = 131/5243 exposed), all cases were identified in NBL (n = 16/63, all treated with melphalan and cisplatin) and brain tumors (n = 130/28, all treated RT at inner ear >50y). The 30y-CumInc in patients with RT at inner ear >50y was 7.4% (95% CI 5.7-9.6) and 39.8% (22.5-60.0) respectively with and without busulfan. **Conclusions:** RT at inner ear has significant deleterious impact on audition, with cumulative incidence still worsening >30 years after RT, and with likely potentiation by busulfan. The deleterious effect of melphalan was related to previous treatment with cisplatin, either by interaction between these drugs, or by the high cisplatin dose by cycle used in NBL.
Background: Diagnosis and treatment of childhood cancer place survivors at risk for lower educational attainment, the increased burden of chronic conditions on attainment has not been examined. Methods: Participants included 16724 survivors (48% female; mean diagnosis age 9.1 years, current age 36.2 years, time since diagnosis 26.6 years) and 4098 siblings (mean current age 39.3 years) Educational attainment was categorized as college graduation (yes/no) among survivors \( \geq 25 \) years. Chronic conditions occurring before age 25 years of age were graded using Common Terminology for Adverse Events 4.3. Modified Poisson regression models estimated relative risks (RR) and 95% confidence intervals (CI) of treatment exposures and chronic conditions on education attainment, adjusting for age at diagnosis and sex. Results: College graduation was reported by 8391 (51%) survivors and 2410 (59%) siblings. Survivors of all diagnoses were more likely to not graduate compared to siblings (all \( p < 0.05 \)), with survivors of CNS tumor (RR 1.36 CI 1.25-1.49), leukemia (RR 1.17 CI 1.07-1.28), and Hodgkin lymphoma (RR 1.17 CI 1.07-1.29) being at a higher risk than survivors of neuroblastoma. Compared to survivors with no history of cranial radiation therapy (CRT), risk of not graduating college was seen in those who received 20-30Gy (RR 1.16 CI 1.09-1.25), 30-50Gy (RR 1.37 CI 1.26-1.49) and \( > 50 \)Gy (RR 1.35 CI 1.28-1.42). Among survivors not exposed to CRT, dexamethasone had a protective effect on college education (RR 0.88 CI 0.80-0.97) compared to non-corticosteroid exposure. Male sex and older age (\( \geq 5 \) years) at diagnosis were associated with being more likely to not graduate college. Survivors reporting any serious/life threatening chronic condition prior to age 25 years (grades 3-4) were more likely to not graduate college (RR 1.14 CI 1.09-1.18) compared to no chronic conditions (grades < 3). Conclusions: Survivors reporting chronic conditions are less likely to complete a college education by age 25 years and may need additional educational or vocational resources.

Background: Immune checkpoint inhibition in children has shown limited success rates until now. This is mostly likely due to the fact that the vast majority of pediatric cancers are so-called immunologic cold tumors, and that patients have been enrolled in an unselected manner in single agent trials. Recently, it has been shown that the class I selective HDAC inhibitor entinostat has significant immune enhancing activity in vitro and in vivo. This is mediated through multiple mechanisms including depletion of myeloid-derived suppressor cells, activation of neoantigen transcription and increase of MHC expression. Methods: INFORM2 NivEnt is an exploratory nonrandomized, open-label, multinational and multicenter seamless phase I/II basket trial of nivolumab and entinostat in children and adolescents with refractory high-risk malignancies. INFORM2 NivEnt: First Author: Cornelis Martinus van Tilburg, Hopp Children’s Cancer Center Heidelberg (KITZ), Heidelberg University Hospital and German Cancer Research Center (DKFZ), Heidelberg, Germany Background: Genetic alterations in the RET kinase, including gene fusions and activating point mutations, are implicated in the pathogenesis of lung, thyroid, sarcoma and other cancers in both children and adults. Currently available multikinase inhibitors with anti-RET activity are non-selective and may be associated with less favorable toxicity profile. LOXO-292 is a novel, highly selective, ATP-competitive small molecule RET inhibitor. LOXO-292 has preclinical nanomolar potency against diverse RET alterations (e.g., fusions, activating mutations and anticipated acquired resistance mutations) and anti-tumor activity in the brain. LOXO-292 has demonstrated clinical activity in adult patients with RET-altered solid tumors. Methods: LIBRETTO-121 (EudraCT 2019-000212-28) is an ongoing multicenter phase I/II dose escalation multicenter trial in patients 6 months-21 years of age with advanced, RET-altered solid and CNS tumors. Dose escalation follows a rolling 6 design starting at the equivalent of the adult recommended phase 2 dose. The study will enroll a maximum of 128 patients in Germany, The Netherlands, Sweden, France, Australia and additional countries under discussion. A comprehensive accompanying biomarker program will investigate a series of immune and epigenetic pharmacodynamic biomarkers. Clinical trial information: NCT03838042.

Background: CIPN is a common, but under-recognized complication of tubulin taxins, which are key to curative therapy for HL. In the absence of validated, self- or proxy-report measures for children, CIPN reporting has depended on clinical grading scales. The goal of this study was to assess the psychometric properties of the FACT-GOG-Ntx measure in a pediatric population. Methods: Youth (11+ yrs) and parents of all children (0-19 yrs) with newly diagnosed high risk HL, enrolled on AHOD1331 (NCT02166463), respectively completed the FACT-GOG-Ntx, a validated measure of CIPN in adults. Cronbach’s alpha coefficient (reliability) and intra-class coefficients (ICC) were calculated. FACT-GOG-Ntx total scale and 4-item sensory subscale scores (Ntx4) at Cycle 5 (dose peak) and 6-8 weeks after last cycle (End Rx) were compared to mandatory clinical grading, using the Balis Scale with any neuropathy defined as >= grade 1 on Balis. Results: 279 youth and 291 parents completed study measures. Cronbach’s alpha exceeded 0.80 for both raters. Inter-rater agreement was strong (ICC=0.89). Sixty (20%) patients had any neuropathy on Balis. Those with CIPN had significantly lower total and Ntx4 scores than those without at cycle 5 and End Rx and for both raters (p<0.05) (Table). Conclusions: This is the first application of the FACT-GOG-Ntx in a pediatric HL trial. We demonstrate that the measure was reliable for both raters and had strong intra-rater agreement. Validity was demonstrated by significantly lower FACT-GOG-Ntx scores among patients with evidence of CIPN on clinical exam. Comparisons between study arms will be evaluated after study accrual is completed.

Mean (SD) Scores on FACT-GOG-Ntx Total and Ntx4 Subscale by Rater and Time.

<table>
<thead>
<tr>
<th>Ntx4</th>
<th>Cycle 5</th>
<th>End Rx</th>
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<tbody>
<tr>
<td>Cycle 5</td>
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<tr>
<td>Parent</td>
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<td>Parent</td>
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<tr>
<td>Any Px?</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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<tr>
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<tr>
<td>Yes</td>
<td>39</td>
<td>28.4 (8.7)*</td>
</tr>
</tbody>
</table>

*p<0.05; Ntx4, Sensory Subscale Score; PN, peripheral neuropathy on Balis > grade 1.
*Higher, better

Background: Genomic alterations in the RET kinase, including gene fusions and activating point mutations, are implicated in the pathogenesis of lung, thyroid, sarcoma and other cancers in both children and adults. Currently available multikinase inhibitors with anti-RET activity are non-selective and may be associated with less favorable toxicity profile. LOXO-292 is a novel, highly selective, ATP-competitive small molecule RET inhibitor. LOXO-292 has preclinical nanomolar potency against diverse RET alterations (e.g., fusions, activating mutations and anticipated acquired resistance mutations) and anti-tumor activity in the brain. LOXO-292 has demonstrated clinical activity in adult patients with RET-altered solid tumors. Methods: LIBRETTO-121 (EudraCT 2019-000212-28) is an ongoing multicenter phase I/II dose escalation multicenter trial in patients 6 months-21 years of age with advanced, RET-altered solid and CNS tumors. Dose escalation follows a rolling 6 design starting at the equivalent of the adult recommended phase 2 dose. The study will enroll a maximum of 128 patients in Germany, The Netherlands, Sweden, France, Australia and additional countries under discussion. A comprehensive accompanying biomarker program will investigate a series of immune and epigenetic pharmacodynamic biomarkers. Clinical trial information: NCT03838042.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Feasibility of implementing a resident oncology video curriculum. First Author: Sam Brondfield, University of California San Francisco, San Francisco, CA

Background: ACGME survey results consistently show that 40% of University of California, San Francisco (UCSF) internal medicine (IM) residents are dissatisfied with their oncology education—higher than the oncology national average and highest among UCSF IM subspecialties. A needs assessment revealed that UCSF residents desire online oncology resources for asynchronous learning. To address this need, we sought online oncology videos targeted to residents but found none. We thus used cognitive theory of multimedia learning principles to develop an oncology video curriculum and evaluated three feasibility components: demand (frequency of use), efficacy, and acceptability.

Methods: We chose common cancers from the ABIM blueprint and filmed five 10-minute videos of UCSF oncologists discussing content they chose for residents. We created modules with pre/post tests derived from video content. After a pilot, we sent links to all IM residents on required oncology clinic rotations over four months (n = 25) and offered protected clinic time for optional completion. We compared pre/post test scores with a paired t-test and surveyed residents. Results: Demand: 72% (18 of 25) completing ≥1 module; 32% completed all 5. Efficacy: The mean pre- vs. post-test score improved (50% vs. 87%, p = 0.002). Acceptability: 64% completed the survey. Of those who completed ≥1 module, 93% (13 of 14) felt strongly that the videos contributed to their knowledge, 93% recommended the videos to others. Residents praised the length, key points, and pre/post tests. Finding time for the modules was difficult, most did them at home. Suggestions included focusing on fundamentals and creating videos for all common cancers.

Conclusions: We present demand, efficacy, and acceptability evidence supporting the feasibility of a resident oncology video curriculum. Formal protected time for module use is critical. We will focus on fundamentals for generalists as we make more videos. We will track ACGME survey results, examination scores, and clinical performance to study impact. We aim to publish the modules online for broader use and as a model solution to address similar needs across specialties and institutions, as complex resident schedules increasingly require asynchronous learning.
Methods: A list of radiation oncology residents from the graduating class of 2022 (PGY-2 academic year of 2018-2019) was obtained through internet investigation. In addition to gender, demographics included dual degree status and presence/absence of a PhD. Research productivity was calculated using PRP number, defined as the number of a resident’s publications listed in PubMed (pubmed.gov) through the calendar year of residency application (2016 for the class of 2022), as previously described. Fisher’s exact test was used for statistical analysis. Results: Of 179 residents examined from the 2022 class, 55 (31%) were women, representing a nine percent increase from the resident class of 2016. Four-fifths had at least one PRP, 33% had dual degrees, and 18% had a PhD. These percentages were comparable to their male counterparts, 73% of whom had at least one PRP, 39% who had dual degrees, and 15% who had a PhD. Specific analyses revealed no statistically significant differences by gender in any of these benchmarks (p > 0.05). Conclusions: While slower than the overall trend of increased female representation in medicine, the proportion of women in radiation oncology residency has increased by approximately 1.4% per year, a rate at which the representation of women in PGY-5 is predicted to be 33% in 2025. There was no statistical evidence of significant differences in PRP productivity between male and female residents, and there are no significant gender differences in the likelihood of dual degree status or PhD status. Further study will be needed to determine how these findings manifest in career choice following graduation.

Methods: In 2015–2016, all 152 second-year University of California, San Francisco (UCSF) medical students in a hematology/oncology course produced a concept map about a single cancer type over four weeks. Two of three graders independently scored each map using a standard rubric. Inter-rater reliability was excellent (r = 0.95 or greater between the graders). Concept maps scored did not correlate with preclinical or clinical performance. 43 of 50 students (86%) rated the helpfulness of concept mapping on a 5-point agreement scale (1=strongly disagree, 5=strongly agree). The median rating was 3, and the mean (SD) rating was 2.81 (1.44). 22 of 50 (44%) students submitted comments about concept mapping. Some (9 of 22) found concept mapping useful, expressing themes such as “learning the material better” and delving into the “details.” Others (7 of 22) did not, expressing themes such as preferring “other study methods” and feeling that concept mapping was “busy work” or “stressful.” Conclusions: Integrating concept maps into a medical student oncology curriculum is feasible, and delving into the “details” of oncology knowledge is preferable to busy work. Future studies should explore whether integrating concept maps earlier in medical school, producing multiple concept maps over time with training and feedback, or developing concept maps collaboratively may increase utility as a learning and assessment tool.
Mindful fellows: Study results from a pilot wellness curriculum in hematology oncology. First Author: Monica Sheila Chatwal, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: Rates of physician burnout, depression, and career dissatisfaction are rising. It is imperative to develop solutions. Studies find mindfulness is an effective therapeutic means for physician burnout, but few programs address this in clinical trainees, specifically hematology oncology fellows. The aims of this pilot study were to determine the feasibility and acceptability of a mindfulness-based wellness curriculum. To our knowledge, this is the first study assessing this type of intervention in this population.

Methods: In this single center, nonrandomized study, six monthly 30-45 minute sessions were integrated within the framework of existing didactic conferences. Each session had two parts—didactics on mindfulness and guided meditation exercises. Sessions were led by a social worker trained in mindfulness techniques. Participants completed pre and post intervention questionnaires, including Mindfulness Attention Awareness Scale (MAAS) (Carlson, 2005), Perceived Stress Scale (PSS) (Cohen, 1983), and reflection questions, with an opportunity for free responses. The primary endpoint was feasibility as determined through recruitment (target 70%) and treatment adherence defined as participation and completion (target 80%). A secondary aim was acceptability determined through self-reflection questions (target 80%).

Results: A total of 27 participants (59% female) enrolled with 37% in post-graduate year 6 (PGY-6). Of the eligible fellows, 96% enrolled and 96% of participants completed questionnaires. On self-reflection questions, 65% reported that the program was useful and 81% reported they would participate again in the future. Participants suggested modifications including location, timing, and a broader scope to include skills in addition to mindfulness (e.g. resiliency-focused). Data on self-reported levels of stress and self-awareness, an exploratory aim, will be presented at the meeting.

Conclusions: Findings indicate that a mindfulness-based wellness curriculum was both feasible and acceptable for hematology oncology fellows. Modifications are being made to expand on this program, and incorporate it as a recurring component of the existing curriculum.

Evaluation of Colorado oncology providers on the use of medical marijuana. First Author: Ashley Elizabeth Glode, University of Colorado, Aurora, CO

Background: There is a lack of knowledge regarding medical marijuana use in cancer patients. More information is needed due to increase in both state approvals and access to medical marijuana. We hypothesized that variation in provider knowledge, attitudes, and behaviors exists across all professions in oncology, which contributes to a lack of both provider awareness of patient use and patient education on marijuana use.

Methods: A survey was distributed to oncology providers in the state of Colorado. The primary objective was to describe provider knowledge, attitudes, and behaviors regarding medical marijuana use in cancer patients. Other objectives were identifying educational needs for oncology providers to feel comfortable recommending medical marijuana and reporting provider interest in future marijuana studies.

Results: We received responses from 172 oncology providers; 48 advanced practice providers, 47 physicians, 53 registered nurses, 17 pharmacists, and 7 other.

Conclusions: Regardless of profession, the majority of oncology providers in Colorado do not recommend and do not feel comfortable recommending or suggesting medical marijuana to a cancer patient, yet most believe it provides medical benefit. Providers believe there is a need for education and research on the use of medical marijuana in oncology patients.
Background: Disparities in current global oncology care are a major concern for many societies. Two-year oncological training in Russia is deficient in evidence-based medicine (EBM) and effective patient communication skills, despite the fact that these dictate the ability to provide optimal cancer care. We report a 3.5-year sustained program aimed at implementing Western-oriented education among young Russian oncologists to combat these educational deficiencies. Methods: The Higher School of Oncology (HSO) is a 5-year national competitive program established to supplement the traditional 2-year Russian oncology curriculum with an emphasis on patient communication, critical appraisal of oncologic articles, multidisciplinary cancer care, and program development. A total of 35 PGY1-4 residents (8-9 residents annually) have enrolled in the program. Expatriate Russian physicians practicing in the US led 140 online educational seminars with journal clubs and clinical case presentations. Communication skills were evaluated by an independent private educational group. Results: Significant improvement of EBM knowledge was marked among HSO residents, from inability to explain basic concepts to practicing and teaching EBM. Beginning in the 3rd year of the program, residents organized educational courses and conducted journal clubs for HSO and non-HSO colleagues. Residents of the program had higher patient communication scores compared to that of residents of standard Russian programs. HSO residents promote the spread and popularization of EBM and a patient-centered approach among attending physicians, improving the quality of cancer care. The HSO also triggered imitation of similar projects in other residency programs. Conclusions: The HSO project has pioneered EBM training and led to systemic changes in cancer patient care for Russian oncologists. This model has shown success and may be useful in overcoming global medical educational disparities in other specialties and in other countries facing similar challenges.

Results:
A total of 195 assessments were completed July 2017-November 2018. 81% were EPA assessments and the remainder multisource feedback, rubrics and field notes. The median number of assessments per faculty was 17 (0-42). 52% of assessments included written “Comments” or “Next steps”. A median of 6 assessments per faculty member included specific or actionable feedback. Lessons learned centered on: 1) Faculty and Resident development and engagement (critical before, during and after implementation); 2) Value of sharing work of CBME (CBME Education Consultant, CBME Lead, Academic Advisors, Competence Committee); 3) Importance of effective communication strategy with stakeholders; 4) Importance of collaboration with other training programs at institutional and national levels; 5) Culture change (a slow process); 6) Resident concerns regarding lack of global assessment; 7) Assessment plan challenges (How many observations required?); 8) Burden of CBME (Resident driven assessments or a better balance?); 9) Limitations of e-portfolio (How to live track and by whom?); 10) Value of continuous quality assurance and improvement. Conclusions: Our first year of implementation was successful in introducing CBME concepts, work based assessments and e-portfolios. Ongoing work is needed, including increasing the number of assessments and quality of feedback.

Implementation of competency-based medical education in a Canadian meditly oncology training program: Lessons from our first year. First Author: Anna T. Tomiak, Queen’s University, Kingston, ON, Canada

As a part of a university wide initiative, CBME was implemented in our MO training program in July 2017. Stages, Entrustable Professional Activity (EPA) assessments and Required Training Experiences established by the Royal College of Physicians and Surgeons of Canada were adopted. MedTech Central, the electronic portfolio developed at our university, was used for assessment collection. We share here observations and experiences from our first year of implementation. Methods: Assessment metrics were obtained through MedTech. Ethics was granted by Queen’s University as part of an ongoing research study on feedback. Lessons learned were compiled from discussions between the Program Director, Residents, Program Administrator, CBME Education Consultant and CBME lead. Results: A total of 195 assessments were completed July 2017-November 2018. 81% were EPA assessments and the remainder multisource feedback, rubrics and field notes. The median number of assessments per faculty was 17 (0-42). 52% of assessments included written “Comments” or “Next steps”. A median of 6 assessments per faculty member included specific or actionable feedback. Lessons learned centered on: 1) Faculty and Resident development and engagement (critical before, during and after implementation); 2) Value of sharing work of CBME (CBME Education Consultant, CBME Lead, Academic Advisors, Competence Committee); 3) Importance of effective communication strategy with stakeholders; 4) Importance of collaboration with other training programs at institutional and national levels; 5) Culture change (a slow process); 6) Resident concerns regarding lack of global assessment; 7) Assessment plan challenges (How many observations required?); 8) Burden of CBME (Resident driven assessments or a better balance?); 9) Limitations of e-portfolio (How to live track and by whom?); 10) Value of continuous quality assurance and improvement. Conclusions: Our first year of implementation was successful in introducing CBME concepts, work based assessments and e-portfolios. Ongoing work is needed, including increasing the number of assessments and quality of feedback.
TeammX integrative oncology scholars: Harnessing the potentials of students in shaping oncological care. First Author: Kin Wai (Tony) Hung, Olive View UCLA Medical Center, Sylmar, CA

Background: Teams are critical in delivering patient-centered care amid the challenge of health care workforce shortages. While conventional team-based collaborative care model involves physician and non-physician professionals, roles for pre-professional students in teams are largely educationally and arguably underutilized. Methods: In a collaborative effort with the University of California Los Angeles (UCLA) Center for East West Medicine (CEWM), TeamX Health, a 501(c)3 nonprofit organization, designed an innovative, team-based curriculum for pre-professional students with our aims to harness the potentials of students in shaping the present and future delivery of oncological care. Over a 10-week academic quarter, students are challenged to explore the evolving evidence-based specialty of integrative oncology, and delivered as a "capstone project", a creative solution to problems facing cancer patients today. Results: From April 2018 through October 2018, two 6-student cohorts have completed the curriculum. 10 participants (83%) were undergraduates and 2 (17%) were post-graduate alumni. Participants were selected based on a competitive application process with commitment to engage in the 2-hour weekly learning session. Sessions were taught in team-based learning format, covering topics ranging from cancer prevention, survivorship, symptoms management, nutrition, complementary therapies, integrative medicine models, and informatics. At completion of the curriculum, cohort one launched a health promotion YouTube channel addressing the physical and emotional burden for cancer survivors, and cohort two published a website for patients and caregivers to share their cancer journey serving as a greater social support platform. Conclusions: Redesigning the educational experience for pre-professional students may unlock unexpected possibilities to shape how we learned and care for our patients. Harnessing the potentials for all levels of stakeholders ought to be part of defining team-based collaborative care.

Support structures for female physicians: Motivations and barriers to gender-specific conferences and symposia. First Author: Shikha Jain, Rush University Medical Center, Chicago, IL

Background: While nearly half of all medical school graduates are female, women remain underrepresented in the physician workforce. Conferences or symposia designed to address issues relevant to female physicians, such as gender-bias, sexual harassment, and work-life balance are one strategy to improve retention and advancement, yet, limited data exists surrounding gender-specific attendance. Methods: An online survey instrument was distributed nationally via social media and shared by respondents. The survey assessed participants' demographics, attendance at gender-specific conferences or symposia, motivations or barriers to attendance, and perceived benefits of attendance. Results: Of 792 respondents, 34% had attended a conference or symposia for women in medicine, while 66% had not. Attendees were significantly more likely to hold a leadership position (68% vs. 43%, p < 0.0001), an academic faculty position (74% vs. 56%, p < 0.0001), and have received a professional accolade within the past year (42% vs. 28%, p < 0.0001). Non-attendees were significantly more likely to be the primary caregiver for children or seniors (64% vs. 56%, p = 0.042). Respondents indicated that an interest in discussion topics, a sense of community, and growth of professional network were key motivations in attendance. The majority of respondents indicated that attendance improved their self-advocacy, self-image, and leadership skills. Of those who did not attend, 51% were unaware of such conferences or symposia. Those who were aware, but unable to attend, cited lack of time as the major barrier to participation. Conclusions: The results of this study provide preliminary data surrounding gender-specific conferences or symposia for women in medicine and highlight opportunities for increased engagement. While not causative, attendees share attributes of professional success and report personal and professional benefits. Lack of awareness and access to child/family care are likely major barriers to participation, which can be addressed through strategic initiatives.

Cross-cultural validation of a medical leadership competencies survey in Latin-American physicians: A multinational study. First Author: Max S. Mano, Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil

Background: Despite the growing complexity in the healthcare sector, physicians rarely receive formal training in leadership skills. In a previous survey, Citaku et el identified a set of leadership competencies (LC) which were evaluated by North-American (NA) and European (EU) leaders involved with medical education. We aim 1) To apply this same survey to a population of Latin-American (LA) physicians from the oncology community and related areas who hold leadership positions of various levels; 2) To compare the results with those of the previous survey and 3) To perform subgroup analyses within the LA cohort. Methods: The survey was sent to close to 8,000 members of contributing medical societies from LA countries. In addition to the 63 questions with 5 possible responses, we also collected data on type of institution (private vs public), country of practice, main specialty, gender, age, years of experience in oncology and years of experience in leadership position. Results: We collected a total of 217 responses on a web-based tool. LA leaders placed the highest value on task-management competencies (89.37% of ‘important’ or ‘very important’ responses vs. 87.0% for NA/EU; p<.0001), followed by self-management (87.45% vs 87.55%; p = NS), social responsibility (86.83% vs 87.48%; p = NS), innovation (86.69% vs 85.31%; p = NS) and leading others (83.31% vs 84.71%; p = NS). Social responsibility, which was first in importance in the NA/EU survey, was only third in the LA survey. Subgroup analyses revealed significant interactions which will be fully presented. Conclusions: We successfully applied the survey to a population of LA medical leaders from the oncology community and related areas. LC valued by LA leaders somewhat differ from those valued by their NA/EU counterparts, implying that cultural aspects might influence the perception of required LC. We also detected significant variations in the responses within the LA population. Our data might indicate that current physician leadership training programs should be tailored to suit specific needs and cultural aspects of each region. Further validation of this survey in other clusters of world culture is warranted.
Operating results.

Background: Female underrepresentation in academic medicine leadership is well-documented; however, oncology specific data are scarce. This study evaluates female leadership representation in academic medical oncology (MO), radiation oncology (RO) and surgical oncology (SO) programs. Furthermore, we examine the impact of female leadership on overall female faculty representation. A total of 264 (96%) Accreditation Council for Graduate Medical Education actively accredited MO (144 of 153), RO (93 of 94) and SO (27 of 27) training programs were included. The gender of overall faculty and those in leadership positions (program director and departmental chair/division chief) of each program was determined using hospital websites from 1/01/18 to 1/27/19. The chi-squared goodness-of-fit test was used to examine whether the observed proportion of females in leadership positions deviates significantly from the expected proportion based on the actual proportion of overall female faculty in MO, RO and SO. Two-sample t-tests were used to compare rates of female faculty representation across each program based on the presence/absence of a female in a leadership position for MO, RO and SO. Results: Female faculty representation in MO, RO and SO was 37.1% (1,554/4,191), 30.7% (389/1,269) and 38.8% (212/546), respectively. Female representation in leadership positions was 31.5% (82/260), 17.4% (31/178) and 11.1% (5/45), respectively. The observed proportion of female in leadership position was significantly lower than the expected proportion of females in leadership positions for RO (17.4% vs. 30.7%, p = .0001) and SO (11.1% vs. 38.8%, p = .0001), and demonstrated a trend towards significance for MO (31.5% vs. 37.1%, p = .063). 47.9%, 33% and 18.5% of MO, RO and SO programs had a female leader. Female faculty leadership position in MO was higher than the female leadership position in SO. In a leadership position had a higher mean percentage of overall female faculty than those that did not: 41.0% vs 35.0% (p = .0006), 36.0% vs 26.0% (p = .0002) and 39.0% vs 32.0% (p = .348) for MO, RO and SO, respectively. Conclusions: Gender disparity exists in academic MO, RO and SO leadership. Demand for programs is magnified at the leadership level. Programs with a female physician in a leadership position are associated with a higher percentage of female faculty.

Developing an inspired leader: How to maximize human talent to maximize operating results. First Author: Aimée Greeter, Coker Group, Charlotte, NC

Background: Healthcare is a personal industry—driven by people, for people. Developing the talent of individuals as leaders is critical to making the entire industry thrive. This session provides practical tools to develop highly competent leaders, who can then develop high-performing organizations. Methods: Using Noel Burch’s framework, this presentation shares effective methods of propelling leaders from uninspired to results-focused performers. With a focus on real-life examples, this interactive session will cover the pros and cons of how to maximize human talent as a means to driving enterprise-wide success. The topics to be covered include: (1) Conscious Competence Ladder: What Is It?; (2) Noel Burch’s work; (3) Key tenets of the Ladder; (4) Common misperceptions of the Ladder; (5) Conscious Competence Ladder and Healthcare: Why Does It Matter?; (6) Application of the Ladder to the healthcare industry; (7) Realities of Human Capital in healthcare; (8) “Exercising” Leadership: Is That Even Possible?; (9) Development of leadership as a skill; (10) Four-Step Process to Leadership Development in Healthcare: But How Do We Do That?; (11) Application of Leadership: But Won’t This Be Hard?; (12) Common pitfalls in leadership development; (12) Success Stories: Has Anyone Ever Even Done This in Healthcare?; (13) Conclusions, Q&A: What Happens Next? Results: This session will enable participants to: (1)Describe the Conscious Competence Ladder model and its relevance to healthcare organizations; (2) Authenticate leadership as a skill that can be developed, and understand how to mature that skill within healthcare leaders using an efficient four-step process; and (3) Provide practical, effective methods to help people understand, process and use leadership skills to maximize the success of their peers, patients and community. Conclusions: In Q4 2017, for the first time ever, healthcare passed both manufacturing and retail as the United States’ largest employer. Simply put, there are now more health care laborers than any other industry. In sheer numbers alone, this is impressive. But, more impressive is the need to utilize and motivate this work force. Using effective and appropriate tools (such as those to be provided in this presentation), this massive healthcare workforce can be empowered to drive significant benefits for an organization, its patients and a broader community.

Medical oncologists’ experience with returning molecular tumor profiling to patients. First Author: Subotheni Thavaneswaran, The Garvan Institute of Medical Research, University of New South Wales, Sydney, Australia

Background: Molecular tumor profiling (MTP) to guide therapy is increasingly being applied in the clinic, although how medical oncologists (MOs) manage this in clinical practice is not fully understood. Methods: An online survey explored MOs’ experience with MTP interpretation, treatment (tx) decisions, identifying resources, and communicating results to patients with cancer. MOs were identified based on their participation in the Australian Mucosal Screening and Therapeutics Program. Results: 108 MOs (57% male, median years of practice, 5-9 years, 83% urban-based practice and median age range, 40-49 years) participated from June 2018 – Jan 2019. Most MOs had experience with MTP (90%), and felt it was their role to discuss results. MOs felt confident discussing the process of MTP, the probability of a “therapeutically actionable finding,” and results (score 70-75, range 0 least confident - 100 completely confident). However, almost two-thirds of MOs needed/wanted assistance with interpretation of results, favouring a Family Cancer Clinic (FCC) helpline, patient information sheets on MTP, and decision aids. In particular, MOs were less confident discussing genetic implications and their implications (median score 56) but were comfortable (median score 96) to refer to an FCC. Most MOs felt there was sufficient information on the MTP report to understand results. Some preferred to receive ‘all cancer gene variants’ (36%), others only those with clinical actionable (45%), and some only those with therapeutic actionable genotypes (9%). Most MOs felt they needed to know a priori indications for MTP, tx recommendations, and/or a list of relevant trials. Interestingly, MOs indicated little confidence that MTP would guide useful tx decisions (median score 51) and most reserved it for the tx-refractory setting. A minimal level of evidence supporting treatment was required by 83% of MOs prior to recommending MTP. Conclusions: Gender equilibrium in MTP interpretation and tx decision making is a priority. MOs can benefit from education in MTP interpretation, tx decision making, and integrating MTP into clinical practice, despite uncertainty about result validity and clinical translation, particularly regarding germline results. Understanding these potential barriers is the first step in developing clinician supports to facilitate clinical translation.

From presentation to paper: Gender disparities in oncological research. First Author: Willemienke P.M. Dijksterhuis, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands

Background: Gender discrepancies have been identified in authorships of scientific publications, grant applications, and peer review in many disciplines, including oncology. The exact share of women presenting results of oncological studies at large conferences is unknown, while the oral presentation of a study at such a podium enhances the international visibility and recognizs, this if the presenting person. Therefore, we aim to identify gender-based differences in contributions to presentations at two major oncological conferences. Methods: We collected consecutive abstracts presented at the plenary sessions of the American Society of Clinical Oncology (ASCO) Annual Meetings and plenary sessions of the European Society for Medical Oncology (ESMO) Congresses. Sex of the presenters and abstract authors, study results (positive vs. negative), and subsequently published papers were identified. Chi square tests were used to compare the distribution of sex over time. The association between presenter’s or last author’s sex and study outcome and impact factors were analyzed using Chi square tests and Mann-Whitney U tests, respectively. Results: Of available abstracts presented at ASCO between 2011 and 2018 (N = 34), and ESMO between 2008 and 2018 (N = 132), presenters were female in 24% and 21%, respectively. Female last authors were seen in 21% and 20% of these ASCO and ESMO abstracts. Of all contributing authors to these ASCO (N = 569) and ESMO (N = 1851) abstracts, 31% and 27% were female, respectively. The distribution of male and female ASCO and ESMO presenters (P = 0.580, P = 0.707, respectively) and abstract authors (P = 0.429, P = 0.062) was similar over the years. Of all abstracts, sex of the presenter or last abstract author were not associated with study outcomes (P = 0.718, P = 0.0131), nor with impact factor of subsequently published papers (P = 0.209, P = 0.661). Conclusions: There is a clear gender disparity in the presentation of oncological research at two main conferences, with less than a third of abstract authors female and less than a quarter of these studies presented by a woman. The lack of visibility of female researchers at plenary sessions on these main conferences could impact acknowledgment for their research, opportunities in their academic career, and even have heterogeneity and outcomes in research.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Creation and development of the National Cancer Control Plan in Russia. First Author: Alexey Petrovsky, Federal State Budgetary Institution "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russian Federation

Background: The absence of the National Cancer Control Plan (NCCP) did not allow to develop oncology in Russia. Methods: Since 2015 experts of the N.N. Blokhin Russian National Comprehensive Center and Russian Oncology Association has initiated the creation of a National Anti-Cancer Strategy. Results: In 2016, the working group presented the first version of this Strategy to the professional community for wide discussion, which was transferred to the Russian Ministry of Health after a broad discussion in 2017. This strategy included prevention, screening, early diagnosis, treatment, rehabilitation and palliative care in patients with malignant tumors. In parallel, we created National Clinical Cancer Guidelines, which were approved by the professional community, and then we submitted them to the Ministry of Health in 2017. Also in the period of 2017-2018, updated principles of creating clinical and statistical groups (CSG) were developed based on the calculation of the real costs of each type of surgery, radiation therapy and drug treatment. More than 1,000 different standards we established for each case of hospitalization and their cost has been calculated. Then, based on these calculations, we ranked four types of treatment (surgery, radiation therapy, chemotherapy and chemoradiation), each of which has 3, 5, 10 and 6 levels, respectively. These calculations formed the basis of the NCCP approved by the Government and the President of the Russian Federation, starting from 2019 with an unprecedented additional level of funding of almost 1 trillion rubles (an increase of almost two times). The major goal of the Russian NCCP is to decrease mortality level from 202 to 185 (8,5%) per 100 000 population by the year of 2024. Conclusions: The effort of the professional community with due consideration and consolidation with the Ministry of Health allows implementation of the NCCP on a national level.

10525 Poster Session (Board #104), Sat, 1:15 PM-4:15 PM
Working together in cancer care: An academic community partnership for a diverse patient population. First Author: Naomi Ko, Boston Medical Center, Boston, MA

Background: The Massachusetts General Hospital Cancer Care Equity Program conducted a qualitative survey health assessment in the inner-city communities of Boston to study Black Bostonian patients' perceptions of the barriers to cancer care. Findings revealed a level of mistrust toward large cancer centers and a request for more interactions with their trusted community health providers. At a subsequent community forum geared toward soliciting solutions to improve relationships with academic medical centers, community members recommended that academic oncologists increase engagement with their community health center (CHC) clinicians with a cancer lecture series. Methods: Academic oncologists from Massachusetts General Hospital and Boston Medical Center met with the leadership at two CHCs prior to the creation of the cancer lecture series. Feedback on how to best support CHC providers was established and a cancer care lecture series was created with continuing medical education (CME) credit provided. Five in-person lectures were given at each CHC. Topics included: Consultative Hematology, Breast Cancer, Prostate Cancer, Thyroid Cancer, Colon Cancer and Adrenal Masses. Survey evaluations (summative and formative) were distributed to all participants. An online portal was established to provide ongoing CME to providers. Results: Six academic physicians specializing in cancer care provided lectures at two CHCs. Currently, we have 176 surveys completed from both CHCs. Thus far, 59% of respondents have indicated that the lectures have been “Excellent” or “Above Average,” and all participants have responded that the objectives of each presentation have been met. We have developed a website to provide ongoing CME for the lectures that were given: http://bcucme.org/cancercare. Conclusions: This project aims to improve cancer care education and communication between providers from academic cancer centers and primary care providers at CHCs that care for a diverse and vulnerable patient population.

Oncology fellows' knowledge and current practice regarding outpatient oncology and palliative care. First Author: Amy Johnson, Indiana University School of Medicine, Indianapolis, IN

Background: Patients with advanced cancers often suffer from a number of symptoms and need guidance when discussing treatment goals as their diseases' progress. Palliative care competencies include the assessment and management of both physical and psychological symptoms, as well as, the conduct of goals of care conversations and advanced care planning. Palliative medicine is a subspecialty that specially addresses these needs in patients with advanced cancers, but is not universally available. Oncology fellowship training must include these competencies and there is little evidence regarding the palliative care educational experiences of oncology fellows. This study examines fellows' experiences with palliative care education and fellows' attitudes about concurrent palliative care in the outpatient setting. Methods: An electronic nationwide survey of medical oncology fellows was conducted in the second half of the academic year in 2018. Results: 43 of 191, 22.5%, of oncology fellows contacted at 17 institutions responded. 96% of fellows indicated they would strongly agree or agree with having a Palliative Care Team in their future outpatient clinics. 93% of fellows agree or strongly agree with being comfortable managing cancer related pain, but only half agree or strongly agree with being comfortable managing depression and anxiety. 91% agree or strongly agree they are comfortable with discussions about transitions to best supportive care, while only 31% of fellows always or often assist patients in completing advance care documents. 70% of fellows are always, often, or sometimes receiving feedback on their communication and symptom management skills. Conclusions: Oncology fellows fell comfortable with some aspects of palliative care more than others. Fellows in this survey report feeling comfortable with goals of care conversations and pain management, but not as comfortable managing other symptoms like depression and anxiety. Respondents are not universally assisting patients in advanced care documentation and only two-thirds of responding fellows are receiving frequent feedback on their communication and symptom skills. There is a consensus among responding fellows about a desire to have palliative care embedded in their future clinics.

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10528 Poster Session (Board #107), Sat, 1:15 PM-4:15 PM
Choosing oncology as specialization: Medical students’ perception after clinical rotation in cancer center. First Author: Omar Orlando Castillo Fernandez, Instituto Oncologico Nacional, Panama City, Panama

Background: Cancer is a leading cause of death worldwide and the demand for oncologist and palliative care specialists is increasing dramatically. Two years ago, The Universidad de Panama incorporated Oncology in the curriculum in order to face the shortage of professionals involved in cancer care. Little information is available concerning young medical students desire to pursue a career in oncology. The aim of this study is to evaluate medical students perception about Oncology as a specialization field. Methods: An electronic survey was sent to medical students from Universidad de Panama after finishing Oncology rotation the last 2 years. Chi square and Mann Whitney U tests were used to compare variables. Results: 145 questionnaires were responded (40%), 60% female and 40% male. Median age was 25 years old. Clinical rotation during Oncology practices were: 37% in Medical Oncology, 24% in Surgical Oncology, 21% in Radiation Oncology and 18% in Palliative Care. 20% (29) of students are highly motivated to pursue a career in Oncology. 8 in Radiation Oncology. 8 in Surgical Oncology. 8 in Medical Oncology and 5 in Palliative Care. Variable associated with a oncology perception were: male gender (p=0.007), lack of human resources (p=0.008), contact with patients and family (p=0.005), good experience with mentor (p=0.002), nature and complexity of disease (p=0.001). Potential emotional burden was negatively associated (p=0.004) with oncology preference. 66% of students acknowledged that clinical rotation changed positively their perception about cancer patient care and a third of students have not ruled out the possibility to choose Oncology in the near future. Conclusions: Early exposition to medical student to cancer care might help to reduce the global shortage of oncologist and palliative specialists.

10529 Poster Session (Board #108), Sat, 1:15 PM-4:15 PM
Satisfaction of general versus specialized continuity clinic in hematology oncology fellowship training: A survey. First Author: Sama Imran Ilyas, UFCCM, Gainesville, FL

Background: At the University of Florida (UF), oncology fellows participate in two general types of continuity clinic as part of their training. One clinic at the Veterans Hospital (VA) allows them to care for patients in a general clinic setting that encompasses a variety of hematology oncology diagnoses. The other clinic, located at the university site, is disease or system specific (such as breast or GI clinic). Considerable research supports the value of continuity clinic in hematology oncology fellowship training, but the differences in having a general versus specialized clinic for oncology fellows have not been explored. The purpose of this study is to investigate the perceived differences of general versus specialized continuity clinics by recent oncology graduates from UF, and what features of a continuity clinic they feel were most important for an effective and meaningful experience. Methods: An anonymous survey was sent to the last six graduating classes of oncology fellows at UF. The survey contained short demographic questions, followed by five open ended questions pertaining to both continuity clinic experiences. Graduates were asked about their opinions of both the general and specialized clinics during their training at UF. Survey responses were reviewed and coded for common themes. Results: The most common themes that emerged from the surveys were concerning autonomy, supervision, and the diversity of cases and patient population. A majority of respondents felt they had more autonomy and personal responsibility at the VA general clinic, but less direct supervision than at the specialized clinics. They also believed there was a broader exposure of different disease types at the VA general clinic. Surveyed participants also commented on the quality of educational seminars and activities, preceptor expertise and teaching, and ability to observe cutting edge practice and clinical trials. Eleven out of thirty surveys were returned and we anticipate a greater than 50% response for the next iteration. Conclusions: Graduated oncology fellows from UF believe that there is a balance that exists between having autonomy and ownership of their patients versus having adequate supervision. Many believe that having “controlled autonomy” and “as much independence as is safe for patients” is key to a meaningful continuity clinic experience during oncology fellowship training.

10530 Poster Session (Board #109), Sat, 1:15 PM-4:15 PM
A novel qualitative methodology study to characterize discrimination among hematology/oncology trainees. First Author: Rahma M. Warsame, Mayo Clinic, Rochester, MN

Background: Learner wellbeing may be adversely affected by the experience of discrimination. Eliciting details from this vulnerable population about these experiences is a challenge. This study characterizes trainee experiences of discrimination and inclusion among hematology/oncology trainees. Methods: An expert panel identified knowledge/competence gaps related to the use of Bruton’s tyrosine kinase inhibitors (BTKi) in B-cell lymphomas. A clinical practice assessment (CPA) survey was launched May 2018 to further assess baseline educational needs. Based on the needs identified, 7 activities were posted online between May-Dec 2018. Multiple-choice questions were asked before and after participation in each activity and were grouped into learning topics. Mean knowledge/competence was assessed using a chi-square statistic (P < .05 level). Results: For all topics except foundational/differentiating BTKi, the audiences participating in the baseline CPA and the other 7 activities, were similar or lower at pre-test, suggesting that learning needs continued until our education addressed them. All changes from pre-to-post-test were significant (P < .001). The largest relative percent change from pre- to post-test was seen with knowledge of resistance mechanisms for BTKi as well as knowledge/competence managing AE of BTKi. Post-test there was a high level of knowledge about the selectivity seen with 2nd generation BTKi. Conclusions: This analysis shows that online CME, utilizing many different formats (video, text, panel discussions) can significantly improve the knowledge and competence of hem/oncs in multiple areas surrounding the use of BTKi for the treatment of B-cell lymphomas. Results also suggest the following areas warrant further education: awareness of clinical trial safety and efficacy data for BTKi and mechanisms for resistance to BTKi.

10531 Poster Session (Board #110), Sat, 1:15 PM-4:15 PM
Targeting B-cell malignancies: Impact of an educational curriculum on BTK inhibitors. First Author: Lauren Willis, Medscape, LLC, New York, NY

Background: We sought to determine if a curriculum of online continuing medical education (CME) activities could improve hematologists/oncologists (hem/onc) knowledge and competence related to clinical decision making in the use of BTKi in patients with B-cell lymphomas. Methods: An expert panel identified knowledge/competence gaps related to the use of Bruton’s tyrosine kinase inhibitors (BTKi) in B-cell lymphomas. A clinical practice assessment (CPA) survey was launched May 2018 to further assess baseline educational needs. Based on the needs identified, 7 activities were posted online between May-Dec 2018. Multiple-choice questions were asked before and after participation in each activity and were grouped into learning topics. Mean knowledge/competence was assessed using a chi-square statistic (P < .05 level). Results: For all topics except foundational/differentiating BTKi, the audiences participating in the baseline CPA and the other 7 activities, were similar or lower at pre-test, suggesting that learning needs continued until our education addressed them. All changes from pre-to-post-test were significant (P < .001). The largest relative percent change from pre- to post-test was seen with knowledge of resistance mechanisms for BTKi as well as knowledge/competence managing AE of BTKi. Post-test there was a high level of knowledge about the selectivity seen with 2nd generation BTKi. Conclusions: This analysis shows that online CME, utilizing many different formats (video, text, panel discussions) can significantly improve the knowledge and competence of hem/oncs in multiple areas surrounding the use of BTKi for the treatment of B-cell lymphomas. Results also suggest the following areas warrant further education: awareness of clinical trial safety and efficacy data for BTKi and mechanisms for resistance to BTKi.
Enhancing evidence-based medicine skills in oncology training with cognitive technology. First Author: Chun-You Chen, Taipei Cancer Center, Taipei Medical University, Taipei, Taiwan

Background: Evidence-based medicine (EBM) requires applying literature evidence to inform practice. Students from Taipei Medical University Hospital, trained in EBM concepts, participated in a preliminary study using Watson for Oncology (WfO), an evidence-based decision-support system to enhance the EBM skills of medical students. Methods: A class of 50 medical students compared traditional search methods (TSM) and WfO in a workshop divided into 2 sequential sessions on colon and lung cancer, respectively. All students were trained on WfO, and 2 groups of 25 students each were randomly assigned to either TSM or WfO in the first session. Those groups were then assigned to the alternate approach in the second session. Students completed a profile that included their clinical experience with each cancer type. Students used either WfO or TSM to help answer a series of questions related to colon or lung cancer. Students then completed a survey of attitudes towards the technology, followed by a constructed-response learning assessment without the aid of TSM or WfO. Assessments were scored and results compared using a Mann-Whitney U Test; outcomes at two different experience levels, based on student profiles, were compared using a Kruskal-Wallis test. Results: In this preliminary study, more than 70% of students reported limited clinical experience with either cancer. On the colon cancer assessment, students in the WfO group performed significantly better than the TSM group (p = 0.001); there was no significant difference detected for lung cancer. Students with more clinical experience reported that TSM was easier to learn than WfO (p = 0.005); students with less experience felt that WfO was clearer and more understandable than TSM (p = 0.002). Conclusions: These preliminary results are consistent with better learning outcomes for students using WfO in the colon cancer module. Students with more clinical experience reported TSM was easier to learn than WfO, which might be due to a potentially greater familiarity with TSM in this more experienced group. More studies are needed to determine what features, if any, of WfO can facilitate EBM approaches in oncology education.

Non-oncologist physician knowledge of radiation therapy at an urban community hospital. First Author: Evan Siau, St. Barnabas Hospital - CUNY School of Medicine, New York, NY

Background: Appropriate referral for radiation therapy (RT) is crucial for cancer care. Previous work suggests that many non-radiation oncologists are unaware of RT effectiveness or indications, which may affect treatment planning. The objective of this study was to assess trends over time in oncologists’ knowledge, competence, and confidence using ICIs in the treatment of melanoma. Methods: A series of online training modules and online surveys were included in a study. A pre-assessment survey design was used, and educational effect was assessed with a post-assessment survey. Analyses were conducted to examine trends in knowledge, competence, and confidence over four years on a quarterly basis. Professional Development

Conclusions: Online CME improves oncologists’ knowledge, competence, and confidence using ICIs in the treatment of melanoma. As new data emerge and indications evolve, new educational offerings are necessary to reinforce existing knowledge, close persistent gaps, and increase oncologists’ confidence using ICIs in this clinical setting.
**Medical oncology trainees’ perceptions of their education and preparedness for independent practice.**

**Background:** This original research assesses Canadian Medical Oncology (MO) residents’ perceptions and satisfaction with their education and preparedness for practice prior to initiation of Competency Based Medical Education (CBME).

**Methods:** Digital surveys were sent to MO residents in Canada training institutions yearly from 2014–2017. Because of lower than expected response rates, invitations were subsequently extended to recent graduates completing training between 2009–2014. Ethics and funding were granted by Queen’s University.

**Results:** A total of 71 surveys were received with representation from 11 training programs. Preparedness for Practice: Current trainees and recent graduates ranked preparedness for practice similarly in all assessment domains except Medical Expert (trainee mean 3.50, graduate mean 4.45, p=0.004; 1=not prepared, 5=well prepared). Means for the combined cohort shown in table. Usefulness of teaching modalities: Participants ranked learning in a clinical setting as most useful (6.53/8, 1=least useful, 8=most useful) and educational sessions by residents (4.24/8) and Journal Club (3.74/8) as least useful. Most participants felt their training was a shared learner-teacher responsibility (56.1%) or was learner-centered (22.5%). Quality of teaching: Participants reported similar levels of satisfaction with teaching across domains except for Manager which scored lowest (3.46/5, 1=poor, 5=excellent). Self-assessment of skills: Participants were most satisfied with the ability to assess their own performance and competence at the end of training (7.16/10, 1=not satisfied, 10=very satisfied). The degree to which their programs set expectations about required knowledge, skills, or attitudes at various points in training (6.63/10) and participants abilities to self-assess these skills during their training (6.64/10) scored lower.

**Conclusions:** Participants reported low satisfaction with their ability to self-assess during their training and their training programs’ ability to communicate expectations. Transition to CBME training may address these issues, and follow-up is required.

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<th>Medical Expert</th>
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**FitFirms: A wellness option for oncology trainees.**

**Background:** Burnout in oncologists has been rising over the past decade. Burnout leads to poor patient outcomes and poor physician health. Younger oncologists are at higher risk for burnout. The FitFirm system was designed by Victor McKusick at the Johns Hopkins hospital in 1975 to integrate faculty and trainees into clinical and psychologically supportive cohorts. Here we describe an adapted Firm System called the FitFirms, which focused on social connectivity and altruistic service as means to combat burnout in oncology trainees.

**Methods:** We divided the Hematology and Oncology Division of an academic Comprehensive Cancer Care center into four cohorts of faculty–fellow teams called FitFirms. Each FitFirm was named after a notable local or national female leader in the field of cancer medicine—The Henrietta Lacks Firm, The Jane Wright Firm, The Padmimi Iyey Firm, and The Rita Mehta Firm. The faculty and fellows interacted on an at-minimum quarterly basis in casual social events and/or community service-oriented events for 15 months. The social events included group dinners, bowling, paint and game nights. The service events included participation in 5K walk/run fundraiser for our institution’s cancer center and support of a National Cancer Survivors Day event for US Veterans. A didactic discussion series was created to explore concepts of resiliency, work-life balance, and the role of art in medicine—mentored by faculty across the spectrum of oncologic disciplines (Surgical Oncology, Gynecologic Oncology, Palliative Care, and Health Communication). The Maslach Burnout Inventory survey was used to survey the oncology trainees before and after the interventions. Results: Nine pre-intervention surveys were collected with 78% of trainees describing themselves as on the burnout spectrum of feeling either ineffective, over-extended, disengaged, or burned out (22% engaged). After 15 months, 10 post-intervention surveys were collected in which 60% of trainees described themselves as on the burnout spectrum (40% engaged). Data analysis involved descriptive statistics and t-test. Conclusions: The FitFirms are a novel system using social capital to reduce the problem of burnout in oncology trainees by engaging in social connectivity and altruistic service through faculty–mentored, historically-named divisional cohorts.

**Using blended learning to improve education on clinical pathways for breast cancer management in Nigeria: Preliminary results.**

**Background:** Most Nigerian clinicians lack adequate skills and resources in screening, diagnosis, and managing women with breast cancer. The absence of locally-sensitive clinical pathways in hospitals in Abia State impact patient outcomes and clinicians job satisfaction. Blended learning (BL), a combination of online and face-to-face teaching methods, has been used in other settings to improve the competencies of clinicians. Research seeks to develop and evaluate a BL course that will train clinicians in Abia State on using NCCN breast cancer management guidelines, and to develop and implement locally-sensitive clinical pathways. Methods: The course is divided into four online modules delivered via Google Classroom and a workshop module to be delivered in 3 cities. Course evaluation involves an objective-focused method, following a mixed-methods design. Data collection includes pre- and post-tests, course evaluation and focus group discussions. Data analysis involved descriptive statistics and t-test. Comments deductively analyzed to identify common themes. A sample size of 107 individuals is required to identify a moderate effect size for the BL course. Results: Forty-three participants (physicians=15, Nurses=28) have been recruited for cohort 1, with average age of 44 (±9.9) years. Most participants have never taken an online class (65%) but use mobile phones (60%) to access the course. With a maximum of 20 points in each test, there is a pattern of improvement in the post-tests performance compared with the pre-tests. Table shows mean scores. Most participants have expressed satisfaction with the course. Conclusions: Results show improvement in learning. More participants are being recruited. The workshops will hold at after the online modules.
Implementing a quality improvement curriculum for medical oncology residents: A pilot study at the Ottawa Hospital Cancer Centre. First Author: Stephanie Yasmin Brule, The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada

Background: With increasing cancer care costs and demands in Canada, quality improvement (QI) efforts are urgently needed. Yet no formal QI education exists in the Canadian Medical Oncology setting. We created an Oncology-specific QI curriculum and sought to assess its feasibility and efficacy among Medical Oncology residents. Methods: In this prospective, pre-experimental pilot study using a pre-post curriculum design, Medical Oncology residents at The Ottawa Hospital Cancer Centre participated in a new QI curriculum. It consisted of four 2-hour sessions encompassing a combination of didactic and interactive learning. The primary measures were self-assessment of confidence in QI skills with the Self-Assessment Program (SAP) and objective assessment of QI knowledge with the revised QIKAT (QIKAT-R). The SAP and QIKAT-R were completed at baseline and post-curriculum. The primary outcome was feasibility of the educational approach. Results: Five Medical Oncology participated, while four (80%) completed the assessments at both timepoints. Self-assessment in the skills needed to execute a process improvement project improved with participation in the curriculum. Mean SAP scores improved from 19.6 pre-curriculum to 33.5 post-curriculum. SAP scores improved for each of the 10 quality improvement skills evaluated. Objective assessment using the QIKAT-R also improved post-curriculum, with a mean score of 17 pre-curriculum and 24 post-curriculum. Mean scores of each domain of “Aim, Measure, and Change” evaluated by the QIKAT-R improved. Conclusions: Self- assessed confidence and objective knowledge in QI concepts in Medical Oncology residents improved after participation in this Oncology-specific QI curriculum. Feasibility of this approach was demonstrated, and therefore a larger scale study will be implemented in the future.

Simulated patient encounter to assess and improve fellows’ ability to manage chemotherapy infusion reactions. First Author: Danielle Elise Zimmerman, University of Florida Health, Gainesville, FL

Background: Medical educators have adopted simulation-based exercises (SBEs) because studies of their use in the aviation industry and other technical fields have shown that they reduce human error. While use of simulation has increased in undergraduate and graduate medical education, it hasn’t been used as frequently in educating subspecialty fellows. Fewer than 5% of participants in a survey of different subspecialists indicated that simulations were part of their fellowship curriculum (1) even though simulation-based training is an ACGME program requirement (2). Chemotherapy infusion reactions (CIRs) occur with about 5% of all cytotoxic chemotherapies and even more frequently with biologics (3). These CIRs present significant morbidity and cost. HFS improves knowledge and confidence in medical trainees (4). Therefore, I designed a high fidelity simulation (HFS)-based curriculum to measure fellows’ current medical knowledge and provide a mechanism for gaining increased understanding and confidence. Across subspecialty graduation medical education, only one SBE with IRs has been performed, and that project aimed only to measure existing knowledge (5). This project aims to measure oncology fellows’ knowledge of and confidence in CIR management, measure attitudes regarding SBEs, measure improvement in knowledge following the SBEs, and assess for changes in behavior (management of CIRS) that may occur following these interventions. Methods: The HFS takes place in the VA Hospital Interdisciplinary Simulation and Education Center, which consists of a programmable mannequin that can “talk” through a speaker and convey physical exam signs in an “outpatient clinic.” Participants will interact with the mannequin, who will be a patient experiencing a paclitaxel infusion reaction. An evaluator will be grading the participant’s actions with an OSCE style checklist. Immediate debriefing will be followed by a didactic. Participants will complete post-intervention surveys regarding their confidence in and knowledge of management of CIRS. Participants will later be evaluated on their attitudes regarding the simulation, their knowledge of CIR management, and will also provide critique of the same interaction done by another provider. These HFS-based activities will allow evaluation of fellows’ current knowledge of and comfort with CIRS, fellows’ attitudes regarding the intervention, improvement in knowledge occurred following the intervention, and anticipated change in management.
Neoadjuvant chemotherapy in high-risk soft tissue sarcomas: Final results of a randomized clinical trial from the Italian Sarcoma Group, the Spanish Sarcoma Group (GES), the French Sarcoma Group (FSG), and the Polish Sarcoma Group (PSG). First Author: Alessandro Gronchi, Sarcoma Service, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

**Background:** A ISG randomized trial on 5 cycles of adjuvant epirubicin+ ifosfamide (EI) versus no chemotherapy suggested an OS benefit in localized high-risk STS (JCO 2001;19:1238). A subsequent trial showed no difference between 5 cycles of the same neoadjuvant regimen (JCO 2012;30:850). The aim of this trial was to compare 3 cycles of EI versus a HT regimen: gemcitabine-docetaxel in undifferentiated pleomorphic sarcoma (UPS), trabectedin in high-grade myxoid liposarcoma; high-dose prolonged-infusion ifosfamide in synovial sarcoma (SS); etoposide+ifosfamide in malignant peripheral nerve sheath tumors (MPNST); gemcitabine+dacarbazine in leiomyosarcoma (LMS). Patients had localized high-risk (grade ≥ 3; size ≥ 5 cm) STS of extremities or trunk wall. Primary end-point was Disease Free Survival (DFS). The final analysis was planned after the observation of 130 events. This allows an 80% power to detect a significant difference at the 5% 2-sided level, if the true HR is 0.6 in favor of EI, as shown by the interim analysis (Lancet Oncol 2017;18:812-822). Results: From May 2011 to May 2016, 287 patients were randomized (57 = UPS; 65 = myxoid liposarcoma; 70 = SS; 27 = MFNST; 28 = LMS). The median follow-up was 51.75 months for the alive patients (IQ 28.03). The DFS and OS probability at 5 years were 51.75% and 58.7% (49.5- 66.7%) (HR = 1.01, 95% CI 0.71-1.44, p=0.954) in RT/S versus S groups. In the sensitivity analysis, 3-year ARFS was 66.0% (57.1-73.5%) and 58.7% (49.6-66.7%) in RT/S versus S groups (HR = 0.84, 95% CI 0.58-1.21, p=0.340). In the LPS subgroup, 3-year ARFS (sensitivity analysis) was 71.6% (61.3-79.6%) and 60.4% (49.8-69.5%) in RT/S versus S groups (HR = 0.64, 95% CI 0.40-1.01, p =0.049). Conclusion: STRASS failed to demonstrate a benefit of pre-operative RT for RPS. In the exploratory analysis, pre-operative RT may benefit the LPS subgroup. Funding Source: EORTC and EUROSARC FP7 278472. Clinical trial information: NCT01710176.

Preoperative chemoradiation +/- pazopanib in non-rhabdomyosarcoma soft tissue sarcoma (NRSTS): A report from Children’s Oncology Group in collaboration with NRG Oncology. First Author: Aaron R. Weiss, Maine Medical Center, Portland, ME

**Background:** Pazopanib is a multi-targeted tyrosine kinase inhibitor with activity in advanced soft tissue sarcoma. ARST1321 is a phase II study designed to compare the near complete pathologic response rate (≥ 90% necrosis) of preoperative chemoradiation +/- pazopanib in children and adults with intermediate/high-risk energy-sparing NSTS. Methods: ARST1321 is a jointly designed COG and NRG Oncology study that opened to enrollment in July 2014. Eligible adult (>18 years) and pediatric (<18 years) patients with unresected, newly diagnosed truncal/extremity NRSTS were enrolled into the Chemotherapy Cohort (>5 cm, grade 2-3, protocol-designated chemotherapysensitive histology). Following a dose-finding phase, patients were randomized to receive (Regimen A) or not receive (Regimen B) pazopanib (>18 years: 350 mg/m²/day; >18 years: 600 mg/day) in combination if ifosfamide (7.5 gm/m²/cycle) and doxorubicin (75 mg/m²/cycle) + 45 Gy preoperative RT followed by primary resection at week 13, then adjuvant chemotherapy. Results: As of June 30, 2018, 81 eligible patients were enrolled and randomized. Week 13 response is available for 42 patients (60% of expected information). The rate of ≥ 90% pathologic necrosis was 58.3% for Regimen A and 22.2% for Regimen B. Based on the significance level of 0.081 (for the second efficacy analysis with overall one-sided significance level of 0.20, power of 0.80, and O’Brien-Fleming-type cumulative error spending function), the 83.8% confidence interval for the difference was between 16.5% and 55.8%. At this predetermined interim analysis, the efficacy bound was crossed indicating that Regimen A is more efficacious than Regimen B. Given these findings, enrollment was stopped. Grade 3/4 toxicities were 73.8% for Regimen A and 29% for Regimen B with neutropenia, thrombocytopenia and febrile neutropenia being the most common toxicities. Conclusions: The rate of near complete pathologic response was significantly greater with the addition of pazopanib to preoperative chemoradiation in children and adults with intermediate/high risk NRSTS. The comparison of survival outcomes requires longer follow-up. Clinical trial information: NCT02180867.

Safety and efficacy of tazemetostat, a first-in-class EZH2 inhibitor, in patients (pts) with epithelioid sarcoma (ES) (NCT02279034). First Author: Silvia Stacchiotti, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

**Background:** ES is a rare soft tissue sarcoma that metastasizes in approximately 30% to 50% of cases. More than 90% of ES tumors lack expression of EZH2, an important component of epigenetic regulation. Loss of EZH2 function allows another epigenetic modifier, EZH2, to become an oncogenic driver conferring resistance to conventional chemotherapy. Tazemetostat, a selective inhibitor of EZH2, has demonstrated tumor regression and favorable safety in phase 1/2 trials. Methods: Data from a phase 2 open-label, multicenter trial of pts with locally advanced or metastatic ES are reported. Efficacy was assessed with primary and secondary endpoints including objective response rate (ORR) by RECIST 1.1, disease control rate (DCR; objective confirmed response of any duration or stable disease (SD) lasting ≥32 weeks), duration of response (DOR), progression-free survival (PFS), overall survival (OS); safety and tolerability were also evaluated. Results: As of September 17, 2018, 62 IN1-negative ES pts were enrolled and treated with tazemetostat 800 mg BID. The median number of prior lines of therapy was 1 (range: 0-9). There were 9/62 (15%) confirmed partial responses (PRs) with an ORR of 15% and DCR of 26%. The DOR ranged from 7.1+ weeks to 103.0+ weeks (median: not reached) with a median OS of 82.4 weeks (95% CI: 47.4, not estimable) for all 62 pts. Tazemetostat was generally well tolerated. Treatment-emergent adverse events (TEAEs) were generally mild to moderate with the most commonly reported adverse events (AEs; ≥10% incidence) regardless of attribution being fatigue (24/62; 39%), nausea (22/62; 35%), and cancer pain (20/62; 32%). Any treatment-related TEAEs of grade ≥3 were reported in 10/62 (16%) pts. TEAEs grade ≥3 reported in ≥2 pts included anemia (6%) and decreased weight (3%). There were no drug-related deaths and a low discontinuation rate (1.7%). Conclusions: In the largest prospective clinical trial of ES to date, tazemetostat achieved disease control in 26% of pts with advanced ES who entered this study. Durable clinical response of the drug was documented. Tazemetostat demonstrated favorable safety with few pts with treatment-related AEs grade ≥3. Clinical trial information: NCT02601950.
Background: The oncogene cyclin-dependent kinase 4 (CDK4) is amplified in > 90% of de-differentiated liposarcomas (DDLS). We previously demonstrated that treatment with the CDK4 inhibitor abemaciclib results in favorable progression-free survival (PFS) in DDLS. Abemaciclib is a newer and more potent CDK4 inhibitor. This single-arm phase 2 study was designed to test the activity of abemaciclib in DDLS. Methods: Participants were adults with advanced DDLS, measurable disease by RECIST 1.1, any (or no) prior therapy, and progression by RECIST in the 6 months prior to study entry. The primary endpoint was PFS at 12 weeks. Based on historical data, promising drugs have 12-week PFS of ≥ 40% and not meeting ≥ 20%. This study would be positive if 12-week PFS was ≥ 60%. The study was approved by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center and all patients provided written informed consent. The study was registered at Clinicaltrials.gov (NCT02846987) and study drug was provided by Eli-Lilly.

Results: Treatment was abemaciclib 200 mg by mouth twice daily continuously. 30 patients were treated and 29 were evaluable for the primary endpoint. Patient characteristics: Median age 62 (range 39-88), 60% male.

Lines of prior therapy: 0 (50%); 1 (33%); 2 (17%). The most common TRAEs were diarrhea (74%), hand-foot syndrome (58%), fatigue (46%), hy-

pertension (46%), weight loss (38%) and oral mucositis (28%), with 33 (66%) pts requiring dose reductions, 25 (50%) treatment interruptions and no cabo-related deaths.

Conclusions: EORTC 1317 met its primary endpoint. Ongoing, with 5 pts >1 yr and 2 pt >2 yrs on Rx (all ongoing). Other IA outcomes: median DOR 9.4 months (95% CI: 5.2-13.6), median PFS 30.4 weeks (95% CI: 28.9-NE). There was one partial response. A 36% decrease in tumor size by RECIST failed to meet the criterion for partial manageable toxicity. Updated response data and results of paired tumor primary endpoint were not achieved in 40 pts (80%, 95%CI 66-90%). Median progression-free survival was 76% (95% CI 57-90%). Median PFS was 30.4 weeks (95% CI 28.9-NE). The most common (≥10%) TRAEs were diarrhea (32%), the most common (≥15%) hematologic TRAEs: anemia (44%) and thrombocytopenia (18%). Pneumonitis (15%) was G1/G2. The most common (≥10%) G3 TRAEs: mucositis (18%), anemia (12%); No grade ≥4 TRAEs. TSC1 or TSC2 mutations occurred in 5 and 9 (no overlap) of 25 pts with known mutational status, respectively. PR was seen in 100% of pts with TSC2 mutation, 20% (1/5) pts with TSC1 mutation, and 9% (1/11) pts without mutation in TSC1 or TSC2. P < 0.0001 (2x3 Fisher exact test). PR was significantly higher in pts with TSC2 mutations vs pts without mutation in TSC1 or TSC2. P < 0.0001 (Fisher exact test). Disease control (PR+SD) was seen in 93% (13/14) pts with TSC1 or TSC2 mutation, 75% (6/8) pts with TSC1 mutation in TSC1 or TSC2, P = NS. Preliminary IA outcomes showed that EORTC 1317 treatment of PEComa resulted in substantial and durable responses with manageable toxicities. TSC2 mutations were associated with IA response. Clinical trial notification: NCT02494570.
11008 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Phase II trial of gemicitabine (G) with pazopanib (P) or gemicitabine with docetaxel (T) in advanced soft tissue sarcoma (STS). First Author: Neeta Somadhal, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: P is a multi-tyrosine kinase inhibitor with efficacy in many sarcoma subtypes. We designed a trial to assess the benefit of adding P to G as an alternative regimen to the commonly used combination of G+T in pts with STS (NCT01593748). Methods: We performed an open-label, randomized phase 2 trial in pts with advanced non-adipocytic STS who had received prior anthracycline based therapy. Pts were assigned (1:1 stratified randomization based on leiomyosarcoma and prior pelvic radiation) to receive G 1000 mg/m² on days 1 and 8 with P 800 mg daily or G 900 mg/m² on days 1 and 8 and T 100 mg/m² on day 8, repeated q 3 wks. The primary objectives were estimating median PFS and rate of grade ≥3 adverse events (AEs). Secondary objectives included estimating the hazard ratio (HR) and response rates. Cross-over was allowed for RECIST progression. Sample size of 90 was derived based on the precision of 95% confidence intervals (CI) for estimating toxicity and PFS in each arm. Results: A total of 90 pts enrolled; 45 on each arm. Pt characteristics and results are detailed in Table. Median PFS was 4.1 months for each arm (p=0.3, based on stratified log-rank test). The clinical benefit rate (PR+SD) was 29% for each arm (p=0.99, based on Fisher's exact test). The rate of related grade ≥3 AEs were 20.6% with G+T and 19.9% with G+P. Related grade ≥3 AEs occurring in ≥10% of pts (G+G+P): anemia (36, 20), fatigue (29, 13), low platelets (56, 51), low neutrophils (20, 49), AST increase (2, 13) and hypertension (2, 20). Conclusions: This study demonstrates comparable efficacy between G+P and G+T, suggesting that G+P can be considered for second-line therapy in advanced non-adipocytic STS. Pt. Characteristics and Results. Clinical trial information: NCT01593748.

11010 Clinical Science Symposium, Mon, 11:30 AM-1:00 PM

Pilot study of NKTR214 and nivolumab in patients with sarcomas. First Author: Sandra P. D’Angelo, Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Monotherapy checkpoint inhibitors have minimal efficacy in most patients with metastatic sarcoma. NKTR-214 is a CD122-preferential IL-2 pathway agonist that activates and expands natural killer and CD8+ T cells. Phase I/II data demonstrated the safety and efficacy of nivolumab plus NKTR-214 in multiple tumor types. A trial of NKTR-214 plus nivolumab was initiated in patients with selected sarcomas. Methods: To date, a multi-arm, single center, phase I/IIb trial enrolling patients (pts) failing prior regimens within 9 cohorts: leiomyosarcoma (LMS), undifferentiated pleomorphic sarcoma (UPS), dedifferentiated liposarcoma (DDLPS), chondrosarcoma (CS), osteosarcoma (OS), angiosarcoma (AS), alveolar soft part sarcoma (ASPS), synovial sarcoma/small blue round cell and other. Pts received NKTR-006mg/kg with nivolumab 360 mg every 3 weeks. Primary endpoint was objective response rate (ORR), secondary endpoints were adverse events (AEs), progression-free, overall survival (PFS,OS) and clinical benefit rate (CBB). Results: Enrollment completed with 100 patients in cohorts below. 50 pts enrolled (median age 58, range 14-80), 54% female. Median follow-up time is 13m. 50% of patients were refractory prior lines of therapy. Grade 3/4 treatment related adverse events occurred in 26% of patients. 2% of patients stopped due to AEs. Median time to response was 3.8 months (95% CI: 2.0, 5.0). Responses seen in LMS, UPS, dedifferentiated CS; on-going in UPS/CS. Conclusions: NKTR-214 and nivolumab is well-tolerated, with improved clinical outcomes observed compared to historical controls. This is consistent with findings in other cancers, such as head & neck, where improved clinical outcomes were observed without significant increase in RR by RECIST. A randomized trial of Dox+P should be carefully considered in light of recent negative trials in STS. Clinical trial information: NCT02888655.

11011 Clinical Science Symposium, Mon, 11:30 AM-1:00 PM

A phase II randomized study of CMB305 and atezolizumab versus atezolizumab in NY-ESO-1+ soft tissue sarcoma. Analysis of immunogenicity, tumor control, and patient survival. First Author: Sant P. Chawla, Sarcoma Oncology Research Center, Santa Monica, CA

Background: CMB305 (C) is an immunotherapy designed to generate an anti-NY-ESO-1 immune response (IR). C consists of a dendritic cell-targeting lentiviral vector encoding NY-ESO-1 gene (LV305), and a TLR-4 agonist (MO) and response rate (RR) of 14%. Dox sensitizes tumors to Pem through calreticulin release and killing of immunosuppressive cells. Thus we hypoth-
A three-gene signature to predict survival in pediatric osteosarcoma (OS) to follow patients toward liquid biopsy: A collaborative work in OS2006 protocol. First Author: Natacha Entz-Werler, Pediatric Oncology Department, CHRU Strasbourg, Strasbourg, France

Background: The survival of pediatric OS is stable worldwide since two decades. The management of OS is lacking new approaches to classify children according to the molecular type and adapt subsequent therapies. Therefore, to improve our molecular study, using allelotypeing, quantitative PCR (qPCR) and droplet digital PCR (ddPCR), to determine the survival impact of molecular profiling in the initial tumor biopsy, in the tumor resection after neoadjuvant chemotherapy and on circulating DNA at different treatment steps. The gene panel based on biomarkers of bone dedifferentiation was already identified in the large tumor cohort of the French national protocol OS94 and demonstrated a significant prognostic impact of 3 genes MET, TWIST and APC. To go further and understand its significance throughout protocols, the same study was performed in OS2006 tumors. Methods: We applied retrospectively in the cohort of OS2006 protocol (135 patients) the same molecular assessment comprising the targeting of those 3 genes with 3 techniques evaluating their rearrangement by allelotype, their copy number variations by qPCR and ddPCR. A preliminary cohort of 20 patients with liquid biopsies at diagnosis, before surgery and at the end of chemotherapy was screened by ddPCR. Results: We were able to determine frequent rearrangements in the regions containing these 3 genes and a statistically significant correlation was made between the presence of a gene rearrangement and a worse outcome. The 3-gene signature was significantly predicting the outcome of more than 85% of patients diagnosed for an OS. Furthermore, the concordance of those genes’ rearrangements in the primitive tumor after neoadjuvant chemotherapy comparatively to the initial biopsy was correlated to a higher risk of relapse. This 3-gene signature was also used for assessment of residual disease (RD) in liquid biopsies and was able to determine before tumor surgery the level of RD. Conclusions: This molecular signature should be applied prospectively to help liquid biopsy to provide evidence that this approach is a powerful tool to be used in pediatric OS follow up to determine early relapse or progression.

Clinical activity of pembrolizumab (P) in undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated/pleomorphic liposarcoma (LPS): Final results of SARC028 expansion cohorts. First Author: Melissa Amber Burgess, University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA

Background: Immune checkpoint inhibitors have demonstrated activity in most tumor types in recent years. The activity in sarcomas is more limited. In the multicenter phase II study, SARC028, the anti-PD-1 antibody, P, demonstrated objective responses that were largely restricted to UPS and LPS subtypes. We now report outcomes from 2 expansion cohorts of SARC 028 in advanced UPS and LPS. Methods: To further confirm the clinical activity of P in UPS and LPS, we enrolled an additional 30 pts in each of 2 expansion cohorts for a total of 40 UPS and 40 LPS pts. Primary endpoint was investigator-assessed response by RECIST v1.1. Secondary endpoints were safety, progression-free survival (PFS), 12-week PFS rate, and overall survival (OS). An ORR of 25% was considered clinically acceptable, and < 10% was considered to show lack of efficacy. P was to be considered a success if 8 or more of 40 enrolled patients had a PR or better (1-sided α = 0.042, 82% power). Pts age ≥18 with advanced, refractory UPS or LPS received 200 mg of P IV every 3 weeks until progression or unacceptable toxicity. Results: Preliminary results from the first 10 pts in each of the UPS and LPS cohorts have been reported. We now present summary data after enrolling an additional 30 pts in each cohort. The ORR in the UPS cohort was 23% (9/40), with an additional 5/30 PRs observed in the expansion cohort (total 2 CRs, 7 PRs). In the UPS cohort, the ORR was 10% (4/39 evaluable pts), with an additional 2/30 PRs observed (total 4 PRs). Results of previous study showed high objective response but short-term activity of apatinib in advanced osteosarcoma. Given the recent success of immunotherapies, combinations of antiangiogenics with immunotherapy have become an attractive strategy. We aimed to investigate the activity of apatinib in combination with camrelizumab in patients with inoperable high-grade osteosarcoma progressing after chemotherapy. Methods: We did this open-label phase 2 trial in Peking University People’s Hospital. We enrolled patients ≥14 years of age with advanced osteosarcoma progressing after chemotherapy. Patients received 500 mg apatinib orally taken once daily plus 200 mg camrelizumab intravenous infusion every 2 weeks until disease progression or unacceptable toxicity. The primary endpoint was 6 month progression-free survival (PFS). All patients were enrolled in this trial. This result is registered with ClinicalTrials.gov. (NCT03359018). Results: We enrolled 41 patients between January 1, and September 4, 2018. 20 (48.8%, 95%CI 32.8%-64.8%) of 41 patients were progression free at 6 months. Until final follow-up, the objective response rate was 21.9% (9/41). And the 6-m PFS rate and 4-m PFS rate were 54.32% (95% CI 37.62%-68.33%) and 70.00% (95% CI 53.24%-81.73%) respectively. Median PFS was 6.50 (95% CI 4.23-7.50) months while the median OS has not reached yet. And there were no statistical differences in the response rates or PFS between different PD-L1 expression groups (P=0.153 and 0.231). Whereas target lesions with only PD-L/L1 positive tumor cells had obviously longer than lesions located at other places (P=0.001). We also summarized all those lesions’ progression patterns as follows: slow pulmonary lesions’ progression(N=7), stable disease with lung but new lesions outside lung(N=4) and bone lesions’ progression(N=2). In which we found that there was obvious difference in PFS (P=0.009) between different progression groups.Toxic effects led to dose reductions, or short interruptions, or both in 20 (48.78%) of 41 patients. There were no treatment-related deaths. Conclusions: The combination of apatinib and camrelizumab obviously prolonged PFS than single apatinib in the treatment for patients with advanced osteosarcoma progressing after chemotherapy. Those with pulmonary metastatic lesions obviously had longer PFS. Whether patients benefit from overall survival needs further observation. Clinical trial information: NCT03359018.
Background: Sarcoma cells are most immunogenic earlier in the disease course and prior to treatment when the immune system can recognize and destroy them. Hypothesis: Immune checkpoint inhibitors would be most effective when given as first-line therapy. Methods: This is an IRB-approved, dose-seeking Phase 1/2 protocol using defined doses of I (1 mg/kg i.v. q 12 weeks), N (3 mg/kg i.v. q 2 weeks) and escalating doses of T (1.0, 1.2, 1.5 mg/m² i.v. q 3 weeks), employing the “Cohort of Three” design, followed by a Phase 2 using the MTD of trabectedin. Results: Nine subjects were treated in Phase 1 of the study, and 31 subjects in Phase 2. Safety analysis; at Dose 1: Grade 3 treatment-related adverse events (TRAEs) included fatigue (n = 1), increased TSH (n = 1), At Dose 2, Grade 4 TRAEs included thrombocytopenia with bleeding, DLT (n = 1), increased CK (n = 1); Grade 3 TRAEs included anemia (n = 1), myalgia (n = 1), increased TSH (n = 1), decreased TSH (n = 1), increased AST (n = 1). Efficacy analysis (evaluable patients): At Dose 1: Disease Control Rate (DCR = CR, PR, SD) was 67%, median PFS, 18 weeks; median OS, 50 weeks; At Dose 2; PR (n=1), DCR 60%, median PFS, 24 weeks; median OS, > 46 weeks. At Phase 2, MTD Dose 2 (PUPS): Safety analysis (n = 31); Grade 3 TRAEs included fatigue (n = 2), increased ALT (n = 1), hyperglycemia (n = 1), hyperuricemia (n = 1), dehydration (n = 1), rash (n = 1), port cellulitis (n = 1), psoriasis exacerbation (n = 1), increased TSH (n = 1), decreased hemoglobin (n = 2), neutropenia (n = 1). Efficacy analysis (N = 23 evaluable): PR (n=2); UPS, 1 synovial sarcoma, 1 liposarcoma, 1 leiomyosarcoma), BORR 22%, DCR 96%. Median PFS and OS not yet reached. Dose 2 was selected as the MTD for Phase 2. Treatment doses were selected: Dose 2 tumor showed 80% necrosis and a greater number (30%) of CD8+ killer T cells, in the TME compared to archived pre-treatment tumor. Conclusions: These data suggest that the SAINT protocol (1) is safe with manageable adverse events, with no additive toxicity, and (2) may control tumor growth. Phase 2 of the study is on-going. Clinical trial information: NCT03138161.

Background: Retrospective genomic analysis of archived liposarcoma (LPS) and leiomyosarcoma (LMS) samples from phase III trial of trabectedin (T) versus dacarbazine (D). First Author: Shibu Thomas, Janssen Research and Development, Spring House, PA

Methods: To explore tumor genomic associations with response/resistance and potential pre-TKI biomarkers to inform prospective LPS and LMS tumor samples. Methods: Genomic alterations [single nucleotide variants (SNVs) or gene copy number variations (CNVs)] were identified using whole exome sequencing (WES) of archived tumor samples from NCT01343277. Association of tumor subtype or genetic alterations with clinical outcomes including maximum tumor volume reduction (MTVR), overall survival (OS), progression-free survival (PFS) and treatment cycles was assessed using multidimensional Cox proportional hazard models. Results: A total of 178 uterine LMS (ULMS), 121 non-uterine LMS (non-ULMS), 60 de-differentiated LPS (ddLPS), 40 myxoid LPS (mLPS) and 14 pleomorphic LPS (pLPS) tumors underwent WES. Homozygous deletions (HD) were observed at relatively high frequency in 4 genes -AC092821.1 (36.4%), LCE3B (35.4%), LCE3C (32.1%), HEATR4 (24.4%) across all sarcoma subtypes. These genes are involved in cell proliferation, innate immune response and differentiation. HD in any of these genes was associated with improved OS in the T treatment arm. Tumors with MDM2 amplifications showed worse clinical outcome in the T treatment arm in terms of PFS and OS consistent with T-mediated induction of p-53 dependent apoptosis (Table). Conclusions: HD in any of 4 genes was associated with longer OS in patients treated with T. This molecular signature, which covers 40% of total sarcoma and 0.4% of overall solid tumors population, warrants further prospective validation. Novel genetic alterations and clinical associations.
Pathologic discordance in sarcomas: Prospective comparison of external and sarcoma center pathologic diagnosis. First Author: Mark A. Eckardt, Department of Surgery, Yale School of Medicine, New Haven, CT

Background: With more than 80 different histologic subtypes, sarcomas are a unique pathologic challenge. As therapeutic decisions have become histology-specific, obtaining an accurate pathologic diagnosis is critical in guiding treatment decisions. The aim of this study is to determine the discordance between the diagnosis rendered by an external non-specialized pathologist and pathologic re-review by a specialized sarcoma pathologist at a high-volume sarcoma center. Methods: Patients who presented at the UCLA Multidisciplinary Sarcoma Conference (MSC) in 2017 that had a pathologic diagnosis from an outside facility were included in this study. All specimens underwent pathologic re-review at UCLA by an experienced sarcoma pathologist. The pathology was classified as concordant (identical diagnoses), minor discordance (difference with minor impact on prognosis/therapy) and major discordance (difference with significant impact on prognosis/therapy).

Results: 1350 patients were presented at the UCLA MSC in 2017. Of the 635 new patients, 196 presented with an outside pathologic diagnosis and underwent pathologic re-review at UCLA. 44% (n = 87) were concordant, 22% (n = 43) had minor discordance, and 34% (n = 66) had major discordance. Major discordance included substantial discrepancies in histologic subtype (n = 24, 36%), benign/malignant mismatch (n = 23, 35%), diagnostic from non-diagnostic (n = 10, 15%), major grade (n = 8, 12%), and major grading discrepancy was most often seen in biopsies (n = 27, 32%), incisional (n = 30, 44%) as compared to resection (n = 9, 21%). Conclusions: 56% of external non-specialized sarcoma pathologic diagnoses were discordant from specialized sarcoma pathologist review, 34% of which were major discordances. Pathologic re-review of a presumed sarcoma by a specialized sarcoma pathologist is critical for both patient care and investigational studies.

ALT-GIST: Randomized phase II trial of imatinib alternating with regorafenib for previously treated GIST. First Author: Desmond Yip, The Canberra Hospital, Canberra, Australia

Background: Imatinib (IM) is the standard first-line treatment for advanced GIST and regorafenib (REG) is approved for third line therapy. We studied an alternating regimen of IM and REG. Apatinib is a potent and selective kinase inhibitor with broad activity against oncogenic KIT/ PDGFRA mutations, including PDGFRA D842V and other primary or secondary resistance mutations. Updated results from the phase I NAVIGATOR (NCT02508532) study of apatinib in pts with advanced GIST are presented. Methods: Adult pts with unresectable PDGFRA D842V or other mutant GIST who progressed on imatinib and ≥1 other tyrosine kinase inhibitor (TKI) were treated with oral, daily, continuous apatinib. Adverse events (AE) and response by mRECIST 1.1 per centralradiology were assessed. Safety from the overall population (30-600 mg doses) and efficacy in the response evaluable 4L+ and PDGFRA Exon 18 gastrointestinal stromal tumors (GIST). First Author: Michael C. Heinrich, Portland VA Health Care System and Knight Cancer Institute, Oregon Health & Science University, Portland, OR

Results: Seventy-six eligible patients (ALT 40, IM 36) enrolled from June 2015 to September 2018 were evaluable for the OTR. The patients (pts) were predominately male (n = 51, 67%). Median age was 58 (range, 24-81) in the ALT arm and 65 (range, 35-82) in the IM arm. KIT was mutated in 63, PDGFRα in 2, and wildtype in 5 tumors. Relative dose intensity in the ALT arm 102% for IM and 82% for REG and was 93% in the IM arm. Median follow-up time was 19.3 months (range 6.0-40.0). The best responses to the ALT and IM treatments were similar at 9 months, 1 vs 0 pts had complete response, 23 vs 23 partial response, 15 vs 13 stable disease, and the OTR was 60% (95% CI, 45-74%) and 64% (95% CI, 48-78%), respectively. Seven (18%) pts in ALT arm and 10 (28%) in IM arm discontinued treatment due to progressive disease. Seven pts (18%) in the ALT arm stopped protocol therapy due to unacceptable toxicity, and none in the IM arm. Fifteen (38%) pts in the ALT arm and 14 (38%) in the IM arm had serious adverse events, mostly grade 3. Progression free survival (PFS) at 1 year was ALT 0.86 (95% CI 0.69, 0.94) and IM 0.83 (95% CI 0.65-0.92), p logrank = 0.57. Conclusions: There was no meaningful difference in the primary endpoint of OTR between the two arms and in this first in human study, there were no unexpected safety signals. The study is ongoing and other endpoints will be reported in due course. Clinical trial information: ACTRN12614000950662.
Background: Ewing sarcoma (ES) is the second most common bone cancer in children and young adults. The prognosis of recurrent or metastatic ES is poor, with a 5-year event-free survival <30%. Early metastatic ES is characterized by bone locations involving ETS transcription factors (EWS–FLI and EWS–ERG translocations are the most common). Secondary somatic alterations in ES are infrequently described. Aberrations in fibroblast growth factor receptor 4 (FGFR4), a receptor tyrosine kinase that plays an important role in cellular processes, have been shown to contribute to carcinogenesis in different types of cancer. More recently, the FGFR4-Gly388Arg (G388R) single nucleotide polymorphism (SNP), with the substitution of arginine instead of glycine in the transmembrane domain of the receptor, is found to significantly increase the risk of breast and prostate cancer. Mouse embryonic fibroblasts derived from knock-in strain of homologous FGFR4-G388R mice display a transformed phenotype, and TGFα-induced mammary carcinogenesis in this strain is significantly enhanced. The association between FGFR4 G388R SNP and ES has not been evaluated. We evaluated the frequency of FGFR4 G388R and whether comprehensive genomic profiling (CGP) might uncover additional, potentially targetable, genomic alterations (GA) in ES.

Methods: Tissue from 253 patients with ES was assayed by hybrid-capture based CGP (FoundationOne Heme, next generation sequencing (NGS), analysis which includes both DNA sequencing of 406 genes and RNA sequencing of 265 genes), performed in the course of clinical care to evaluate GAs, including base substitutions, indels, amplifications, copy number alterations and gene fusions/rearrangements. Tumor mutational burden (TMB) was calculated from a minimum of 1.4 Mb sequenced DNA and reported as mutations/Mb. Microsatellite instability (MSI) status was determined by a novel algorithm analyzing 114 specific loci. Results: CGP identified additional GAs in ES: TPS3 (n= 50, 20%), MLL3 (n=15, 6%), MSH3 (n=14, 5%), ARID1A (n=11, 4%) and FGFR4 (n=3, 1%). FGFR4 G388R SNP was found in almost half of the patients (n=123, 49%). Conclusions: Secondary GAs in TPS3, MLL3, MSH3, ARID1A and FGFR4 were found in more than one third of patients with ES (n=93, 37%). FGFR4 G388R SNP was detected in the majority of patients, and may represent an alternative method of sarcomagenesis. Overall, the frequency of these GAs is significantly greater than previously reported. These GAs may inform the potential for targeted therapies.

Outcomes of extra-skeletal versus skeletal Ewing sarcoma patients treated with standard chemotherapy protocol. First Author: Sameer Salah, King Hussein Cancer Center, Amman, Jordan

Background: Extra-skeletal ewing sarcomas (ES) are rare, and data on outcomes following standard ES chemotherapy protocols are very limited.

Methods: We retrospectively collected data on skeletal and extra-skeletal ES patients who presented with localized disease from January, 2006 to June, 2018. Disease and treatment characteristics were compared between the two groups by the chi-square test. Overall survival (OS) and local recurrence free survival (LRFS) were estimated by the Kaplan-Meier method and compared by the Log-rank test.

Results: A total of 120 patients were included. Twenty-nine (24%) had extra-skeletal and 91 (76%) had skeletal ES. Location was in the extremity in 51 (43%) and non-extremity in 69 patients. Twenty-nine (24%) had extra-skeletal and 91 (76%) had skeletal ES. For extra-skeletal ES, tumors originated from soft tissue in 23 (79%), compared by the Log-rank test. Overall survival (OS) and local recurrence free survival (LRFS) were estimated by the Kaplan-Meier method and compared by the chi-square test. Mean cumulative ifosfamide dose (%*)

Conclusion: Extra-skeletal ES patients are at significantly higher risk of local recurrence.

Interval-compressed vincristine, doxorubicin, cyclophosphamide (VAC), alternating with ifosfamide and etoposide (IE) for adults with Ewing-like sarcoma. First Author: Eric Lu, Knight Cancer Institute, Oregon Health & Science University, Portland, OR

Background: In Children’s Oncology Group trial AEWS0031, VAC alternating with IE administered every 2 weeks rather than every 3 weeks resulted in a superior event-free survival (EFS). In the 2-week dosing group, a median interval of 15 days (mean 17.3) was achieved. Only 12% of patients enrolled in the trial were age 18 and thus the feasibility of interval-compressed VAC/IE for the adult population remains poorly described. We conducted a retrospective analysis of our institutional experience using this regimen.

Methods: Pharmacy administration records at Oregon Health and Science University were reviewed to identify patients age 18+ with Ewing and Ewing-like sarcoma who received VAC/IE q2wk, with first dose between January 1, 2011 and March 2018. Results: 24 patients were identified. Median age was 28 (range 18 to 60). At diagnosis, 67% had localized disease. The most common primary sites were extremity (38%) and pelvis (17%); another 25% had extra-osseous primary tumors. Local therapy included surgery in 50% and XRT in 33% of subjects. The median interval between cycles was 16.7 days (mean 17.5). The median number of admissions for toxicity per patient was 2. The median number of dose delays (toxicity prolonging the 2 week interval) per patient was 4. Early treatment discontinuation occurred in 17%. Cumulative doses are outlined in Table. 5-year overall survival was 41%. 5-year EFS was 52% among patients with localized disease and 0% among those with metastatic disease. Conclusions: For adults with Ewing and Ewing-like sarcoma, chemotherapy administered every 2 weeks is a feasible and effective therapy, without significant dose reduction required. Our results are comparable to prior studies involving a primarily pediatric population.

Mean cumulative doxorubicin dose (%*)

Mean cumulative cyclophosphamide dose (%*)

Mean cumulative ifosfamide dose (%*)

Mean cumulative etoposide dose (%*)

Patients receiving all 7 planned vincristine doses

*Total planned dose: doxorubicin in 375 mg/m2, cyclophosphamide 8400 mg/m2, ifosfamide 63 g/m2, etoposide 3500 mg/m2.

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Background: Non-osteogenic sarcoma of the bone is a rare entity comprising a heterogeneous group of malignant tumors. Clinical characteristics and outcome data are sparse in the literature. We evaluated the characteristics and long-term outcomes of patients (pts) with this disease. 

Methods: Pts with non-osteogenic sarcoma of the bone treated at the Toronto Sarcoma Program from 1987-2017 were identified from our institutional sarcoma database. Patient characteristics (ie: age, gender, tumor size, histology, grade, necrosis, tumor location), treatment modality (ie: surgical management, chemotherapy, radiotherapy), and survival information were collected. Survival was estimated by Kaplan-Meier (log-rank). Multi-variante analysis (MVA) was used to evaluate characteristics for sarcoma specific survival. 

Results: Of 130 pts identified, 106 had non-metastatic disease with a median age of 46 (range 18-89). Male-to-female predominance was 1.5:1. Common histologies were undifferentiated pleomorphic sarcoma (UPS; 42%), leiomyosarcoma (21%), and fibrosarcoma (11%). Tumors were generally high grade (59%) (95%CI:7.00-not reached [NR]). Median sarcoma specific survival was 5.5 years (95%CI:2.52-18.02), and a mOS of 11.72 years (95%CI:7.00-not reached [NR]). Median DFS of 8.13 years (95%CI:2.52-18.02), and a mOS of 11.72 years (95%CI:7.00-not reached [NR]). Median sarcoma specific survival was 5.5 years (95%CI:2.52-18.02), and a mOS of 11.72 years (95%CI:7.00-not reached [NR]). Median DFS of 8.13 years (95%CI:2.52-18.02), and a mOS of 11.72 years (95%CI:7.00-not reached [NR]). Median sarcoma specific survival was 5.5 years (95%CI:2.52-18.02), and a mOS of 11.72 years (95%CI:7.00-not reached [NR]). Median DFS of 8.13 years (95%CI:2.52-18.02), and a mOS of 11.72 years (95%CI:7.00-not reached [NR]). Median sarcoma specific survival was 5.5 years (95%CI:2.52-18.02), and a mOS of 11.72 years (95%CI:7.00-not reached [NR]). Median DFS of 8.13 years (95%CI:2.52-18.02), and a mOS of 11.72 years (95%CI:7.00-not reached [NR]).

Conclusions: Non-osteogenic sarcoma of the bone is a rare tumor entity, with a predominant UPS histology. Patient outcomes are reasonable, with measurable long-term survival. Axial tumor location, absence of chemotherapy, and high-grade disease predict for worse survival outcome. Further evaluation with larger data series is warranted to more fully understand this disease.

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Clinical characterization of patients with SDHC epimutation in gastrointestinal stromal tumors. First Author: Maran Ilanchezhian, National Institutes of Health, Bethesda, MD

Background: Gastrointestinal Stromal Tumors are the most common malignancy in the GI tract. While the vast majority exhibit somatic mutations in KIT and PDGFRA, approximately 15% of GIST patients do not have this feature. This group of KIT and PDGFRA “wildtype” GISTs have in common a negative expression of SDHB when interrogated by immunohistochemistry. Succinate dehydrogenase (SDH) is a conserved enzyme that plays a critical role in cellular metabolism and energy production. A loss in SDH function is a mechanism observed in several types of cancers, and germline SDH mutations are considered a tumor predisposition syndrome. This group has reported that SDH-deficient gastrointestinal stromal tumors often harbor germline mutations in the SDH subunit genes (SDHA, SDHB, SDHC, and SDHD), termed SDHx. There is, however, a defined group that shows lack of SDH expression in the absence of mutation. Methods: We performed targeted exome sequencing on GIST patients’ tumor samples from the NIH GIST clinic and identified 25 SDHx-WT cases. Genome-wide DNA methylation and expression profiling showed SDHC promoter-specific CpG island hypermethylation and gene silencing in these 25 SDHx-WT, SDH-deficient GISTs. Results: Clinical characterization of this cohort revealed that 24 of 25 SDHC-epimutant GISTs occurred in female patients, with a median age of 12 years upon diagnosis. The median tumor size of this cohort of patients was 4.0 cm. Of the 16 patients from whom we were able to obtain complete clinical information, 15 showed epithelioid or mixed-epithelioid morphology. All of them showed negative immunohistochemical staining for SDHB. 15 of 16 patients had multifocal tumors, which is a common finding in this population. Conclusions: The profiling of this cohort provides further insights into the natural history and pathogenesis of SDHC-epimutant GIST tumors.

Neurofibromatosis 1 (NF1) and gastrointestinal stromal tumors (GISTs): Five-year experience from a regional center in United Kingdom. First Author: Venkata Ramesh Bulusu, Addenbrooke’s Hospital, Cambridge, United Kingdom

Background: NF1 is an inherited autosomal dominant condition characterised by multifocal neurofibromas, café au lait spots, Lisch nodules, freckling. GISTs are the most common mesenchymal tumour of the gastrointestinal tract occurring in NF1 patients. We present our 5 year experience of NF1 associated GISTs from a regional centre in United Kingdom. Methods: 15 patients with GISTs associated with NF1 syndrome were identified from the database. Clinical, pathological, molecular and treatment outcomes were analysed. Results: N= 15. Male-3 and female-12. Median age 46 years. 33% were multifocal and 67% unifocal. Primary site Stomach-6.6%, duodenum-33%, small bowel-67%, colon 6.6%. Presenting symptoms: Abdominal pain-47%, anemia/bleed-40% and incidental finding-13%. Tumour size 0.5-23 cm, median 9 cm. Mitotic index 0-15, median 4 mitoses/5mm2. Risk stratification-Low/intermediate risk 15%, high risk 5%. Histology was spindle cell in 87% and mixed in 13%. All GISTs were CD117 and DOG-1 +ve. SDHB expression was preserved in all GISTs. No activation mutations were detected in KIT (exons 9, 11, 13, 17), PDGFRA (exons 12, 14, 18) and BRAF. Treatment: 67% had the primary GIST resected. None had adjuvant imatinib. 6 patients had been treated with tyrosine kinase inhibitors. 1 partial response lasting 1 year of diagnosis. Conclusions: GISTs associated with NF1 syndrome are rare. Median age of diagnosis is a decade earlier than KIT/PDGFRA mutated GISTs. We observed that NF1 associated GISTs occur predominantly in small bowel, are mostly well defined histology and have female preponderance. No durable responses were noted with imatinib or Sunitinib or Regorafenib. All patients with metastatic disease died within one year of diagnosis. Conclusions: GISTs associated with NF1 syndrome are rare. Median age of diagnosis is a decade earlier than KIT/PDGFRA mutated GISTs. We observed that NF1 associated GISTs occur predominantly in small bowel, are mostly well defined histology and have female preponderance. No durable responses were noted with imatinib or Sunitinib or Regorafenib. There is an urgent need for systematic international collaboration to identify druggable pathways/targets in NF1 GISTs. Any trials should be multicentre/multinational to expedite recruitment.

Correlation of imatinib plasma trough concentrations with adverse reaction in Chinese gastrointestinal stromal tumors patients. First Author: Yanzhe Xia, Dept of Pharmacy, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Imatinib is the standard treatment for patients of Gastrointestinal Stromal Tumors (GISTs), but the intra- and inter-variability of imatinib plasma trough concentration (Cmin) is significant. Few studies investigated the association between Cmin and adverse reaction in Chinese GIST patients. The distribution of imatinib Cmin at different adverse reactions, i.e. Cmin with adverse reaction in Chinese GIST patients from a high-volume center were evaluated. Methods: From 1 Jul 2017 to 31 Dec 2018, a total of 400 patients who were under imatinib treatment were prospectively studied. All patients received continuous treatment for at least one month. The primary GIST resected. None had adjuvant imatinib. 6 patients had been scheduled to administer imatinib 100 to 800 mg/d, with continuous similar timing of daily dosage for more than 14 days. The adverse reaction was recorded during regular follow-up at outpatient clinic, and blood sample was collected 2 ± 2 hours to the next dosage of imatinib. Liquid chromatography tandem mass spectrometry was applied to determine the concentration. Adverse reaction grades were referred to CTCAE v4.0. Results: A total of 368 patients who followed the same dose of imatinib with good compliance, and having at least 2 times of tests were investigated. The imatinib Cmin was 384 ± 53 ng/mL, 776 ± 337 ng/mL, 986 ± 327 ng/mL, 1078 ± 498 ng/mL, 1309 ± 712 ng/mL, 1620 ± 469 ng/mL, 2117 ± 597 ng/mL and 3844 ± 987 ng/mL in patients who were administrated with 100 mg/d (n = 3), 200 mg/d (n = 15), 250 mg/d (n = 5), 300 mg/d (n = 80), 400 mg/d (n = 230), 500 mg/d (n = 3), 600 mg/d (n = 22) and 800 mg/d (n = 5), respectively. In correlation analysis, imatinib Cmin was highly correlated with peripheral and limbs edema (p < 0.01), anemia (p < 0.01) and rash (p < 0.01), correlated with diarrhea and conjunctival hemorrhage but not significant. Much higher Cmin was observed in severe adverse reaction (grade 3) of peripheral and limbs edema and rash. There was no correlation between Cmin, the other adverse reaction, nausea, vomiting, muscle cramp or hematopoietic disorders. Conclusions: In Chinese GIST patients, imatinib Cmin at steady state was seems higher than Western populations previous reported, especially in higher doses (>800 mg/d). Imatinib Cmin was correlated with anemia, peripheral and limbs edema, diarrhea and conjunctival hemorrhage, suggesting that imatinib Cmin monitor might be considered when patients were subjected to severe adverse reactions which were caused by excessive imatinib plasma concentration.

Sequenced circulating tumor (ct) DNA to detect the molecular landscape in advanced GIST. First Author: Ciara Marie Kelly, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: Molecular (mol) characteristics-guided precision therapy has well-established utility in GIST management. The GIST mol landscape is poorly represented by selective tumor biopsy (bx) material, especially in metastatic and treatment-refractory GIST. ctDNA can overcome some of the limitations of selective tissue bx specimens and provide comparable or greater genomic information. Here we report an analysis of advanced (adv) GIST. Methods: Next generation sequencing analyses (MSK-IMPACT or custom-capture GIST specific panel) were performed on ctDNA prospectively collected from patients (pts) with adv GIST. MSK-IMPACT was performed on tumor material (archival tissue or paired tissue bx specimens taken in parallel with ctDNA collection from clinical trial participants). The primary objective was to determine the concordance between the mol landscape of GIST identified by sequenced tumor tissue versus ctDNA. Secondary objective was to correlate characteristics of sequenced ctDNA with standard measurements of response assessment. Results: 47 ctDNA samples collected from 25 pts with adv GIST were sequenced using MSK-IMPACT (>400 genes). MSK-IMPACT was performed on archival tumor material. Sequenced ctDNA detected the mutational spectrum of tumor tissue in 48% of cases. In 50% of these cases, ctDNA identified novel treatment-resistance mutations not previously identified in the archival tissues. To optimize sensitivity of detection, a custom-designed GIST specific ctDNA sequencing panel was developed incorporating 19 of the most commonly altered genes observed from MSK-IMPACT analysis performed on >75 imatinib-refractory adv GIST tumor samples. 52 ctDNA samples collected from 30 pts with paired tumor bx samples have been sequenced using the MSK-IMPACT panel. The tumor bx samples have been sequenced using MSK-IMPACT. Results are pending and will be presented. A separate cohort of ctDNA samples serially collected in the setting of a prospective clinical trial are being sequenced. The mol results with correlated treatment response by RECIST will also be presented. Conclusions: ctDNA could detect a broad spectrum of mol heterogeneity and potentially be used as a biomarker to guide precision therapy in adv GIST. Further research is necessary to determine the optimal ctDNA sequencing assay and the appropriate clinical setting to utilize in GIST.

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11037 Post Session (Board #360), Sat, 8:00 AM-11:00 AM
Racial disparity in incidence and survival for gastrointestinal stromal tumors (GIST): An analysis of SEER database. First Author: Mark Bilinya Ulana, University of Nevada, Reno School of Medicine, Reno, NV
Background: Gastrointestinal tumors (GISTS) represent the most common mesenchymal tumors of the gastrointestinal tract. There has been limited data on GISTS incidence and survival disparities between ethnic groups. We assess disparities in incidence and survival among race in the United States in the era of available GIST histologic codes and treatment. Methods: We queried Surveillance, Epidemiology, and End Results (SEER) database for GIST from 2002 to 2015, with diagnostic code 8936. Results: Of the 7,204 patients identified, 4,928 (68.4%) were White; 1,308 (18.2%) African American (AA) and 968 (13.4%) were classified as Other (American Indian/Alaskan Native, Asian/Pacific Islander). The overall incidence rate (IR) was 0.753 per 100,000. IR was highest among AA at 1.372/100,000, but 0.648/100,000 for Whites, 1.075/100,000 for Asians/Pacific Islanders and 0.276/100,000 for American Indians/Alaskan Natives. The GIST incidence was twice as high for AA as for Whites (Rate ratio [RR]: 2.12; 95% CI: 1.98-2.26; p<0.001). Lower proportion of AA underwent surgery as compared to white and Other. Median overall survival (OS) [116 months] and GISTS specific survival (GSS) was significantly lower in AA as compared to White and Other. In multivariate Cox model, belonging to Other had better OS.

Conclusions: Significant racial disparity in incidence and survival for GIST exists, and efforts should be made to bridge this gap and improve outcomes for all races.

GIST Overall Survival for Different Race.

<table>
<thead>
<tr>
<th>African American (reference)</th>
<th>Overall survival (OS)</th>
<th>95% CI</th>
<th>Rate ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>0.88</td>
<td>0.79-0.98</td>
<td>0.018</td>
<td>0.93</td>
<td>0.83-0.87</td>
</tr>
<tr>
<td>Other</td>
<td>0.78</td>
<td>0.66-0.91</td>
<td>0.002</td>
<td>0.81</td>
<td>0.69-0.91</td>
</tr>
</tbody>
</table>

*Other = American Indian/Alaskan Native, Asian/Pacific Islander. GIST = Gastrointestinal stromal tumor.

11038 Post Session (Board #361), Sat, 8:00 AM-11:00 AM
Multi-institutional European single-arm phase II trial of pazopanib in advanced typical solitary fibrous tumors (SFT): A collaborative Spanish (GIE, Italian (ISG), and French (FGST) sarcoidosis group study. First Author: Josefina Cruz Jurado, Hospital Universitario de Canarias, GEICAM Spanish Breast Cancer Group, Santa Cruz de Tenerife, Spain
Background: SFT is a ubiquitous uncommon soft tissue sarcoma with a pronounced hemangiopericytoma-like vascular pattern, exhibiting rich VEGF (tumor and endothelial cells) and VEGFR1/2 (endothelial cells) expression. Pathologists distinguish typical SFT (T-SFT) and malignant SFT (M-SFT) based on mitosis (>4 vs. <4), pleomorphism or necrosis. Yet, not clear boundaries are always seen between both subtypes. We have recently published a phase II trial exploring the activity of pazopanib (P) in M-SFT (Lancet Oncol Dec 2018). Here, we present the outcome of the T-SFT cohort of the same trial. Methods: Most relevant inclusion criteria were: unresectable or metastatic, T-SFT (tumor size from diagnostic time) confirmed by central pathology review before accrual, with evidence of STAT6 overexpression (ICH and FISH and/or NGS), ≥18 years, ECOG 0-2, progressive, measurable disease and no previous antiangiogenic agents. Main endpoint was response rate according to Choi criteria. Central radiological assessment was mandatory. P was administered at 800 mg/d continuously till progression or toxicity. Results: From June 2014 to December 2018, 34 patients were enrolled in this cohort. The median age was 64 y (31-81). At baseline, ECOG 0/1 was distributed as 16/15/3, whereas, locally advanced/metastatic distribution was 11 (32%) and 23 (68%) respectively. At the time of the present analysis, 24 patients were deemed eligible and available for response. Response rates according to local and central assessment were 23/24 (96%), SD 15 (62%), PD 3 (12%) and PR 125 (50%), SD 11 (46%), PD 1 (4%). With a median follow-up of 21 months, the median PFS following local and central assessment were 184 (6.6-30.1) and 9.8 (7.5-12.2) months respectively, both were clearly superior to that previously published in M-SFT cohort (5.57 m). The median of OS was 49.8 months. High tumor burden at baseline > 116 mm, ECOG 1-2 vs 0, and PD by local or central assessment showed significantly worse OS. Metastatic vs locally advanced patients had a similar outcome regarding OS. Conclusions: T-SFT cohort exhibited clearly longer PFS than previous reported M-SFT cohort to pazopanib treatment, and pazopanib showed to improve the historical outcome obtained with chemotherapy in advanced SFT. Clinical trial information: NCT02066285.

11040 Post Session (Board #363), Sat, 8:00 AM-11:00 AM
Immune signature and molecular profiling of radiation-induced sarcoma (RIS). First Author: Eoghan Ruadh Malone, 3601, Dublin, Ireland
Background: RIS is a rare subset of soft tissue sarcoma (STS) with poor prognosis and limited treatment options. We hypothesize that subsets of STS that carry genomic complexity, such as RIS, will have a neoepitope and immune signature that predicts response to immunotherapy as these mutations act as strong antigenic targets for eliciting immune response. Methods: Cases of RIS were identified from an institutional database. Formalin fixed paraffin embedded (FFPE) samples were stained for PD-1, PD-L1, PD-1, CD3, CD4, CD8. Immune scoring was performed. Tumor-infiltrating lymphocytes (TILs) were assessed using a 4-tiered scale: 0 (no lymphocytes); 1 (1-100HFP); 2 (11-50HFP); 3 (51-100HFP); 4 (> 100HFP). TIL staining with PD-1 and PD-L1 was also scored whereby the overall percentage of positive cells on the entire slide was quantified. Tumor DNA was extracted from FFPE samples and underwent whole exome sequencing (WES). Results: FFPE samples from 20 cases of RIS were selected for analysis. PD-1 and PD-L1 expression (threshold set at ≥ 1% positive cells) was seen in 35% and 45% of the cases respectively. CD3+, CD4+, CD8+ T cell infiltration (threshold set ≥ 11 cells HFP) was seen in 45%, 15% and 20% of cases respectively. 12 exomes of unpaired RIS samples were successfully sequenced. The most common histologies were angiosarcoma (n=3), undifferentiated spindle cell sarcoma (n=3), de-differentiated liposarcoma (n=2) and radiation induced spindle cell sarcoma (n=2). Provisional analysis did not reveal any pattern to the relative mutational burden between the RIS’s. There does however seem to be relatively higher rate of mutation than that seen in other cancer subtypes. Half the samples had at least one pathogenic or likely pathogenic variant. Different HRAS mutations were seen in two samples (sarcoma NOS and angiosarcoma) and FGFR4 mutation was present in both samples, both spindle cell sarcomas. Conclusions: To our knowledge this is the first study to investigate the immune profile in RIS. Up to 45% of these tumors were positive for PD1/PDL1 expression, as well as presence of tumour infiltrating lymphocytes. Results from WES demonstrate that RIS may benefit from immunotherapy due to a relatively higher mutational burden.
11041 Poster Session (Board #364), Sat, 8:00 AM-11:00 AM
Retropertioneal soft tissue sarcoma (RTS): Recent outcome improvement and refinement of treatment strategies at a single institution. First Author: Marco Fiore, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Retropertioneal surgery in retropertioneal soft tissue sarcoma (RTS) has resulted in less recurrences and better survival. We investigated whether outcome further improved, after the recent understanding of behavior of different RTS subtypes and introduction of multimodal therapies. Methods: Consecutive primary RTS operated at our center were analyzed comparing 3 periods (2002-2006, 2007-2011, 2012-2016). We included 1119 patients overall and survival analysis with Kaplan-Meier, log-rank test and Cox proportional hazards were used. Results: Overall 437 RTS were operated: 82, 128 and 227 in the 1st, 2nd and 3rd period. Median follow-up was 125, 86 and 39 months. Complete resection (R0/R1) improved from 93.9% to 98.2% (p=0.059), median number of resected organs increased from 2 to 4 (p=0.001). Postoperative morbidity did not change (18.3%, 16.4%, 22.5%; p=0.269). Administration of radiotherapy and chemotherapy (CT) differed over time according to different subtypes. 5 yr OS improved (63.2% to 74.7%, p=0.005), along with a non-significant reduction in LR CCI (18.2% to 16.4%, p=0.379) and no change in DM CCI. At multivariable analysis, study period remained an independent prognostic factor for OS among the other known risk factors (3rd vs 1st period HR: 0.33, p<0.001). Subgroup analysis showed the following associations with better prognostic index: 1. Improvement in 5-yr OS from 55% to 70.7%, p=0.024, and LR (from 45.0% to 19.8%, p=0.060) in G2DDLPS, associated with more high risk RPS subtypes are eagerly awaited.

11042 Poster Session (Board #365), Sat, 8:00 AM-11:00 AM
Pexidartinib for advanced tenosynovial giant cell tumor (TGCT): Long-term efficacy and safety from the phase 3 ENLIVEN and phase 1 PLX108-01 (TGCT cohort) studies. First Author: Hans Gelderblom, Leiden University Medical Center, Leiden, Netherlands

Background: TGCT is a rare, locally aggressive neoplasm of the joint/tendon sheath linked to colony-stimulating factor 1 (CSF1) overexpression. Pexidartinib (pex), a selective inhibitor of CSF1 receptor, KIT, and FLT3-ITD, had a compelling tumor response rate in the TGCT cohort of a phase 1 study (NCT02371369) and in a phase I study (NCT02371369) with a tumor response rate of 12% (39% vs 0%, P< 0.0001) and tumor volume score (TVS) (56% vs 0%, P< 0.0001) in the randomized, 2-part, crossover phase 3 ENLIVEN study (NCT02371369). Updated efficacy and safety with longer treatment are reported. Methods: Patients (pts) were ≥18 yrs with TGCT that was inoperable or for which surgery would likely be associated with unacceptable functional limitations or severe morbidity. Best overall response (complete or partial [CR/PR]) and duration of response (DOR) by RECIST and TVS were assessed by independent central review. Data cutoff was Jan 31, 2018, 16-67 mo after pts’ first dose.

Results: In both studies 130 pts received pex, 61 ongoing at data cutoff. Median treatment duration was 17 mo (1, 60+). CR/PR rates were high and consistent and, together with DOR, improved with prolongation of treatment (Table). Most frequent adverse events were hair color change (75%), fatigue (60%), nausea (45%), arthralgia (38%), AST increase (30%), and diarrhea (30%). In ENLIVEN part 1, 3 of 61 (5%) pts had reversible ALT and AST ≥3× ULN with TBil and ALP ≥2× ULN; all started in the first 8 weeks of treatment, and no new cases emerged with continuation of treatment. Conclusions: Tumor response rate improved with continuation of pex treatment. The safety profile remained similar, with no new mixed or cholestatic hepatotoxicity. Clinical trial information: NCT02371369 and NCT02371369.

11043 Poster Session (Board #366), Sat, 8:00 AM-11:00 AM
Identification of genomic alterations by circulating tumor DNA in leiomyosarcoma characterized by the WWTR1-CAMTA1 fusion. First Author: Nathan David Seligson, Baptist Memorial Healthcare, Columbus, OH

Background: Epithelioid hemangioendothelioma (EHE) is a rare vascular sarcoma characterized by the WWTR1-CAMTA1 fusion (WC-F) in a majority of cases. EHE demonstrates a biphasic clinical course; remaining indolent for many years before suddenly demonstrating aggressive progression. Cell cycle mutations have been previously noted to account for some secondary alterations; however, the role of other commonly altered genes, which surgery would likely be associated with worsening functional limitations or severe morbidity, is not known regarding the chronicity of these secondary alterations or their clinical implications. Here we present the largest assessment of secondary genomic variants and their clinical import.

Methods: Comprehensive genomic profiling from 45 WC-F positive EHE patients (pts) were provided by Foundation Medicine (FMI). Of these 45 pts were treated at The Ohio State University (OSU) and were evaluated retrospectively through chart review. Known deleterious alterations, variants of unknown significance (VUS), and genomic copy quantification for the WC-F was included in our analysis. Targetable gene variants were defined by OncoKB. Chi-square and student’s t-tests were used as appropriate. Results: Genomic copy number of the WC-F best fit a normal distribution (range: 13-2,131 copies). 20 pts (44%) did not exhibit any secondary genomic variants. The most commonly altered genes included: CDKN2A/B (7 variants), RB1 (3 variants), and ATRX (3 variants). Commonly identified pathways included: cell cycle (9 pts, 20.0%), epigenetic modulators (7 pts, 15.6%), and DNA damage (7 pts, 15.6%). Light deletions exhibited targetable gene variants (18%) as defined by OncoKB. Subjects ≥50 yrs of age exhibited a greater proportion of clinically targetable variants (27.6% vs 0%; p=0.02). Pts with a secondary genomic variant exhibited elevated WC-F copy numbers (p < 0.001). OSU pts with aggressive EHE were more likely to have a secondary genomic variant (80% vs 0%; p=0.03) when compared to indolent EHE, with trends toward higher WC-F copy numbers (809 ± 315 vs 207 ± 147; p = 0.2) and older age at diagnosis (59.5 ± 5.5 vs 36.7 ± 8.8; p = 0.1). Conclusions: In this study, secondary genomic variants in WC-F driven EHE are more common in older patients (≥ 50 yr). Further, the presence of secondary genomic variants is associated with an aggressive phenotype and may drive poor prognosis. Prospective research is needed to confirm these findings.
Angiosarcoma of bone: A European Musculoskeletal Oncology Society (EMOSOS), multicenter, retrospective study. First Author: Emanuela Palmerini, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

**Background:** Angiosarcoma of bone (B-AS) is an exceedingly rare malignant tumor of vascular origin. The aim of this EMOSOS retrospective study is to report on natural history, type of treatment and prognosis of B-AS. **Methods:** Patient data were collected according to the national rules for observational studies through electronic dataset available on EMOSOS Website. **Results:** 80 patients (51 male and 29 female, median age 54 years, range 17 to 92 years, 56% with localized disease, 44% metastatic) from 8 EMOSOS Centers were collected. Surgery of the primary tumor was performed in 76% of patients (amputation in 30%), with intralesional margins in 26%. A surgical complete remission status (SCR) was achieved in 47% of the patients. Radiotherapy (RT) was delivered in 41% of the patients (in 15 patients as definitive local treatment), chemotherapy (CT) in 47% (56% in metastatic and 41% in localized cases). With a median follow-up of 31 months (range 40 to 309 months), 68% of patients died, 16% were disease-free, 12% were alive with disease and 4% dead for other causes. The 5-year overall survival (OS) was 27% (95%CI 16-30); 41% (95%CI 25-56) for localized patients (45% SCR, 17% no SCR, p = 0.03) and 8% (95%CI 0-20) for metastatic patients (p = 0.002). Among metastatic patients, 29/35 have died, with a median time to death of 6 months (1-45), while 6 patients were alive with a median follow-up of 22 months (8-106). Improved survival was observed for male patients (30% vs 8%, p = 0.04), while type of treatment (surgery, chemotherapy, radiation), pattern of metastasis and age had no effect outcome. We conclude that, in contrast to the literature, our results suggest that the presence of DDR or HRD status (p = 0.05). Conclusions: Metastatic B-AS is a fatal disease and inclusion in experimental trials is warranted. In localized patients, a better probability of survival is expected in younger and surgically treated patients. The use of chemotherapy was associated with improved DFS.

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Background: Efficacy of low-dose chemotherapy with methotrexate (MTX) and vinblastine (VBL) for desmoid-type fibromatosis (DF) has been reported and approved by many physicians. However, significant factors including biomarker could not be identified to better predict the efficacy of this chemotherapy. Since 2003, meloxicam, which is a selective COX-2 inhibitor, has been applied consecutively as a first line treatment. We applied the low-dose chemotherapy with MTX+VBL for refractory patients. The aim of this study was to reveal the clinical outcome of low-dose chemotherapy with MTX+VBL, and determine the useful factors to predict the efficacy including CTNNB1 mutation status. Methods: Since 2003, 176 cases were histologically diagnosed as DF. Among them, 36 cases were treated with MTX (30mg/M2) + VBL (6mg/M2) chemotherapy. Treatment interval was basically 2 weeks according to our previous study. Effectiveness was evaluated with MRI and/or CT every 3 months according to Response Evaluation Criteria in Solid Tumors (RECIST). Frozen or FFPE (Formalin-Fixed Paraffin-Embedded) specimens obtained at biopsy or previous surgery were subjected to the analyses for CTNNB1 mutation status by Sanger method. Clinical outcome and factors correlating with the efficacy were analyzed. Results: Among 36 cases with this chemotherapy, male was 13, mean age at the treatment was 36 ± 18 years. Mean maximum diameter of tumor was 15 ± 18 cm. Twenty-nine cases (81 %) harbored CTNNB1 or APC mutation. Mean treatment duration of cycles of MTX+VBL were 20 months and 29 cycles, respectively. According to RECIST, PD in 2, PR in 15, and SD in 19. According to CTCAE, Grade 3 or more adverse events were observed in only one case. CTNNB1 mutation status, gender, age, size, and location did not affect the outcome of RECIST. Longest treatment duration of cycles of chemotherapy was associated with the outcome (P = 0.002 and 0.004, respectively). In 15 cases of PR, recurrent tumors significantly took longer time to get efficacy (P = 0.027), and tumors arising in trunk and extremities tended to take longer time (P = 0.1). Conclusions: Low-dose MTX+VBL chemotherapy is effective and feasible treatment for refractory DF regardless of CTNNB1 mutation status. Occasionally it takes time to obtain objective response.

Clinical outcomes of sunitinib (Su) for patients (pts) with desmoid tumors (DT). First Author: Salvatore tindara Miano, Azienda Ospedaliera Universitaria Senese, Siena, Italy

Background: The incidence of DT is steadily increasing in pts affected by familial adenomatous polyposis (FAP) and represents the first cause of death for pts who underwent preventive proctocolectomy. Currently, there is no standard therapy for DT and Tumoxifen (20 mg once daily) + Meloxicam (15 mg once daily) (TM) is the most commonly used regimen in clinical routine. We sought to evaluate the efficacy of Su, the most active PDGFR TKI, as first-line therapy for pts with DT. Methods: In this phase II IRB approved prospective study, pts with progressive, symptomatic, or recurrent DT were randomized to receive either Su (52 mg once daily) or TM. The approved prospective study, pts with progressive, symptomatic, or recurrent DT and Tamoxifen (20 mg once daily) + Meloxicam (81%) harbored CTNNB1 or APC mutation. Mean treatment duration and disease-control rate (DCR: CR+PR+SD) were 35 % and 70 %, respectively. The median progression-free survival was 6.5 (2.8-9.8) months. When adding C to T and B, DCR was improved from 64 % (TB) to 75 % (TBC). Median administration of cycles is 7 (TB) and 5 (TBC). There were 2 dead cases from perforation, but toxicity was almost mild and manageable. Conclusions: We have experienced 5 cases of CR by TB or TBC. Moreover, addition of C to T and B resulted in better disease-control rate. Compared to other treated patients, TB combined with C could be substantially effective in cases with heavily pretreated uterine sarcomas. These results warrant further prospective and randomized studies.
11054 Poster Session (Board #377), Sat, 8:00 AM-11:00 AM
Does the addition of chemotherapy to neoadjuvant radiotherapy impact survival in high-risk extremity and trunk soft tissue sarcoma? First Author: Mounika Choudhary, Rush University Medical Center, Chicago, IL

Background: Large, high-grade extremity/trunk (ET) non-rhabdomyosarcoma soft-tissue sarcoma (STS) is at high risk for distant recurrence and death. The integration of chemotherapy (C) to standard of care neoadjuvant radiotherapy (RT) remains controversial, even for these patients. This study examines the impact of adding C to neoadjuvant RT on overall survival (OS) in high risk ET-STS. Methods: The National Cancer Data Base (NCDB) was queried for patients >18 years with high risk (>5 cm + high grade) non-rhabdomyosarcoma ET-STS (WHO histology) who received neoadjuvant RT and limb sparing surgery from 2006-2014. Patients were next stratified based upon receipt of C (RT and CRT cohorts). Overall survival (OS) for RT vs CRT cohorts was analyzed using the Kaplan-Meier (KM) method, log-rank test, and Cox proportional hazards models. Propensity score-matched analysis (PSM) was employed to account for potential treatment selection bias between cohorts. Results: A total of 848 (71.1%) and 344 (28.9%) patients received RT and CRT, respectively. Patient cohorts were well-balanced except for the CRT cohort having higher rates of treatment in the West (22.1% vs 10.6%) & Midwest (28.3% vs 22.7%), Charlson-Deyo (CD) score 0 vs >1 (85.6% vs 79.4%), younger age (<50) (45.9% vs 21.7%), synovial sarcoma histology (18.9% vs 3.2%), earlier year of diagnosis (2006-2010) (39.5% vs 32.3%), and positive lymphovascular invasion (2.0% vs 1.5%). (p < 0.05 each). The KM 5-year OS was significantly higher in the CRT vs RT cohort: 69.2% vs 58.1% on univariate (p < 0.0001) and multivariate analysis. Rate of C failure: 66% (RT); 95% (CRT) (p = 0.001) even after adjusting for age, race, income, CD score, histology, tumor size, grade, and primary site (lower extremity; upper extremity; trunk). PSM identified evenly matched cohorts of 300 patients each with respect to age, income, CD score, histology, grade, tumor size, and primary site. The additional of neoadjuvant (C) increased progression-free survival (PFS) (HR: 0.74 [0.56-0.99], p = 0.042). Conclusions: The addition of C to neoadjuvant RT was associated with improved OS in patients with high risk non-rhabdomyosarcoma ET-STS in the NCDB. These hypothesis generating results support prospective evaluation.

11055 Poster Session (Board #378), Sat, 8:00 AM-11:00 AM
Phase 1 combination therapy with pezdartinib (PEX) and sirolimus (S) to target tumor-associated macrophages in pigmented villonodular synovitis, malignant peripheral nerve sheath tumors, and other soft tissue sarcomas. First Author: Gulum Abbas Manjji, Columbia University Medical Center and New York-Presbyterian Hospital, New York, NY

Background: No effective therapy exists for unresectable malignant peripheral nerve sheath tumors (MPNSTs). We previously reported that the combination of PEX and the mTOR inhibitor S synergistically inhibited MPNST growth (CCR 20: 3146, 2014) by depleting M2 TAMs and by inhibiting receptor tyrosine kinases (RTKs) including c-KIT, PDGFR, CSF1R. We characterized the safety, tolerability, recommended phase 2 dose (RP2D) of PEX plus S in all sarcoma sub-types. Methods: Patients (pts) received PEX plus S orally in 28 days cycle as per Table. The RP2D was determined using time-to-event and continual reassessment method (TITE-CRM) in advanced sarcoma who have progressed on standard therapy. DLT was defined as any need for a dose reduction. Results: 24 pts were accrued (Acr) of which 18 were evaluable (MPNST – 6, pigmented villonodular synovitis (PVS) – 3, leiomyosarcoma – 5, and other – 9). The mean age was 46y, 56% were male, and 67% had greater than 2 prior therapies. Most common ( > 20%) grade 2 or higher TEAEs were anemia (33%), WBC count decrease (28%), fatigue, neutropenia, and lymphopenia (22%) each. There were 5 dose limiting toxicities (DLT); 2 elevated LFTs both of which resolved with dose reduction, 2 for supra-therapeutic S trough levels, and 1 for grade 4 dehydration at dose level (DL) 3. Four subjects experienced a partial response (PR); 44% to -77% by RECIST, 18 – 61 wks on therapy. Seven subjects experienced stable disease (SD; +19.7% to -20.7% by RECIST; 9.4 – 30 wks on therapy). Five subjects progressed on therapy and two subjects experienced early DLTs and did not undergo tumor assessment. The RP2D is DL 3 (3 mg/kg PEX 1000mg) with an estimated probability of DLT of 26.7% as determined by TITE-CRM. This recommendation is based on a target DLT rate of 25%. TAMs and immune subtypes from available tissue specimens and historical controls will be presented in future publications: 1000mg of PEX in combination with 2mg of S daily has an acceptable safety profile. Objective responses and durable SD was observed in PVS and MPNST patients justifying proceeding with a multi-center single arm phase 2 study in advanced MPNST. Clinical trial information: NCT02586467.

11056 Poster Session (Board #379), Sat, 8:00 AM-11:00 AM
Improved local relapse-free and overall survival with secondary surgery after a first R1 resection in soft tissue sarcoma (STS) of the extremity or trunk wall: An analysis 10,931 patients (pts) in NETSARC. First Author: Francois Gouin, Centre Leon Berard, Lyon, France

Background: We previously reported that secondary resection (2Surg) improved local relapse free (LRFS) but not overall survival (OS) in a retrospective series of pts with localized STS after unplanned 1st excision. Here we investigated the impact of 2Surg specifically after a first R1 or R2 resection in the 10931 pts with STS of the limb or trunk wall included in the nationwide NETSARC database from 2010 to 2017. Methods: NETSARC (netsarc.org) is a network of 26 reference sarcoma centers with specialized multidisciplinary tumor boards (MDT), funded by the French NCI (INCa). Since 2010, presentation to an MDT and second pathological review are mandatory for sarcoma pts. Statistics were performed with SPSS23.0. LRFS, metastasis-free survival (MFS), OS compared with the logrank test. Results: The series included 5598 (51.2%) males. Median age was 56.7. Tumor sites: 5295 (49.4%) lower limb, 3670 (33.6%) trunk wall. 1966 (18.0%) upper limb. As calculating doses are 75 and 100 mg/m2. The primary endpoint is to identify the maximum-tolerated dose (MTD) of ABI-009 + nivolumab, secondary endpoints include disease control rate, progression-free survival (PFS), and overall survival (OS). Exploratory endpoints include correlation of PFS and OS with PD-L1 and other biomarkers. The Phase 2 part of study will enroll 31 additional patients to further assess efficacy and safety at the MTD. Results: 9 patients were treated in Phase 1 (n = 3 each dose level); 5/9 patients had OS, 3/9 CS, and 1 had Ewing sarcoma. No dose-limiting toxicities (DLTs) were observed, the MTD was not reached, and 100 mg/m2 ABI-009 was designated as the recommended phase 2 dose. Safety analysis: At Dose 1: Grade 3 treatment-related adverse events (TRAES) included hyper dyslipidemia (n = 1), and hyperglycemia (n = 1). At Dose 2: Grade 3 TRAEs included increased ALT (n = 1). At Dose 3: Grade 3 TRAEs included hypophosphatemia (n = 1) and hyperglycemia (n = 1) for a total of 9 patients who met criteria for dose escalation to PD-1, 2 with SD opted to stop treatment due to drug-related Grade 2 AEs (pruritus, acneiform rash, and 2 with SD are still on therapy at Dose 3. The median PFS at dose level 3 has not yet been reached. Conclusions: The MTD was not reached and Dose 3 (100 mg/m2) has been designated as the phase 2 dose of ABI-009, combinable with nivolumab. Enrollment to phase 2 is ongoing. Clinical trial information: NCT03190174.

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Synovial sarcomas (SS) are rare, mesenchymal tumors that exhibit heterogeneous clinical behavior. SS is characterized molecularly by a fusion of the SS18 and one of three SSX genes. While fusion type has been shown to play a role in prognosis, little is known regarding the role of secondary genomic variants in SS. We hypothesized that frequently mutated secondary mutations corresponded to altered molecular pathways associated with accelerated disease progression. Here we present further analysis of the largest study of secondary SS genomic alterations and their potential clinical implications particularly in regard to Histone H3 modifying genes.

**Methods:** Comprehensive Genomic Profiling (CGP) from 203 SS18-SSX fusion positive SS subjects were obtained from Foundation Medicine (FMI). Correlation between gene expression and survival endpoints were assessed in two independent datasets (GSE40018, n = 34; GSE40021, n = 58). A histone H3 score (H3h3score) was calculated through summation of expression values of MLL2, MLL3, SETD2. Altered expression was assessed for genes mutated in > 5% of SS in the FMI dataset. Datasets were also combined with appropriate adjustments for multivariate analysis. Cox proportional hazard, and Chi-squared test were used as appropriate.

**Results:** In CGP profiling of SS, only 4 genes were seen in > 5% of subjects (MLL3 9%, SETD2 7%, MYO18A 6%, MLL2 6%). 3 of these variants are known to regulate histone H3 activity and are collectively altered in 22% (44 of 203) of the FMI SS subjects. Notably, these H3 targeting gene alterations were found in SS with metastasis (H3h3score) and were correlated with survival endpoints (Log-rank Test, p < 0.01). In 2 independent SS datasets, subjects with high histone H3 modifying gene RNA expression levels (H3h3score) demonstrated worsened outcomes with earlier tumor metastasis (GSE40018: HR = 0.41, 95%CI 0.22-0.77, p = 0.01; GSE40021: HR = 0.22, 95%CI 0.09-0.52, p = 0.001). Altered expression remained significantly correlated to metastasis-free survival (HR = 0.41, 95%CI 0.22-0.77, p = 0.01) when subjects’ age (p < 0.001) and fusion type (p = 0.60) were taken into consideration. **Conclusions:** Altered expression of histone H3 modifying genes may serve as a key driver for SS progression. Further prospective research is necessary to confirm its prognostic importance.
EHE is a rare vascular mesenchymal tumor for which there is currently no standard for treatment particularly for metastatic disease. EHE often present metastatic evolution but metastases are not a poor prognostic factor. The aim of this study was to improve knowledge of outcome of EHE patients and see the impact of active surveillance on outcome for metastatic EHE patients. **Methods:** Patients with EHE treated at three centers in France were included in this retrospective cohort. Univariate analysis of prognostic factors was performed using the Cox model. Survival was estimated using the Kaplan-Meier method and long rank analysis. **Results:** Fifty-seven patients with EHE were collected in this analysis: 27 (47%) women and 30 (53%) men, with a median age at diagnosis of 39 years (range: 12-81). At diagnosis, 17 (29.8%) patients had a localized tumor, while 40 (70.2%) patients had synchronous metastases. The most commonly affected organs were liver (23.8%), bones (14.0%), skin, lungs and soft tissues (10.5% each). For the 17 patients with localized EHE, the median distant recurrence-free survival after resection of primary was 64.6 months, 95% CI (23.4, NA), (median follow-up of 62.7 months, range, 12.5-234.8). For the 40 patients with metastatic EHE, the median progression-free survival (PFS) was 59.0 months, 95% CI (121.3, NA), (median follow-up of 121.1 months, range, 1.0-202.0). No prognostic factor was identified for localized EHE. For metastatic EHE, age was associated with progression-free survival (p = 0.019), 1 patient with previous history of pleura/ascites/pericarditis effusion adversely affected overall survival (OS) (p = 0.002). An initial "wait and see" attitude was proposed to 23 patients (57.5%) while 17 patients (42.5%) were treated at diagnosis with local or systemic treatment (monotherapy or combination of chemotherapy with anthracyclin, taxane, mTOR inhibitor). **Conclusions:** In our series of patients, 174 months and 121 months for chemotherapy treated patients and active surveillance patients respectively (p = 0.56). **Conclusion:** Presence of effusion was a significant poor prognostic factor in metastatic EHE patients. Active surveillance could be proposed for asymptomatic patients without effusion but this strategy need to be confirmed in larger or prospective randomized trials.

**Objective:** sirolimus is an mTOR inhibitor used in the treatment of sarcomas. 321 soft tissue sarcoma patients were treated with the combination of an IGF1R inhibitor plus mTOR inhibitor, 26 patients (6%) had a PR as best response using novel immunotherapies targeting PD1, PD-L1 plus CCR4, CTLA4 plus KIT, and TLR7/8 and novel targeted therapies against TRK, LRR15, cMET, mTOR, VEGFR, FGFR, 95% CI 11-16). Responses were seen with the following subtypes - ASPS, UPS, myxoid sarcoma, liposarcoma, GIST, carcinosarcoma, clear cell sarcoma, embryonal rhabdomyosarcoma, epithelioid sarcoma, fibrous histioclasia, and Ewing’s sarcoma. **Conclusions:** Our analysis identifies a reasonable survival in heavily pretreated, metastatic refractory sarcoma patients with sarcoma seen who were treated with targeted therapy. 321 soft tissue sarcoma patient treated with the combination of an IGF1R inhibitor plus mTOR inhibitor, 26 patients (6%) had a PR as best response using novel immunotherapies targeting PD1, PD-L1 plus CCR4, CTLA4 plus KIT, and TLR7/8 and novel targeted therapies against TRK, LRR15, cMET, mTOR, VEGFR, FGFR.

**Conclusions:** This study is the first one to report the activity of sirolimus in a retrospective series of 18 EHE treated within the RTOG 0333 study. The main conclusion of this group is the observation of a large number of pts. **Methods:** Adults pts affected by advanced, progressive, and centrally confirmed EHE treated with sirolimus within the RTO from 2006 to 2018 were retrospectively reviewed. Sirolimus was administered at the starting dose of 5 mg/day, until toxicity or progression. Sirolimus dose was adjusted according to plasma levels (target: 15–20 ng/dL). Response was assessed by RECIST 1.1. Survival was estimated by Kaplan-Meier method. **Results:** 33 patients were retrospectively identified (median age = 47 years, female = 20 (60%), male = 13 (40%); pretreated = 8, naïve = 25; presence of pleural effusion at baseline = 6). All patients had metastatic disease and evidence of disease progression before starting sirolimus. Mean sirolimus daily dose was 5 mg (range 2-10). 9 pts are still on therapy, 24 stopped sirolimus (13 progression, 5 toxicity, 6 other). 31 pts were evaluable for response (2 pts too early). Best RECIST response was: 1 (3.2%), PR, 26 (83.8%) SD, 4 (12.9%) progression. At a 14-mo median FU, median PFS (m-PFS) was 12.3 mos (range 8-15) and median OS (m-OS) was 19 mos (range 1-40). Pleural effusion correlated with a short m-PFS (3.4 vs 14.3 mos in patients without pleural effusion, p = 0.006) and m-OS (10.6 vs 40 mos in patients without pleural effusion, p < 0.0001). Amongst those without pleural effusion, the proportion of pts being progression free at >24 mos was 23%, with 54% being alive. **Conclusions:** We selected pts with advanced EHE with clear evidence of disease progression. This singles out a subgrupo of EHE pts with a bad prognosis. Prognosis was shown to be exceedingly bad when there was evidence of serosal effusion, and sirolimus was not effective. Though in an uncontrolled setting, apparently sirolimus is able to slightly prolong PFS, and, above all, to allow mid-term freedom of progression in roughly 25% of pts.
Activity of hormonal treatment in uterine smooth muscle tumors of uncertain malignant potential (STUMP): A mono-institutional referral center experience in advanced disease. First Author: Roberta Santilippo, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: STUMP ecompass a group of uterine mesenchymal neoplasms in which the clinical behavior cannot be predicted on morphological grounds. A malignant clinical evolution is seen in approximately 10-20% of cases. When STUMP relapse, the label of “low-grade leiomyosarcoma” is sometimes found to be appropriate, though current histopathological criteria for uterine leiomyosarcoma (so called “Stanford criteria”) would exclude even the existence of low-grade uterine smooth muscle neoplasms. As they express ER and PR, hormonal treatment with GnRH inhibitors or aromatase inhibitors (AIs) may represent a therapeutic option. Methods: From October 2015, we have been treating with hormonal therapy relapsing patients with an initial diagnosis of STUMP, whose pathological aspect on retrospect was consistent with a “low-grade uterine leiomyosarcoma”. We identified 8 patients. Pathological diagnosis was centrally reviewed by expert sarcoma pathologists. Results: Eight pts were treated: 7 in first line; 1 pt in 4th line, following failure of chemotherapy (gemcitabine and taxotere, adriamycin and dacarbazine, trabectedin). Two premenopausal pts were treated with GnRH inhibitors, 2 with a combination of GnRH inhibitors and an aromatase inhibitor, 3 with aromatase inhibitors only and 1 with selective progesterone-receptor modulator. 7 patients are evaluable for response and all of them had a partial response as best response. Median progression-free survival was 31 months. Conclusion: In our series, all patients with a centrally reviewed diagnosis retrospectively consistent with a “low grade uterine leiomyosarcoma” responded to hormonal treatment. Therefore, these pts may make up a subgroup with therapeutic and prognostic relevance. “Stanford criteria” need to be re-assessed, in an effort to improve prognostic and therapeutic stratification of uterine smooth muscle neoplasms, possibly shrinking the scope of currently defined STUMP.

Sarcopenia (SMI(+)) in patients (pts) with advanced or metastatic soft tissue sarcoma (a/mSTS): Potential parameter for risk prediction during multimodal therapy (MT)? First Author: Dennis Strassmann, Department of Radiology, Hannover Medical School, Hannover, Germany, Hannover, Germany

Background: Objective parameters identifying ideal pts for MT from pts with a/mSTS remain scarce. Here, we analysed the impact of sarcopenia in a/mSTS pts on treatment outcome of MT, retrospectively. Methods: Pts. with a/m STS treated at our centre (12/98-5/16) were identified. 89/181 pts were evaluable for analysis (CT-scans: -14 days before MT onset). Lumbar skeletal muscle index (SMI) was measured with MeVisLab 2.7 by manually segmentation of preinterventional CTs. SMI cut-off were defined through optimal fitting method (sarcopenia = SMI(+) in male: 44 , in female: 38).

Results: At MT onset 28/89 pts (31%) suffered from sarcopenia, and SMI(+) pts were older than SMI(-) pts (p = 0.025). SMI(+) pts tend to receive lower numbers of medical treatments, received less often surgery, and more frequently radiotherapy, although differences were not significant. Further on, SMI(+) pts tends to profit less from first line medical treatment, compared to SMI(-) pts (objective responses: 14.3% vs. 27.9%, p = .161, clinical benefit rate: 25% vs. 65.6%, p = .032, PFS: 1 (95%-CI: 35-1.65) vs. 16 (95%-CI:8.8-23.2) months, p = .002). OS was inferior in SMI(+) compared to SMI(-) pts. (4 (95%-CI:2-6) vs. 16 (95%-CI:8.8-23.2) p = .002). Multivariable analysis showed a trend for SMI(+) to be associated with PFS (HR: 1.7 (95%-CI: 0.9-2.8), p = .067) and were independently associated with OS (HR: 2.53 (95%-CI: 1.5-4.2), p < .001). Conclusions: In our cohort sarcopenia tends to be associated with less aggressive therapy in a/mSTS pts. However, sarcopenia tends to be associated with inferior PFS and survival as compared to non-sarcopenic pts. This analysis is limited due to its sample size sarcopenia might offer an attractive tool as guidance for treatment intensity modulation in a/mSTS patients, avoiding overtreatment in this cohort with dismal prognosis.

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Results of the dose-finding phase of ARST 1321 from the Children’s Oncology Group and NRG Oncology. Neoadjuvant chemoradiation or radiation therapy with pazopanib in soft tissue sarcoma (STS). First Author: Yen-Lin Chen, Massachusetts General Hospital, Boston, MA

Background: Pazopanib is a tyrosine kinase inhibitor approved globally for advanced soft tissue sarcomas. The dose finding phase of this cooperative group trial assessed the dose limiting toxicities (DLT) and the maximally tolerated dose (MTD) of adding pazopanib to neoadjuvant chemoradiation or radiation therapy in children and adults with unrespectected intermediate/high-risk trunk and extremity non-rhabdomyosarcoma soft tissue sarcomas (NRSTS). Methods: ARST1321, a jointly designed intergroup study lead by Children’s Oncology Group and NRG Oncology opened for enrollment in July 2014. Eligible adult and pediatric patients with newly diagnosed, unrespectected trunk/extremity NRSTS with plans for primary tumor resection were enrolled into either the Chemotherapy Cohort (those with chemosensitive NRSTS > 5 cm, grade 3, including all synovial sarcoma) or the Non-Chemotherapy Cohort (those with chemotherapy insensitive NRSTS of any size, grade 2/3, or any chemosensitive NRSTS for whom no chemotherapy was planned per discretion of patients and treatment teams). In the Chemotherapy Cohort, pazopanib was given with ifosfamide (7.5 grams/m²) and doxorubicin (75 mg/m²) plus 45 Gy preoperative RT starting after cycle 2. Primary tumor was resected at week 13, followed by chemotherapy and pazopanib to week 25. In the Non-Chemotherapy Cohort, pazopanib was given with 50 Gy preoperative RT, primary tumor was resected at week 10, and pazopanib continued to week 25. Although feasibility was assessed to determine pazopanib dose escalation/de-escalation based on DLT, total doses of pazopanib, and overall adverse event profile. Results: In the Chemotherapy Cohort, MTD was reached at Dose Level 1 (350 mg/m² pills; 600 mg adults) with two DLTs (1 grade 3 ALT rise, 1 intolerability to therapy) in 10 patients. In the Chemotherapy Cohort, 11 patients enrolled (1 grade 3 dermatitis and 1 intolerability to therapy) and 9/10 receiving >75% of full dose. Conclusions: Pazopanib in combination with chemoradiation or radiation therapy alone was found to be safe in children and adults with NRSTS. Following this finding, ARST1321 opened in both arms using the newly determined pazopanib MTDs. Clinical trial information: NCT02180867.

Poster Session (Board #394), Sat, 8:00 AM-11:00 AM

Retrospective analysis of adjuvant treatment for localized, operable uterine leiomyosarcoma. First Author: Jomjit Chantharasamee, UCLA, Santa Monica, CA

Background: Surgery is the standard of care for uterine leiomyosarcoma, but recurrence rates are high and outcomes are poor. Standard adjuvant treatment of localized uterine leiomyosarcoma(uLMS) has not yet been established as clinical trials to address this question have been small or hindered by slow accrual. Methods: We reviewed the medical records of patients with uLMS who underwent surgery between 2000-2018. With patient and tumour characteristics and treatment outcomes were described using descriptive statistics. Kaplan-Meier survival analysis was used for DFS. Cox proportional hazard regression was used to compare difference between groups. Results: 59 patients with a median age of 52 years were analyzed and the median time from surgery to adjuvant treatment was 47 days. 48/59 (81.4%) underwent TAH-BSO. 64.4% were FIGO stage I, 16.9% were stage II and 6.7% were stage III. The median tumor size was 11 cm (range: 3-21cm) and the median mitotic rate was 13 mitoses/10-high-power fields (HPF), (range: 1-63). 34/59 (57.6%) of patients received adjuvant chemotherapy +/- radiation therapy and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 25 patients (42.3%) did not receive adjuvant treatment.
Phase VII clinical trial of NY-ESO-1-specific TCR-engineered T-cell transfer combined with a novel T-cell stimulator CHP:NE1 for patients with refractory soft tissue sarcoma.

First Author: Mikiya Ishihara, Mie University, Tsu, Japan

Background: Combination therapy to enhance the efficacy of T cell receptor (TCR)-engineered T cells (TCR-T) has received increasing attention. We found that a combination therapy of TCR-T and a long peptide vaccine with CpG adjuvant without lymphodepletion regimen caused regression of immune checkpoint inhibitor-resistant sarcoma in a preclinical mouse model.

Based on this finding, we initiated a clinical trial of TBI-1301 combined with CHP:NE1 without lymphodepletion for the patients with NY-ESO-1 expressing advanced soft tissue sarcoma. TBI-1301 is an NY-ESO-1:115-126/HLA-A*02:01- or A*02:06-specific TCR-T engineered to reduce endogenous TCR mRNA expression. CHP:NE1 is a novel T cell stimulator consisting of NY-ESO-1 long peptide antigen, cholesteryl pullulan (CHP) nanogel, and CpG oligoDNA. CHP nanogel is used for efficient delivery of long peptide antigen into the lymph nodes. CpG oligoDNA is a TLRL agonist and used as an adjuvant. CHP:NE1 is expected to reinforce TBI-1301 T cells in the lymph nodes.

Methods: This is an investigator-initiated multi-institutional first-in-human phase I/II clinical trial. TBI-1301 is infused at 5×10⁶ cells one day after subcutaneous injection of CHA:NE1, which is injected again 7 days after TBI-1301 infusion. This cycle is repeated once more. Lymphodepletion using cyclophosphamide and/or fludarabine is not performed. Key inclusion criteria include: refractory soft tissue sarcoma with NY-ESO-1 antigen expression, HLA-A*02:01- or HLA-A*02:06-positive, ECOG Performance Status 0 or 1, and adequate organ function. The primary objective is to assess safety and tolerability. The secondary objective is to assess efficacy and immune response.

Enrollment of patients started in April 2018 and is ongoing. As of February 2019, 32 patients have been enrolled. The study is sponsored by AIO-Studien-gGmbH, Berlin, Germany. Clinical trial information: NCT01903546.

CBT-1 in combination with doxorubicin in patients with metastatic, unresectable sarcoma that are previously progressed on doxorubicin.

First Author: Gregory Michael Cote, MGH, Boston, MA

Background: The response rates of advanced soft tissue sarcomas (STS) to single-agent, first-line anthracycline are typically less than 25%, P-glycoprotein 1 (P-gp), a cell membrane drug efflux pump, is believed to be a resistance mechanism in STS. CBT-1 is a small molecule, orally administered, P-gp antagonist currently under clinical development. This is a multi-institutional open label, non-randomized, phase 1 study of CBT-1 in combination with doxorubicin in patients with anthracycline-refractory sarcoma. The study is designed to determine a maximum tolerable dose (MTD), recommended phase II dose (RP2D), and the safety/ tolerability of the combination of CBT-1 and doxorubicin. The study will evaluate anti-cancer activity as a secondary objective as measured by Disease Control Rate (DOR), complete response (CR) + partial response (PR) + stable disease (SD) at 12 weeks. Objective Response Rate (ORR; CR+PR) and Progression Free Survival (PFS) will be monitored. Correlative studies include assessment of pharmacokinetic and pharmacodynamic endpoints.

Methods: Patients 18 years or older with locally advanced metastatic, unresectable STS, prior progression on ≤150 mg/m² of doxorubicin (or another anthracycline equivalent), ECOG PS ≤1 and normal organ function, are eligible for this study. Dosing includes fixed doxorubicin (37.5 mg/m² IV day 5 and day 6) and escalation of CBT-1 on days 1-7 of a 21 day cycle. This study follows a standard 3+3 dose escalation design where dose escalation will occur if ≤3/6 patients experience a dose-limiting toxicity (DLT). Tumor assessments are conducted at Week 6 and Week 12. For patients with response or stable disease, treatment is allowed to continue for 4-5 cycles to a maximum of 450 mg/m² lifetime doxorubicin exposure. Once RP2D is defined, an additional 10 patients will be enrolled into the dose expansion phase. To date, Cohorts 1 (50 mg CBT-1) and 2 (100 mg CBT-1) have been completed with one DLT of grade 4 neutropenia lasting longer than 7 days in Cohort 1. Enrollment to Cohort 3 began December 2018. (References: Oldham, R. K., Reid, W. K., Preisler, H. D., and Barnett, D. (1998) Cancer Biother. Radiopharm. 13, 71-80; Kelly, R. J., Robey, R. W., Chen, C. C., Draper, D., Luchenko, V., Barnett, D., Oldham, R. K., Caluag, Z., Fye, R. A., Steinberg, S. M., Fojo, T., Bates, S. E. (2012) The Oncologist 17 (4) 512-e523; Robey, R. W., Shukla, S., Finely, E. M., Oldham, R. K., Barnett, D., Ambudkar, S. V., Fojo, T., Bates, S. E., (2008) Biochemical Pharmacology 75, 6, 1302-e1312). Clinical trial information: NCT03002805.
Benefit of intensified perioperative chemotherapy within high-risk CINSARC patients with resectable soft tissue sarcomas (CIRSARC). First Author: Antoine Italiano, Institut Bergonié, Bordeaux, France

Background: We have recently identified a gene expression signature so-called “CINSARC” which is related with chromosomal instability and highly predictive of metastasis-free and overall survival in soft-tissue sarcoma (STS) patients. The prognostic relevance of this signature has been validated recently in an independent set of sarcomas from the Cancer Genome Atlas (TCGA) consortium. Despite optimal locoregional treatment, patients with high-risk CINSARC have a very poor outcome. However, the main issues with peri-operative chemotherapy in STS patients are the identification of patients who are more likely to benefit from this approach and the characterization of the best chemotherapy regimen. Indeed, in all clinical trials investigating peri-operative chemotherapy in STS, patients were included on the basis of classical histological criteria (grade, tumor size, deep location). The CINSARC is more discriminant than grade to evaluate the prognosis of STS patients (35% of grade 3 are low-risk CINSARC and 40% of grade are high-risk CINSARC). We hypothesize than: (1) 6 cycles of anthracyclines-ifosfamide is associated with improved outcome in comparison to 3 cycles of chemotherapy (ISG-STS 10-01) in patients with high-risk CINSARC STS; (2) Chemotherapy-free strategy is not associated with detrimental outcome in low-risk CINSARC STS. Methods: This is a multicenter phase III trial (sponsor: Institut Bergonié) which aims to evaluate the efficacy (intent-to-treat analysis) of 6 cycles of neoadjuvant doxorubicin + ifosfamide based chemotherapy + surgery +/- radiotherapy (Arm B) in comparison with 3 cycles of neoadjuvant doxorubicin + ifosfamide based chemotherapy + surgery +/- radiotherapy (Arm A) in terms of 3-year progression-free survival (PFS) in high-risk CINSARC patients with resectable STS. Patients with low-risk CINSARC signature will be treated at investigator discretion. 334 patients will have to be recruited over 36 months in 10 centers of the French Sarcoma Group. This is the first study assessing the impact of peri-operative chemotherapy in STS based on a prognostic molecular signature. The study is open for accrual at time of submission. Clinical trial information: NCT03805022.

A phase II study of ADI-PEG 20 in combination with gemcitabine and docetaxel for the treatment of soft tissue sarcoma. First Author: Brian Andrew Van Tine, Washington University in St. Louis, St. Louis, MO

Background: The combination of gemcitabine (G) and docetaxel (D) is a standard second line therapy for soft tissue sarcoma (STS) with a modest response rate. Recent studies have looked to add agents to enhance response. We have shown that argininosuccinate synthase 1 (ASS1) expression is silenced in 88% of all sarcomas (n = 708) (Bean et al., 2016, Cell Death and Disease), and that this loss is associated with a reliance on extracellular sources of the amino acid arginine. The arginine depleting enzyme PEGylated arginine deiminase (ADI-PEG 20) depletes extracellular arginine. Preclinical studies have demonstrated that arginine starvation and D administration induce c-Myc-driven hENT1 surface expression overcoming intrinsic cell surface G transporter related resistance. To test this hypothesis, we opened this multi-institutional randomized phase II trial examining the safety and efficacy of ADI-PEG 20 with G + D in STS (NCT03449901) in July of 2018. Methods: Eligible patients are adults with metastatic or unresectable histologically or cytologically confirmed FNCLCC grade 2 or 3 STS that would be standardly treated with G and/or D. Patients are treated with ADI-PEG 20 at a dose of 36 mg/m2 via intramuscular injection on Day -7 of Cycle 1 and then on Days 1, 8, and 15 of each subsequent cycle. G will be given intravenously at a dose of 750 mg/m2 over 90 minutes on Days 1 and 8 and D will be given intravenously at a dose of 75 mg/m2 over 60 minutes on Day 8 of each cycle. The median PFS of metastatic sarcoma patients receiving the standard G + D treatment was estimated to be 6.2 months in a randomized phase II study (Maki et. al., 2007, JCO). With the addition of ADI-PEG 20, we target to improve the median PFS to 9 months, a 45.2% (2.8 months or 12 weeks) improvement in patients treated on G + D + ADI-PEG 20 against the null hypothesis median PFS of 6.2 months to achieve 80% power to detect the improvement in PFS at a 5% alpha level. Tumor specimens (pre- and post-ADI-PEG 20 during week -1) and blood are collected for correlative studies including metabolomics, pharmacodynamics, immunogenicity and ASS1 biomarkers. Quality of life will be measured using FACT-G7. Clinical trial information: NCT03449901.
A randomized trial comparing four-weekly versus 12-weekly administration of bone-targeted agents (denosumab, zolendronic, or pamidronate) in patients with bone metastases from breast or castration-resistant prostate cancer. First Author: Mark J. Clemons, Division of Medical Oncology, Department of Medicine, The Ottawa Hospital and University of Ottawa, Ottawa, ON, Canada

Background: Defining the optimal dosing interval of commonly used bone-targeted agents (BTAs), such as denosumab and bisphosphonates, for patients with bone metastases remains an important clinical question. We performed a pragmatic randomised trial comparing the non-inferiority of 12- versus 4-weekly BTAs in patients with bone metastases from breast and prostate cancer.

Methods: Patients with bone metastases, who were either BTA-naïve, or already receiving, denosumab, pamidronate or zoledronic acid were eligible. They were randomised to receive their chosen BTA every 12- or 4-weeks for one year. The primary endpoint was Health related quality of life (HRQL) (EORTC-QLQ-C30 Functional Domain - Physical Subdomain). Secondary endpoints included: pain (EORTC-QLQ-BM22 - pain domain), Global Health Status (EORTC-QLQ-C30), symptomatic skeletal events (SSE) rates and time to SSEs. Adverse events and toxicity profiles were also compared. Results: Of 263 patients (60.8% breast and 39.2% prostate), 130 (49.4%) were randomised to 4-weekly therapy. 138 (52.5%) were between-group differences in reported rates of renal impairment (2.3% vs. 3.0%), symptomatic hypocalcaemia (1.5% vs. 1.5%) or osteonecrosis of the jaw (0.8% vs. 0.8%). Conclusion: The findings of this trial are consistent with those previously reported for de-escalating zoledronic acid. This trial also included patients receiving de-escalated denosumab and pamidronate. While the results of the Swiss REDUCE trial are awaited, the data presented would suggest that de-escalation of all commonly used BTAs is a reasonable treatment option.

Clinical trial information: NCT02721433.
Olanzapine (OLN) versus aprepitant (APR) in patients receiving high-emetogenic chemotherapy. Results of a randomized phase II trial. First Author: Aleyx Rumjanek, Federeal State Budgetary Institution "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCCO, Moscow, Russian Federation)

**Background:** Management of chemotherapy-induced nausea and vomiting (CINV) remains challenging. OLN might provide several benefits over APR which is current standard of care – particularly in terms of nausea control and cost effectiveness. However, sedation associated with recommended doses of olanzapine precludes its wide use in oncology practice. **Methods:** This was randomized phase II single center study aimed to compare OLN and APR in CINV prophylaxis. Key inclusion criteria were: chemo- and radio-therapy naive patients, planned administration of high-emetogenic chemotherapy (cisplatin, carboplatin AUC=4, doxorubicin etc.). Patients were randomized 1:1 ratio in the following arms: olanzapine 5 QD day 0-4 or aprepitant 125 mg d1, 80 mg day 2,3. All patients received ondasetron 16 mg day 1 and dexamethasone 8 mg day 1-3. Primary endpoint was complete nausea control (no nausea and no rescue medication) 0-120 hours after chemotherapy. Complete response (no emesis and no rescue medication) was a key secondary end point. Nausea was assessed using MASCC Anticemesis Test. **Sample size:** 94 patients to increase nausea control rate from 40 to 70% (α = 0.05; β = 0.80; 10% of estimated data loss). **Results:** We included in the analysis 93 patients who could be evaluated. The groups were well balanced, median age was 49 years, vast majority of patients (95.6%) were females. The proportion of patients with complete nausea control in OLN and APR groups was 44.2% and 24.0%, respectively (RR 2.5; 95% CI 1.04-6.08; p = 0.039). Complete response was achieved in 74.4% and 54.0% patients respectively (RR 2.48; 95% CI 1.026-5.99; p = 0.041). No differences in rates of undesired sedations were detected. **Conclusions:** Our data suggests superiority of OLN regimen in terms of nausea control. This regimen deserves further investigation. Clinical trial information: NCT03478605.

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Association of baseline cardiovascular risk factors and health care utilization and costs in elderly breast cancer patients enrolled in SWOG clinical trials. First Author: Dawn L. Henahan, Columbia University College of Physicians and Surgeons, New York, NY

Background: Cardiovascular-disease risk factors (CVD-RFs) increase the risk of cardiac events in women undergoing chemotherapy. Less is known about the impact of CVD-RFs on healthcare utilization and costs. Methods: We examined breast cancer patients treated uniformly on SWOG clinical trials from 1999-2011. We identified baseline diabetes, hypertension, hypercholesterolemia, and coronary artery disease (CAD) by linking trial records to Medicare claims; obesity was identified using clinical records. The outcomes were emergency room visits (ER), hospitalizations and costs. Multivariable logistic and linear regression were used. Results: Among the 708 patients included in the analysis, 160 (22.6%) experienced 234 separate hospitalizations, and 173 (27.3%) experienced 311 separate ER visits. Diabetes, hypertension, hypercholesterolemia, and CAD were all associated with increased risk of hospitalizations and ER visits. Hypertension had the strongest association, with more than a threefold risk of hospitalization for those with hypertension compared to those without (OR [95% CI], 3.16 [1.85-5.40], p < 0.001). For those with ≥3 CVD-RFs, there was a 3-fold increase in hospitalizations (OR [95% CI], 2.74 [1.71-4.38], p < 0.001). Similar results were seen for ER visits. In the first 12 months after trial registration, patients with diabetes ($38,324 vs $30,923, 23.9% increase, p = 0.05), hypercholesterolemia ($34,168 vs $30,661, 11.4% increase, p = 0.02), and CAD ($31,695 vs $23,681, 34.1% increase, p = 0.04) had statistically significant higher total healthcare costs. Additionally, those with 2 significant CVD-RFs ($35,353 vs $28,899, 22.3% increase, p = 0.005) had higher total healthcare costs. Conclusions: Our study demonstrates that the presence of both CVD-RFs and ER visits and hospitalizations are frequent among elderly BC patients. The risk of ER visits and hospitalizations is higher among patients with CVD-RFs, and increases with the number of RFs. Better management of CVD-RFs and more aggressive symptom management may be required to reduce both physical and financial toxicities to elderly patients undergoing BC therapy.

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Reduced 90-day postoperative mortality through geriatric comanagement after cancer surgery. First Author: Amin Shahraki, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** We explored the association between geriatric comanagement and 90-day postoperative mortality of cancer patients aged 75 or older. **Methods:** A retrospective review of a prospectively maintained database was performed on patients over 75 years old who underwent elective surgery with hospital length of stay of ≥ 1 day at Memorial Sloan Kettering Cancer Center from 2015-2018. Geriatric comanagement group (GCG) patients had geriatric preoperative evaluation and inpatient geriatric comanagement. Patients in the surgical management group (SMG) did not have geriatric preoperative evaluation or postoperative geriatric comanagement. We utilized a multivariable logistic regression model with 90-day mortality as the outcome, geriatric co-manangement as the predictor, and adjusted for age, gender, American Society of Anesthesiology score, Memorial Sloan Kettering Frailty Index, preoperative albumin level, operation time, and estimated blood loss. The same logistic model was used to assess the association between adverse surgical events within 30-days (any major complication, readmission, or urgent cancer center visit) and geriatric comanagement. **Results:** Of 1,855 patients (median age 80, 1,009 patients (54%) were co-managed by geriatricians. GCG patients were slightly older, less likely to be male, had longer operation time, and stayed in the hospital longer. Adjusted rates of 90-day mortality was lower in GCG vs. SMG (4.3% and 9.2%, respectively; 95% CI around difference -7.3%, -2.5%; p-value < 0.0001). We did not find evidence of a difference in adverse surgical events between groups (OR 0.96, p-value = 0.8). A greater proportion of GCG patients received inpatient physical therapy (80% vs. 64%) and occupational therapy (37% vs. 25%) compared to SMG patients. **Conclusions:** Our study shows that geriatric comanagement is associated with reduced 90-day postoperative mortality in cancer patients aged ≥75. A randomized trial study is needed to confirm this finding.

A randomized controlled trial of a novel artificial intelligence-based smartphone application to optimize the management of cancer-related pain. First Author: Mihr Kamdar, Massachusetts General Hospital, Boston, MA

**Background:** Cancer pain is a significant problem that impairs patient quality of life and increases healthcare utilization, ePAL is a smartphone application that utilizes patient-reported outcomes (PROs) and artificial intelligence (AI) to optimize cancer pain management. This randomized controlled trial examined the impact of ePAL on cancer pain severity, attitudes toward cancer pain, and healthcare utilization. **Methods:** Patients with pain from metastatic solid tumors (n = 112) undergoing treatment in a palliative care clinic were randomized to either a control group (n = 56) that received usual care or an intervention group (n = 56) that received ePAL in addition to usual care for 8 weeks. Measures of pain severity (Brief Pain Inventory), attitudes towards cancer treatment (Barriers Questionnaire II) and anxiety (General Anxiety Disorder-7) were assessed. We used repeated measures mixed modeling to assess change in outcome measures over time. We also conducted a chart review to identify pain-related hospital admissions and emergency department (ED) visits and compared risk between study groups. **Results:** Pain severity (BPI) and negative attitudes toward cancer treatment (SQ-II) decreased significantly for those assigned to ePAL compared to controls (B = -0.09, p = 0.034 and B = -0.037, p = 0.042, respectively). Patients assigned to ePAL reported higher anxiety scores compared to controls (B = 0.21, p = 0.015). Patients assigned to ePAL had significantly fewer pain-related hospital admissions (n = 4 vs. n = 20, per patient risk ratio 0.31, p = 0.018) and fewer pain-related admissions through the ED (n = 2 vs. n = 14, per patient risk ratio 0.18, p = 0.008) compared to control group. **Conclusions:** To our knowledge, this is the first mobile app to optimize the management of cancer-related pain. Future directions include examining the efficacy of ePAL in settings with limited access to palliative care.

A randomized trial of a hospice video decision aid for patients with advanced cancer and their caregivers. First Author: Areej El-Jawahri, Massachusetts General Hospital, Boston, MA

**Background:** Although hospice provides high-quality end-of-life (EOL) care for patients with advanced cancer and their family caregivers, the service remains underutilized in part due to lack of adequate information provided to patients and families about hospice care. **Methods:** We conducted a single-site randomized clinical trial of a hospice video decision aid versus a verbal description in 150 hospitalized patients with advanced cancer and their caregivers. Patients without an available caregiver were still eligible to participate. Intervention participants (75 patients; 18 caregivers) received a verbal description about hospice plus a six-minute video depicting hospice care. Control participants (75 patients; 26 caregivers) received only the verbal description. The primary endpoint was patient preference for hospice care immediately after the intervention, adjusting for baseline preferences. Secondary outcomes included patient and caregiver knowledge and perceptions of hospice (Hospice Perception and Knowledge Questionnaire). **Results:** Between 2/2017 and 1/2019, we enrolled 55.7% (150/269) of potentially eligible patients and 44 caregivers. Post-intervention, patients assigned to the video group were more likely to prefer hospice care at the EOL (86.7% vs. 82.7%, OR = 2.85, P = 0.08), but this was not statistically significant. Patients in the video group reported greater knowledge about hospice (B = 0.50, P = 0.024) and were less likely to endorse that hospice care is only about death (6.7% vs. 21.6%, OR = 0.28, P = 0.035). Post-intervention, caregivers assigned to the video were more likely to prefer hospice care for their loved ones (94.4% vs. 65.4%, P = 0.031), reported greater knowledge about hospice (B = 1.94, P = 0.001), and were less likely to endorse that hospice care is only about death (0.0% vs. 23.1%, P = 0.066). **Conclusions:** Patients with advanced cancer and their caregivers who viewed a hospice video decision support tool were more informed about hospice care and reported more favorable perceptions of hospice. Future work should examine the impact of the video on hospice utilization and length-of-stay among patients with advanced cancer. Clinical trial information: NCT03040102.

**Prediction of treatment (tx)-induced fatigue in breast cancer (BC) patients (pts) using machine learning on genome-wide association (GWAS) data in the prospective CANTO cohort.** First Author: Sangkyu Lee, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** Many BC survivors report fatigue. The relevant genomic correlates of fatigue after BC are not well understood. We applied a previously validated machine learning methodology (Oh 2017) to GWAS data to identify biological correlates of fatigue induced after tx. **Methods:** We analyzed 3825 BC pts with GWAS data (illumina InfiniumExome24 v 1.1) from the CANTO study (NCT01993498). The outcome of this study was post-tx fatigue 1 year after the end of primary chemotherapy/radiotherapy/surgery using the EORTC C30 fatigue subscale (overall fatigue) and the EORTC FA 12 fatigue domain (physical/emotional/cognitive). For each domain, we limited the study group to those with zero baseline fatigue and defined severe fatigue change as score increase above the third quartile. We tested univariable correlations between severe fatigue in each domain and 49,653 SNPs as well as relevant clinical variables. The machine learning prediction model based on preconditioning random forest regression (PRFR) (Oh et al., 2017), was then built using the SNPs with ancestry adjusted univariate p-value < 0.001 and clinical variables with Bonferroni adjusted p-value < 0.05. The model was validated in a holdout subset of the cohort. Gene set enrichment analysis (GSEA) was performed using MetaCore to identify key biological correlates relevant to tx-induced fatigue. **Results:** Distinct results were found by domain (table). GSEA showed that the cognitive fatigue model SNPs included biomarkers for cognitive disorders (p = 1.6 x 10^-12) and glutamategic synaptic transmission (p = 1.6 x 10^-6). **Conclusions:** A SNP based model had differential performance by fatigue domain, with a potential genetic role on risk and biology for tx induced cognitive fatigue. Further research to explore biomarkers of tx induced fatigue are needed.

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Clinical Science Symposium, Sat, 8:00 AM-9:30 AM

Using machine learning to predict mortality in older patients with cancer: Decision tree and random forest analyses from the ELCAPA and ONCOCIDE prospective cohorts. First Author: Diane Auperin, Public Health Research Institute, New York City, New York, USA; and 1 other institution; Second Author: Claire Courtin, Hospital Henri Mondor, AP-HP, Créteil, France, EA7376 CepA (Clinical Epidemiology and Ageing Unit), UPEC, Créteil, France

Background: Accurate prognosis is crucial to decision making in oncology, but remains challenging in older patients due to the heterogeneity of this population and the lack of ability of current models to capture complex interactions between oncological and geriatric predictors. We aimed to develop new predictive algorithms based on machine learning to refine individualized prognosis in older patients with cancer. Methods: Data were collected from 3409 patients ≥70 years referred to geriatric oncology clinics for completion of a geriatric assessment (GA), including 2012 and 1397 patients from the ELCAPA (training set) and ONCOCIDE (validation set) French prospective cohorts, respectively. Candidate predictors included baseline oncological and geriatric parameters, C-8 score and routine biologic data (CRP/albumin ratio). Prognostic models for 12-months mortality were built using Cox regression model, single decision tree (DT) and random survival forest (RSF). Models performance was compared based on externally validated Harrell’s C-indexes. Results: During the 1-year study period, 875 (43%) and 219 (16%) patients died in the training and validation sets, respectively (mean age: 81 ± 6 / 78 ± 5, women 47% / 70%, metastasis 50% / 34%). Cox model identified 9 independent predictors of mortality: tumor site/metastatic status, antecedent treatment, weight loss >3kg in the last year, physical activity (IPAQ), male sex, increased C-8 and altered TGU. DT identified more complex combinations between features, yielding 16 patient groups with highly differentiated survival, notably depending on the G-8 (< 10 vs. ≥ 10 as the root). RFS had the highest C-index (0.86 [RFS], 0.82 [Cox], 0.81 [DT]), identifying the G-8, C-8 score and physical activity as independent predictors of survival. Conclusions: While Cox modeling confirmed known independent prognostic factors, DT revealed more complex interactions between them and random forest achieved superior prognostic performance by better capturing patient’s complexity. The latter model has been implemented into an interactive web interface for easy and direct use in clinical practice. Clinical trial information: NCT02884375.

Poster Discussion Session, Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Efficacy of a structured intervention program to improve physical activity (PA) of adolescents and young adult cancer survivors (AYAs): Final results of the randomized Motivate AYA—MAYA trial. First Author: Jannike Lisa Salchow, University Cancer Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Major cardiovascular (CV) events are the most common late toxicities among AYAs. Although regular PA of vigorous intensity (towards metabolic equivalent (MET)hours/week) lowers the risk for CV events and mortality, no larger randomized controlled trials on interventions are available. Our aim was to assess whether a 12-week structured intervention increases the vigorous PA of AYAs. Methods: AYAs aged 15 to 39 years, after curative intent cancer treatment with at least one CV risk factor, were randomized to usual-care control group (CG) and to intervention group (IG). The IG received standard recommendations, and the IG participated at a semi-structured interview and phone consulting focusing on PA and behavioral change. At baseline, post-intervention (12 wks), and at follow-up (52 wks), participants completed the International Physical Activity Questionnaire (IPAQ) and quality of life assessment (EORTC QLQ-C30). Primary endpoint was the rate of AYAs with ≥ 9 MET-hours/week of vigorous activity (IPAQ) at 12 weeks. This single center trial was registered (DRKS00009453). Results: Among 115 screened AYA 89 eligible patients were randomized, 69 (77%) completed the intervention and the Health Impact Assessment; 36 (52.2%) were in the IG and 33 (47.8%) in the CG. Median age was 24.3 years (range, 18 to 39). CV risk factors were use of anticholinergics (94.2%), chest radiation (47.8%), or both (44.9%). At baseline 49.2% of all AYAs reported to perform vigorous PA with at least 9 MET-hours/week, although reporting was individually biased. Post-intervention this rate significantly increased in the IG from 45.7% to 69.7% (p = 0.007), whereas in the CG only a modest non-significant increase was noted (53.3% to 65.6%, p = 0.134). Notably, upon long-term follow up (52 wks) AYAs did not keep their increased vigorous PA, whereas improved moderate PA was achieved (MET score in IG p = 0.044). Also, both groups showed significantly the time they spent sitting hours 6.5 (SD, 2.9) to 5.4 (SD, 2.7) hours/day (p = 0.001). Conclusions: Intensified PA counseling improves short term vigorous PA and long term moderate PA of AYAs and should thus be part of survivorship programs. Further studies with AYAs will be required to establish reliable PA screening methods and to confirm the results in larger cohorts. Clinical trial information: DRKS00009453.

Poster Discussion Session, Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM

Predictors of suicide risk in adolescent and young adults (AYA) with cancer. First Author: Jeremy Howard Lewin, Department of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, Australia

Background: Whilst AYA accounts for a small proportion of annual cancer cases, the complexity of this subgroup places them at a disproportionately high risk of psychological distress and poor mental health. This study aimed to identify independent predictors of suicide risk in AYAs and identify risk factors associated with suicide in AYA patients. Methods: A retrospective analysis of AYA (aged 15-39) between the years 1973 to 2015 from the Surveillance, Epidemiology, and End Result Research database were included. A training and test set were used to develop a model predicting suicide. The SMOTE sampling algorithm was used for the training set due to severe class imbalances. A random forest model was trained with 10 clinical features (cancer subtype, age, sex, race, marital status, diagnosis year, number of in situ/malignant tumours, chemotherapy, surgery, and radiation therapy) with recursive feature elimination (RFE) via 10-fold cross validation. Results: There were 139,394 AYA included with 974 (0.7%) having a documented suicide or self/inflicted injury yielding an incidence of 1499 suicides / 100,000 person years. The standardized mortality ratio (SMR) for AYA was 34.4 (95% CI: 32-37)Aged 15-24: 47.4 (39-57); Aged 25-39: 32.3 (29-35)). Suicide rates increased over time (1973-1980: SMR = 18.0 (15-22), 2001-2015: SMR = 127.0 (102-155)). Univariate analyses observed high rates of suicide in: females (43.8 (38-51)); single/unknown relationship status (47.1 (42-52)); “other” race (85.2 (52-132)) and by cancer type: leukaemia (77.1 (42-129)), soft tissue sarcoma (73.7 (57-94)), unspecified malignancy (71.0 (9-256)) and brain (63.6 (43-91)). We randomly assigned AYAs to a training set (n = 97,576) and test set (n = 41,818), stratified by age: cause of death, and All 10 clinical features were retained with RFE. The prediction model achieved an AUC of 0.59, accuracy of 0.78, sensitivity of 0.40 and specificity of 0.78. Conclusions: Risk of suicide in AYA is high compared to normative data, further heightened in females, single/unknown relationship and certain tumour subtypes. The prediction model performed poorly on unbalanced validation sets, and the variables included were not collected by the SEER dataset. Our findings suggest that dedicated psychosocial supports and targeted mental health assessments are critical components of care for AYA.

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11520 Poster Discussion Session; Displayed in Poster Session (Board #212), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM
Candidate SNPs enhance prediction of cognitive impairment after blood or marrow transplantation (BMT) for hematologic malignancy (HM). First Author: Noa Sharafeldin, Univ Alabama at Birmingham, Birmingham, AL

Background: We tested the hypothesis that candidate genetic variants are associated with cognitive impairment in BMT recipients for HM, and that inclusion of genetic variants improves the performance of a risk prediction model that includes only clinical and demographic characteristics. Methods: We used standardized tests to assess cognitive function in 277 adult BMT recipients at City of Hope (COH), Global Deficit Score (GDS) ≥:0.50 was used as indicator of cognitive impairment. Generalized estimating equation models and logic regression were used to identify single-SNP and gene-level associations with cognitive impairment post-BMT. Three risk prediction models were developed in the COH cohort using elastic net regression: Base Model (sociodemographics); Clinical Model (Base Model + clinical characteristics, therapeutic exposures and baseline cognitive reserve); Combined Model (Clinical + Genetic Model). The Genetic Model included significant SNPs in blood brain barrier, telomere associated with cognitive impairment in BMT recipients for HM, and that inclusion of genetic variants improves the performance of a risk prediction model that includes only clinical and demographic characteristics. Results: The Genetic Model included significant SNPs in blood brain barrier, telomere associated with cognitive impairment in BMT recipients for HM, and that inclusion of genetic variants improves the performance of a risk prediction model that includes only clinical and demographic characteristics.

11522 Poster Discussion Session; Displayed in Poster Session (Board #214), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM
Acupuncture versus cognitive behavioral therapy for cognitive impairment in cancer survivors with insomnia: Implications for personalized medicine. First Author: Jun J. Mao, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Cognitive impairment is a prevalent condition among cancer survivors that lacks effective treatment and can be maintained and exacerbated by poor sleep. This study explored whether treating insomnia with acupuncture or Cognitive Behavioral Therapy for Insomnia (CBT-I) improves subjective and objective cognitive functions in cancer survivors. Methods: We analyzed cognitive outcomes from a pragmatic randomized trial comparing acupuncture versus CBT-I for cancer survivors with insomnia. Analysis was limited to those reporting cognitive impairment at baseline. Acupuncture and CBT-I were delivered over 8 weeks. Perceived cognitive ability was assessed using the Brown Attention-Deficit Disorder Scale (BADDs). Objective cognitive function was evaluated with the Buschke Selective Reminding Test (BSRT). All outcomes were evaluated at baseline, Week 8 (end of intervention), and Week 20 (12 weeks post-intervention). Results: Among 99 cancer survivors, mean age was 60.4 years, 56.6% were women, and 26.3% were non-white. The most common cancer types were breast (31.3%) and prostate (19.2%). Perceived cognitive ability improved in both acupuncture and CBT-I groups at weeks 8 and 20 relative to baseline (all P < 0.001). No significant between-group differences were noted in BADDs total score (p = 0.28), but the CBT-I group demonstrated a better BADDs attention subscale score than the acupuncture group at weeks 8 and 20 (p = 0.031). With regards to objective cognitive functions assessed by BSRT, acupuncture improved attention (p = 0.017), learning (p = 0.040), and memory (p = 0.0020) at Week 8, whereas CBT-I only improved attention at Week 20 (p = 0.0002); between-group differences were not statistically significant. Conclusions: Among cancer survivors with insomnia, both acupuncture and CBT-I improved cognitive impairment relative to baseline, but their relative effects differed: the CBT-I group showed slightly better subjective attention, whereas the acupuncture group may have improved objective memory. Further investigation of these two therapies is warranted to develop effective interventions for cancer survivors. Clinical trial information: NCT02356575.

11521 Poster Discussion Session; Displayed in Poster Session (Board #213), Mon, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Mon, 4:30 PM-6:00 PM
Cognitive rehabilitation program to improve cognition of cancer patients treated with chemotherapy: A randomized controlled multicenter trial. First Author: Mélanie Dos Santos, Centre François Baclesse, Clinical Research Department, Caen, France

Background: Cognitive impairment induced by cancer chemotherapy (CT) has been identified as an important side-effect with negative impact on quality of life (QoL) without specific treatment. We evaluated the impact of computer-assisted cognitive rehabilitation (CR) on cognitive complaint, objective cognitive dysfunction and QoL among cancer patients treated with CT. Methods: We included cancer patients with cognitive complaint occurring during CT or within 5 years of the end of CT. Patients were randomly assigned in a 1:1:1 ratio to face-to-face CR with a neuropsychologist (group A), home cognitive exercises (group B) or phone follow-up (group C) with 9 sessions over 3 months. Cognition was assessed by the Functional Assessment of Cancer Therapy Cognitive Function (FACT-Cog) completed by a neuropsychological battery of test and QoL assessment by the FACT-General (FACT-G). The primary endpoint was the proportion of patients with 7-point improvement in the perceived cognitive impairments (PCI) of the FACT-Cog between baseline (TO) and the end of the program (T3). Results: 167 patients were enrolled, median age was 50 years [43-59] and 96% were women with mainly breast cancer. Compliance rate with completion of all sessions was 76, 61 and 75% respectively. Proportion of patients with 7-point PCI improvement were 73, 55 and 56% without reaching the statistical significance between groups A (p = 0.05), B (p = 0.09) and C (p = 0.08). The mean difference in PCI score were 17, 10 and 10 (p = 0.03). Patients with CR improved their working memory with significant difference between group A and C (1.4 versus 0.3, p < 0.001) but not between group A and B (1.4 versus 1.1, p = 0.43). There was a significant impact of CR on FACT-Cog subscales QoL (p = 0.01) in favor of the group A but not on the different dimensions of the FACT-G. Patients in group A presented improvement in depression compared to group B and C: -6.5 versus -1.7 and -2.3 (p = 0.03). Conclusions: CR with a neuropsychologist improves cognitive complaint. Cognitive stimulation showed improvements in working memory. CR was associated with better QoL linked to cognitive disorders and lower levels of depression. Clinical trial information: NCT01788618.

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Accelerated sarcopenia and outcomes in older adults with cancer: The Health ABC Study. First Author: Kah Poh Loh, University of Rochester Medical Center, Rochester, NY

Background: Progressive loss of muscle mass and strength (sarcopenia) is a well-known phenomenon of aging; however, little is known about the contribution of a cancer diagnosis to sarcopenia and its subsequent impact on disability. Using a prospective cohort of older adults from pre- to post-cancer diagnosis and a similarly-followed non-cancer cohort, we examined the trajectory of sarcopenia measures and their association with overall survival (OS) and major disability among those with cancer. Methods: The Health, Aging, and Body Composition (Health ABC) Study is a prospective longitudinal study where 3,075 community-dwelling older adults (70-79y) underwent 6 annual assessments of body composition and were followed for longitudinal study. First Author: Kah Poh Loh, University of Rochester Medical Center, Rochester, NY

Methods: Patients were recruited from 4 academic centers. Before and 1-7 days after consultation, patients were asked about their perceived chance of cure (options < 10%, 10-15%, and up to 90-100% in 10% increments, and "do not wish to answer"). Oncologists were asked the same question after consultation. Discordance was defined as a difference in response by 2 levels in the patient-oncologist dyads. We used multivariate analysis to assess the demographic and clinical predictors of patient-oncologist discordance. Results: We included 216 patients (median age 95 years, range 22-79) and 46 oncologists (47, 30-70). Overall, >On multivariate analysis, discordance before consultation (Odds Ratio (OR) 6.05, 95% Confidence Interval (CI) 2.96-12.36) and < college education (vs. postgraduate education; OR 2.34, 95% CI 1.09-5.14) were associated with discordance after consultation. Other patient demographics, comorbidity, cancer type, psychological distress, social support, decision-making preference, and coping strategies were not associated with discordance. Conclusions: Patient-oncologist concordance in prognostic understanding improved after subspecialty consultation, but over half of patients' views of their prognosis remained discordant with those of their oncologists. Interventions to improve patient-oncologist communication about prognosis are needed, especially in patients with lower education level.

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Age disparities among cancer clinical trial participants: The role of industry sponsorship. First Author: Ethan B. Ludmir, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Randomized controlled trials (RCTs) in oncology, which often establish the standard of care for cancer patients, do not necessarily enroll trial participants representative of the broader patient population. We sought to characterize age disparities for cancer patients enrolled on RCTs, and asked whether certain trial-related factors (such as industry sponsorship) predispose trials to larger age disparities among trial enrollees and the general population. Methods: All phase 3 RCTs in clinical oncology with results available were identified through ClinicalTrials.gov. Only randomized multi-arm trials assessing a therapeutic intervention for cancer patients were included. The scope of trials was limited to breast, colorectal, lung, and prostate disease sites. Trial participant median ages were compared to national SEER data for population median ages by disease site. Results: Three-hundred and two trials met inclusion criteria. For all trials, the trial median age was an average 6.23 years younger than the population median age (95% CI: 5.55 to -6.91 years, p < 0.001). Trials with industry sponsorship had significantly younger trial patient populations compared with non-industry-sponsored trials (mean difference from population -6.57 vs -4.48 years, p = 0.02). Younger patients were enrolled on trials evaluating targeted agents (p = 0.04), superiority-design trials (p = 0.02), and trials utilizing a surrogate primary endpoint (p = 0.03). By disease site, lung cancer trials enrolled the youngest patients relative to the population median (-8.98 years), followed by breast (-7.76 years), colorectal (-6.96 years), and prostate (+2.66 years, p < 0.001). Conclusions: Industry-funded clinical trials are associated with larger age disparities among trial participants; we believe this represents a novel finding both in clinical oncology and academic medicine more broadly. Underrepresentation of older patients on RCTs has major ramifications for the generalizability of results as well as equity of access to care; future efforts to address trial participant age disparities may focus on those trials at greatest risk for disparities based on the identified risk factors, including industry sponsorship.

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Cumulative burden of new-onset chronic health conditions (CHCs) among older cancer survivors. First Author: Kelly Kenzik, University of Alabama at Birmingham, Birmingham, AL

**Background:** In the US there are an estimated 11 million survivors of cancer diagnosed at ≥65y of age. Description of the morbidity in these survivors has been limited to single complications or to prevalence of comorbidities. The cumulative burden of CHCs remains unstudied, and is critically needed to inform healthcare delivery in this burgeoning population. Moreover, the recently introduced SEER-Medicare, we identified 300,082 patients with breast (34%), prostate (33%), colorectal (16%), non-small cell lung (NSCLC 10%) or non-Hodgkin lymphoma (NHL 7%) diagnosed between 2000 and 2011 at age ≥ 65y (mean age at diagnosis: 75y; 47% males, 88% non-Hispanic whites). An age-, race-, and sex-similar non-cancer cohort (n = 97,842) was assembled. New-onset non-malignant health conditions (n = 109) were consolidated into 10 organ-specific CHCs. Inpatient CHC visits were used to describe severe CHCs. The cumulative incidence (CI) and cumulative burden (CB) of CHCs was described up to 10y from cancer diagnosis and by attained age – up to six months prior to death or until 12/31/2013. Subsequent malignant neoplasms (SMNs) were described 10y from primary cancer diagnosis.

**Results:** The 10y CI of any CHC and severe CHC was 98% (95%: 98-99%) and 73% (72-73%) in cancer patients and 92% (91-92%) and 55% (54-55%) in non-cancer controls (hazard ratio (HR): 1.65, 95%CI: 1.64-1.66). Cardiovascular conditions were the largest burden of non-malignant CHCs (10y CI: 49%-69%). Prostate cancer survivors had the highest 10y CI for SMNs (19.4%). The CI for severe CHCs was 44% by age 80y and 85% by age 90y, compared to 34% and 54% in controls (p < 0.001). The 10y CB of CHCs was highest among NSCLC (42 CHCs/survivor) and colorectal cancer survivors; lowest among prostate survivors; in controls CHCs/individual in controls. Colorectal cancer survivors had greatest overall burden at age 80y (27 CHCs/survivor) and 90y (36 CHCs/survivor), compared to 13 and 16 CHCs/individual in controls. **Conclusions:** The cumulative burden of new-onset multimorbidity among older cancer survivors is substantially greater than that of their non-cancer counterparts, providing quantifiable evidence that survivor-adapted healthcare management policies and risk-based interventions are needed.

Is there a shift in use of subacute rehabilitation (SAR) instead of hospice referral since immunotherapy became available? First Author: Jonathan Yeh, Johns Hopkins Program in Palliative Care, Baltimore, MD

**Background:** Immunotherapy has rapidly become mainstream treatment. Since the first drug approval in 2011, we have noted a decline in referrals from inpatient oncology to hospice, and an increase in referrals to sub-acute rehabilitation (SAR) facilities, possibly with the aim of “getting strong enough” for immunotherapy and other promising drugs. This study explores outcomes after discharge to SAR, including rates of cancer-directed therapy after SAR, overall survival, and hospice utilization. **Methods:** Electronic chart review of patients discharged from oncology units to SAR facilities from 2009-2017. Demographics, admission statistics, and post-discharge outcomes were gathered from discharge summaries and targeted chart searches. **Results:** SAR referrals increased from 28 in 2012 to 82 in 2016. Age 66, males 52%, solid tumors 58%, 358 patients were referred to SAR 413 times. 174 patients (49%) returned to the oncology clinic prior to re-admission or death, and only 117 (33%) ever received further cancer-directed treatment (chemotherapy, radiation, or immunotherapy). 219 of 358 (61%) died within 6 months. Only 3 individuals who were not on immunotherapy at time of admission went on to receive immunotherapy after discharge to SAR. Among all discharges, 28% led to readmissions within 30 days. 74 patients (21%) were deceased within 30 days, of whom only 31% were referred to hospice. Palliative care involvement resulted in more frequent do not resuscitate (DNR) code status (33 v 22%), documented goals of care (GOC) discussions (81 v 23%), and electronic advance directives (42 v 28%).(All p < 0.05). **Conclusions:** A growing number of oncology inpatients are being discharged to SAR, but two-thirds do not receive further cancer therapy at any point, including a substantial fraction that are re-admitted or deceased within 1 month. Many patients lose the opportunity to use hospice for optimal end of life care, as few SAR facilities offer this. These data can help guide decision-making and discharge planning that aligns with patients’ goals of care. More clinical data are needed to predict who is most likely to benefit from SAR and proceed to further cancer therapy.

Early mortality after resection of locally advanced rectal cancer in elderly United States patients. First Author: Helmneh M. Sineshaw, American Cancer Society, Atlanta, GA

**Background:** Early mortality after resection of locally advanced rectal cancer in patients age 75 and older has not been studied in the United States. This information could inform clinical decision-making for patients who achieve complete clinical response after neoadjuvant therapy and consider watchful waiting versus surgical resection. **Methods:** Using the National Cancer Data Base, we identified patients age 75 years and older who underwent surgery for clinical stage II or III rectal cancer between 2004-2015. We performed multivariable logistic regression analyses to assess associations between patient and facility characteristics and 30-day, 90-day, and 6-month mortality. **Results:** Among 11,326 patients, 94% underwent resection and the remaining 6% underwent local excision. Overall early mortality rates after surgery were 4%, 7.6% and 11% for 30-day, 90-day and six-month, respectively. Six-month mortality varied by age subgroup (8% in 75-79 years old to 17.7% in 85 years and older), and comorbidity score (9.5% for comorbidity score = 0 to 18.5% for comorbidity score ≥ 2). Between 2004 and 2015, six-month mortality declined significantly from 11.9% in 2004-2007 to 9.8% in 2012-2015 (P trend = 0.0029), with the decline larger among patients age 85 years and older (from 19.4% in 2004-2007 to 15.3% in 2012-2015, P trend = 0.0377). In the multivariable analysis, older age, higher comorbidity score, and lower facility case volume were significantly associated with higher odds of six-month mortality. Patients treated at National Cancer Institute (NCI) designated facilities had lower odds of six-month mortality compared with those treated at non-NCI designated teaching/research centers. **Conclusions:** Post-operative six-month mortality among patients age 75 years and older with locally advanced rectal cancer in the US declined steadily over the past decade. Older age, higher comorbidity score, and lower facility case volume were substantially associated with higher odds of six-month mortality. Patients treated at National Cancer Institute (NCI) designated facilities had lower odds of six-month mortality after surgery. Additional efforts are needed to guide elderly patients and their physicians in discussing treatment options for locally advanced rectal cancer.

End-of-life care and immune checkpoint inhibitors. First Author: Hazel O’Sullivan, Cork University Hospital, Cork, Ireland

**Background:** In the era of cytotoxic chemotherapy, aggressive cancer treatment and hospitalization at the end of life (EOL) has been associated with a worse quality of death. Meanwhile, in the era of immunotherapy (IO), little is known of the impact of these novel agents on EOL care. The aim of this study was to evaluate the EOL care of metastatic cancer patients treated with immune checkpoint inhibitors. **Methods:** We conducted a retrospective analysis of patients prescribedPD1/L1 or CTLA-4 antibodies in Cork University Hospital (CUH) and Mercy University Hospital (MUH) between January 2013 to December 2018. Patients treated on a clinical trial were excluded. **Results:** We identified 224 patients treated with immune checkpoint inhibitors (outside of a clinical trial) in CUH and MUH over the described 6 year period. 108 of these patients were deceased, 102 electronic files were available for analysis. Of the 102 patients, 57 had metastatic melanoma, 33 non small cell lung cancer, 8 renal cell carcinoma, 4 had other advanced malignancies. 43% were female and 57% were male. 6% of patients had an ECOG performance status (PS) of 0 at diagnosis, 80% PS of 1 and 10% PS of 2. Median age at death was 62 years. 47 patients were treated with pembrolizumab, 26 nivolumab, 25 ipilimumab, 2 nivolumab/ipilimumab and 2 received atezolizumab. 29 patients received IO as first line treatment, 50 as second line, 17 as third line and 6 as fourth line. Median number of IO cycles received was 4 (range 1 - 41). Progression of disease (62%) and declining performance status (14%) were the most common reasons for discontinuation of IO treatment. 16 of the 102 patients received a further line of systemic therapy. Median time from last dose of IO to death was 57 days. 20 patients (20%) died within 30 days of last dose of IO. Of these 20 patients, the median number of cycles of IO received was 2 (range 1- 7), 8 of these 20 patients received one cycle of IO only. 39 patients (38%) died within the first month of life. 34 of the 102 patients received hospice care. Median time from diagnosis to hospice referral was 21 days. 17 of these patients (17%) had ≥ 3 hospital admissions in the last month of life, the median hospital length of stay was 6 days (range 1-30) and 22 patients died in hospital. 94% of patients were referred to palliative care, the median time from palliative care referral to death was 64 days (range 1- 1010), 62% of patients died in hospice. **Conclusions:** Patients with advanced cancer treated with immune checkpoint inhibitors are at high risk for hospitalization at the end of life with high rates of hospital admissions and ED attendance despite early palliative care involvement. 20% of patients died within 30 days of IO. More research is needed to help physicians identify patients who are least likely to benefit from IO so as not to treat futile cases.
11532 Poster Session (Board #224), Mon, 1:15 PM-4:15 PM

Goals of care designation associated with improved survival and indicators of quality end-of-life care in pancreatic cancer (PC) patients (pts) undergoing palliative chemotherapy. First Author: Matthew Anaka, University of Alberta, Edmonton, AB, Canada

Background: Discussion of goals of care (GoC) is a key part of quality care for pts with palliative cancer. Numerous studies have shown that documentation of GoC in this population remains low. Here we describe changes in GoC documentation and other indicators of quality end-of-life care in PC pts undergoing palliative chemotherapy during a health-system wide initiative to improve advanced care planning (ACP). Methods: This is a retrospective cohort analysis of 106 pts with locally advanced or metastatic PC treated with palliative chemotherapy from 2012-2015 in Northern Alberta (Canada). In 2014, an initiative was launched to provide pts with hard copies of their GoC designation intended to be available at all health-system interactions. Data were obtained from outpatient medical oncology (MO) and palliative care (PAC) notes and the provincial cancer registry. Survival analysis used a multivariate Cox-regression. All other tests were Chi-squared. Results: 50% (53/106) of pts had a documented GoC discussion, with 45% (48/106) receiving a specific GoC designation. In 2012, 31% (6/19) of pts had a GoC designation, which increased to 61% (20/33) in 2015. Of 84 individual GoC discussions documented, 34% (29/84) were by MO, 62% (52/84) were by PAC, and at least 8% (7/84) referenced prior discussions with a family physician or discussion while admitted to hospital. Pts with a GoC designation had increased median overall survival (287 vs 216 days; HR = 0.62; p = 0.041), and were less likely to receive chemotherapy in the last two weeks of life (p = 0.016).

Conclusions: Rates of GoC discussions for PC pts undergoing palliative chemotherapy increased during a health-system wide ACP initiative. Having a GoC designation was associated with greater overall survival and indicators of higher quality end-of-life care.

11533 Poster Session (Board #225), Mon, 1:15 PM-4:15 PM

Immune checkpoint inhibitor use near the end of life. First Author: Chad Glisch, University of Iowa, Iowa City, IA

Background: Studies of chemotherapy near the end of life reveal increased costs, adverse effects and minimal clinical benefit. Immune Checkpoint Inhibitor (ICI) use near the end of life has not been described. We studied factors related to ICI use near the end of life. Methods: We conducted a single-institution retrospective chart review of patients who received ICI and died between August 2014 and December 2018. End of life ICI (EOL-ICI) was defined as treatment within the last 30 days of life and comparisons were made to patients who received treatment >30 days from end of life (non EOL-ICI). Results: 441 patients were reviewed. Mean age was 64 and 182 (41%) were female. 294 (67%) received ICI within the last 90 days of life and 117 (27%) within the last 30 days of life. At time of last ICI, 145 (33%) had brain metastases and 416 (94%) were stage 4. The most common cancers were melanoma (124, 28%), NSCLC (118, 27%) and urothelial carcinoma (34, 8%). The EOL-ICI group had a higher proportion of patients with ECOG ≥3 at time of last treatment (22% vs. 7%, p < .001), higher rate of death in hospital (32% vs. 18%, p = 0.003) and lower hospice enrollment (52% vs. 76%, p < .001). The EOL-ICI group received fewer ICI doses (mean 5.1 vs 6.7, p = 0.016). A higher proportion of patients in the EOL-ICI group were just beginning treatment and received ≤3 doses (60% vs. 40%, p < .001). There was no difference in mean age or presence of brain metastases between the groups. Even when the cutoff for EOL-ICI is extended from 30 to 90 days, there remain significant differences in ECOG, hospice enrollment and starting ICI but no difference in rate of dying in the hospital. Conclusions: One out of four patients studied received ICI within the last 30 days of life. EOL-ICI treatment is associated with higher rates of death in the hospital and lower hospice enrollment. Our results suggest that performance status is important when considering treatment with ICI. Use of ICI in the last 30 days of life had minimal clinical benefit and high cost.

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Write to recover: The impact of group led creative writing on behavioral health outcomes in cancer patients. First Author: Daya Nesterova, Penn State Hershey College of Medicine, Hershey, PA

Background: The diagnosis of cancer can adversely affect mental wellbeing. In addition to treating cancer, the emotional wellbeing of patients must simultaneously be addressed. A previous pilot exploring the feasibility of creative writing workshop (CWW) in cancer patients showed apositve effect on patients’ mental health. Methods: To longitudinally evaluate the efficacy of CWW on mood, we conducted a phase II study with cancer patients (any stage, any cancer type); randomized 2:1 to CWW vs. active control (AC). Patients in the CWW group attended at least 4, 1.5-hour bi-monthly CWW x 8 wks, whereas AC patients completed independent writing at home with the help of a book (bi-monthly x 8 wks). We used validated tools, [Emotional Thermometer Scales (ETS), PHQ-9, GAD-7] to assess changes in overall mood, depression, and anxiety. Primary endpoint; a) ETS scores before and after intervention b) Changes in depression and anxiety based on PHQ-9 and GAD-7 scores. We present results from ETS scores. Descriptive statistics were generated for these quantitative scales measured in each group, pre and post intervention. Comparisons between groups (gp) were made using Wilcoxon Rank-sum tests. All tests were two sided and the statistical significance level used was 0.05. Results: Amongst evaluable patients N = 50 (demographics in table below), twenty-six patients in the CWW gp attended at least one class and 19 attended at least 4 classes. Patients in CWW showed significant mood improvement vs. AC when comparing the final overall ETS (p = 0.0063). Three of the five sub-scale ETS scores were significantly lower for the CWW compared to the AC gp: anxiety (p = 0.0027), depression (p = 0.0027), and anger (p = 0.0027). Conclusions: Group led CWW have a positive effect on mood. Our results suggest potential therapeutic benefit of this intervention on the emotional wellbeing of cancer patients. Larger studies are needed to evaluate the effect of CWW in cancer patients. Clinical trial information: NCT03536702.

Demographics.

| Variable | Categories | Overall (N=50) | CWW (N=33) | AC (N=17) | Prol
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Comparing outcomes data from dedicated oncology-subspecialist hospitalists to those from a traditional care model on an inpatient oncology service. First Author: Kristina Fanucci, Lifespan Health System, Providence, RI

Background: Changes in the complexity and delivery of health care efforts to contain rising costs gave rise to the hospitalist model of care delivery in the 1990s. More recently some hospitals have begun using the hospitalist model on inpatient oncology floors. Oncology patients are a unique population who require high rates of hospitalization for problems arising from their progressive disease burden and side effects of cancer-directed therapy and have high rates of 30 day readmissions (30DR), an important quality metric. The majority of studies in this area have shown similar outcomes comparing care given by internal medicine hospitalists working full time on an inpatient oncology service compared to multiple oncologists working in rotating shifts on the same inpatient oncology service (Traditional). A new care model using dedicated hematologist/oncology subspecialist hospitalists (H-O) to care for patients admitted to the oncology service has been implemented at our academic medical center. Methods: We conducted a retrospective chart review to identify patients with a cancer diagnosis admitted to the oncology service over a six year period. 7/1/2012-6/30/2015 marked the Traditional care model and 7/1/2015-7/1/2018 the H-O model. We compared 30DR, discharge to hospice, and 30DR. Results: We identified a total of 3778 patients admitted to the oncology service over this six year period—1932 patients admitted to the Traditional service and 1846 patients admitted to the H-O service. There was a significant difference in 30DR between the Traditional v. H-O service (36.7% v. 29.5%, \( \chi^2 = 21.1, p < 0.000001 \)) and discharge to hospice (7.6% v. 12.9%, \( \chi^2 = 29.0, p < 0.0000001 \)). There was no significant difference in LOS between the Traditional and H-O services (6.40 days v. 6.03 days, p = 0.122) or in-hospital mortality (2.5% v. 1.9%, \( \chi^2 = 2.16, p = 0.14 \)). Conclusions: The shift to dedicated hospitalist-oncologists caring for patients on the inpatient oncology service significantly decreased 30DR at our institution. There were also significantly more patients transferred to hospice care. We found no significant difference between the two groups in LOS or inpatient mortality. This care model may help reduce the cost of caring for oncology patients by decreasing 30DR.

Variation in the intensity of end-of-life care, hospice enrollment, and the cost of 8 day cancer site. First Author: Shitanshu Uppal, University of Michigan, Ann Arbor, MI

Background: To compare end-of-life (EOL) care intensity across multiple cancer sites and its impact on the cost of care during the last 30-days of life. Methods: Cross-sectional retrospective study using Surveillance, Epidemiology, and End Results Program (SEER)-Medicare linked database from 2008-2013. Utilization of the following in the EOL period (last 30 days of life prior to death) was examined: 2 or more visits to the Emergency Department (ED), hospitalizations, receipt of any life-extending procedures, admission to intensive care unit, any hospice use, hospice use \( \leq 3 \) days, death in hospital, or receipt of chemotherapy (last 14 days). We tallied the claims made during the EOL period for each patient. Median expenditures during the EOL period were tabulated by cancer site and stratified by receipt of hospice care. Results: EOL care utilization varied widely between cancer sites. The rates of any hospice utilization were the highest for breast cancer (48.2%) compared to ovarian (17.4%) (p < 0.001). Chemotherapy during the last two weeks of life was the highest for ovarian cancer (17.1%) and the lowest for colorectal cancer (0.5%). The median cost of care during the EOL period for patients who received hospice care was $7,547.84 (Interquartile range [IQR] $5,422-$17,293) compared to $17,179 (IQR $10,323-$30,824) for those never received hospice care (p < .0001). There was no significant variation in median cost by cancer site for those who received hospice services (range $7,317 - $9,816). However, the cost of care varied for those who did not receive hospice care. Median costs for this subgroup the lowest was for pancreatic cancer ($14,635) and the highest for colorectal cancer ($24,324) (p < 0.001). Conclusions: Despite increasing acceptance of palliative care services and hospice in cancer care, there continues to be intensive and costly care administered during the EOL period. These costs vary considerably across cancer sites when patients do not receive hospice care, but costs are relatively similar when patient are enrolled in hospice. Further research is needed to investigate the causes of this variation should be undertaken to design interventions aimed at improving timely hospice enrollment at the EOL and reducing costly care in the EOL period.

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**First Author:** Armin Shahrokni, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** Prognosis in NSCLC is vital for clinical decision making. With the aging US population and rapidly changing treatment landscape, we aimed to identify prognostic factors among older adults with advanced NSCLC receiving chemo-, immuno-, and/or targeted therapy. 

**Methods:** We conducted a prospective cohort study of adults ≥65 with advanced NSCLC starting a new non-curative systemic treatment (chemo-, immuno-, and/or targeted therapy) at a Comprehensive Cancer Center, Veterans Affairs Medical Center, and safety-net hospital. Prior to treatment initiation, patients completed a geriatric assessment including cognition, function, comorbidities, mood, social support, and quality of life. Cox proportional hazards models were identified to predict prognostic factors for overall survival (OS). 

**Results:** In a sample of 51 patients, median age was 73 (range 65-94). The majority of patients had stage IVB (59%) or IVA (39%) NSCLC. Current treatment included immunotherapy (37%), targeted therapy (29%), chemoimmunotherapy (18%), and chemo (16%). Most patients had received prior NSCLC treatment (80%); chemo (51%), targeted therapy (35%), immunotherapy (22%), radiation (RT; 47%), and surgery (19%). At enrollment, 73% had an abnormal Montreal Cognitive Assessment score < 26 (McCA; median score 23) and 35% had an abnormal Timed Up and Go time ≥ 13.5 sec (TUG; median time 12.7 sec). Median OS was 12.5 months. In univariable analyses, stage IVB disease (HR 6.99, 95% CI 1.35-31.5), prior RT (HR 2.98, 95% CI 1.08-8.21), worse McCA score (HR 1.15 per 1 point change, 95% CI 1.03-1.29), and longer TUG time (HR 1.1 per sec change, 95% CI 1.05-1.23) were associated with worse OS. Of note, age, current NSCLC treatment, line of therapy, and Karnofsky Performance Status were not associated with OS. In multipivariable analysis, McCA score was the only statistically significant prognostic factor (HR 1.15, 95% CI 1.01-1.30). 

**Conclusions:** We found that abnormal pretreatment cognitive impairment is very common and an important prognostic factor among older adults with advanced NSCLC. Pretreatment screening for cognitive impairment should be considered to inform prognostication, decision making, and treatment planning.


**First Author:** Armin Shahrokni, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** Prognosis in NSCLC is vital for clinical decision making. With the aging US population and rapidly changing treatment landscape, we aimed to identify prognostic factors among older adults with advanced NSCLC receiving chemo-, immuno-, and/or targeted therapy. 

**Methods:** We conducted a prospective cohort study of adults ≥65 with advanced NSCLC starting a new non-curative systemic treatment (chemo-, immuno-, and/or targeted therapy) at a Comprehensive Cancer Center, Veterans Affairs Medical Center, and safety-net hospital. Prior to treatment initiation, patients completed a geriatric assessment including cognition, function, comorbidities, mood, social support, and quality of life. Cox proportional hazards models were identified to predict prognostic factors for overall survival (OS). 

**Results:** In a sample of 51 patients, median age was 73 (range 65-94). The majority of patients had stage IVB (59%) or IVA (39%) NSCLC. Current treatment included immunotherapy (37%), targeted therapy (29%), chemoimmunotherapy (18%), and chemo (16%). Most patients had received prior NSCLC treatment (80%); chemo (51%), targeted therapy (35%), immunotherapy (22%), radiation (RT; 47%), and surgery (19%). At enrollment, 73% had an abnormal Montreal Cognitive Assessment score < 26 (McCA; median score 23) and 35% had an abnormal Timed Up and Go time ≥ 13.5 sec (TUG; median time 12.7 sec). Median OS was 12.5 months. In univariable analyses, stage IVB disease (HR 6.99, 95% CI 1.35-31.5), prior RT (HR 2.98, 95% CI 1.08-8.21), worse McCA score (HR 1.15 per 1 point change, 95% CI 1.03-1.29), and longer TUG time (HR 1.1 per sec change, 95% CI 1.05-1.23) were associated with worse OS. Of note, age, current NSCLC treatment, line of therapy, and Karnofsky Performance Status were not associated with OS. In multipivariable analysis, McCA score was the only statistically significant prognostic factor (HR 1.15, 95% CI 1.01-1.30). 

**Conclusions:** We found that abnormal pretreatment cognitive impairment is very common and an important prognostic factor among older adults with advanced NSCLC. Pretreatment screening for cognitive impairment should be considered to inform prognostication, decision making, and treatment planning.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Older patients with advanced cancer face considerable uncertainty related to their disease and treatment. The aim of our study was to evaluate the associations of uncertainty with psychological status and QoL.

Methods: This is a secondary analysis of baseline data from a national geriatric assessment (GA) cluster randomized trial (URCC 13070; PI: Mohile). Patients aged ≥70 years with ≥ 1 GA domain impairment (e.g., function, cognition) and advanced cancer who were considering or receiving any line of cancer treatment were enrolled (n=541). Uncertainty was measured using the modified 9-item Mishel Uncertainty in Illness (MUIS), where respondents with higher scores perceive more uncertainty (range 9-45). QoL and psychological measures consisted of Functional Assessment of Cancer Therapy-General (FACT-G), emotional wellbeing (EWB; FACT-G subscale), distress (distress thermometer), anxiety (Generalized Anxiety Disorder-7), and depression (Geriatric Depression Scale-15). Multiple linear regressions were used to evaluate the associations of MUIS scores with each measure, adjusted for demographics, cancer type, and number of impaired GA domains.

Results: Mean age was 77 years (SD 5, range 70-96); 26% had gastrointestinal cancer and 26% had lung cancer. Mean number of GA domain impairments was 4 (SD 1, range 1-7). Mean MUIS score was 20 (SD 5, range 9-37). On multivariate analyses, higher MUIS score was associated with lower QoL (β=-1.08, SE=0.11) and EWB (β=-0.29, SE=0.03), as well as higher distress (β=0.12, SE=0.02), anxiety (β=0.11, SE=0.04), and depression (β=-0.19, SE=0.03; P<0.01).

Conclusions: Distress associated with uncertainty was common in a vulnerable population of frail older patients with advanced cancer and ≥ 1 GA domain impairment. A higher degree of uncertainty was associated with poorer psychological health and QoL. Our results underscore the important role that uncertainty management interventions (mainly including information and coping strategies) could be revised, tailored and tested to meet the unique needs of older patients with cancer. Clinical trial information: NCT02107443.

Background: Older adults aged ≥65 years with incurable cancer who had discussed palliative chemotherapy with an oncologist and made a decision about whether or not to receive palliative chemotherapy were invited to complete a written questionnaire. Preferred and perceived decision-making roles were assessed by the Control Preferences Scale (CPS). Associations with preferred decision-making role were examined using Wilcoxon rank sum tests. Factors important in making a decision about chemotherapy, and receipt of and desire for information were described.

Results: The 179 respondents had a median age of 74 years (range 65 to 92 years). Most were male (114, 64%) and had chosen to receive chemotherapy (6). Half (92, 52%) were vulnerable by the Vulnerable Elders Survey-13 (score ≥3). Preferred decision-making roles (n = 173) were active in 39%, collaborative in 27%, and passive in 35%. Perceived decision-making roles (n = 172) were active in 42%, collaborative in 22%, and passive in 36%, and matched the preferred role for 63% of patients. Preference for an active role was associated with being single/widowed (p = 0.004, OR 1.49) and declining chemotherapy (p = 0.02, OR 2). Factors ranked most important when making a decision about chemotherapy (n = 159) were “everything possible” (30%), “my doctor’s recommendation” (26%), “my quality of life” (20%), and “living longer” (15%). A minority expected chemotherapy to cure their cancer (14%). Most had discussed expectations of cure (70%), side effects (88%) and benefits (82%) of chemotherapy, though fewer had received quantitative prognostic information (49%) than desired this (67%).

Conclusions: Older adults showed varied preferences for involvement in decision-making about palliative chemotherapy, and most played the role that they preferred. To facilitate shared decision-making, oncologists should seek patients’ decision-making preferences, priorities and information needs when discussing palliative chemotherapy.
Symptoms and Survivorship

11548 Poster Session (Board #240), Mon, 1:15 PM-4:15 PM
Guided geriatric interventions (GI) in older adults with cancer: What, how, and for whom? The French PACA EST Cohort Experience. First Author: Rabia Boullahsassa, Centre Hospitalier Universitaire de Nice, Hôpital de Cimiez, Nice, France

Background: Some previous studies in geriatric oncology have described the GI and their adherence. Today’s challenge is to screen patients needing specific GI and repeated Comprehensive Geriatric Assessments (CGA). We recently analyzed a phenotype of patients requiring more GI (Boullahsassa et al, Cancers 2019). The main purpose of the present study is to compare types of GI implemented, according to patient frailty levels, in order to better understand the necessary care plan. Methods: Between April 2012 and May 2018, 3530 consecutive patients with solid tumors were enrolled in this multicentric, prospective cohort. 3140 patients (mean age: 82y) were finally included and a CGA was performed at Baseline. Twelve GI were standardized, individualized or based on experience if no guidelines were available. Within 1 month, geriatricians including patients in the cohort received standardized training. Logistic regression was performed to compare types of GI in the 3 groups using the Balducci Score (B1/B2/B3). Results: 8819 GI were implemented for the 3140 patients. On average, fit patients had 1.5 GI (n = 1458) and frail patients 3.6 GI (n = 1426). We observed no significant differences between the 3 groups concerning specific pain management (Fit vs B2: p = 0.19; Fit vs B3: p = 0.57) and psychological care (Fit vs B2.p = 0.03; Fit vs B3: p = 0.24). In vulnerable and frail patients, we recorded more significant GI for nutrional care, delirium prevention, and frailty management. GI were primarily the nurse interventions, treatment modifications for optimization or iatrogenic disorders and psychotherapy, with the highest Odds Ratio for nursing interventions (Fit vs B2: OR 2.9 p = 0.011; Fit vs B3: OR 9 P < 0.001) and psychotherapy (Fit vs B2: OR 4.3 p < 0.001; Fit vs B3: OR 9.9 p < 0.001). B3 patients had significantly more GI on cancer related management (p = 0.002) and caregiver care (OR.2, p = 0.049). Conclusions: Fit patients also needed GI. We observed differences in types of GI between the groups. However, the aims and levels also seemed to differ and need further studies to analyze their impact.

11550 Poster Session (Board #242), Mon, 1:15 PM-4:15 PM
Predicting severe toxicity of targeted therapies in elderly patients with cancer (PreToXE): A multicenter, prospective, and retrospective study. First Author: Coriolan Lebretón, Institut Bégonia, Bordeaux, France

Background: It is crucial that targeted therapies are also studied in senior patients to establish predictive factors of severe toxicity. Methods: The PRE-TOXE study includes 3 multicentric independent cohorts of patients ≥70 years old with advanced solid tumor (2 retrospectives and one prospective) and treated with a tyrosine/kinase inhibitor (TKI) as per drug label. Data on clinical and biological characteristics of the patient, disease and treatment were centrally collected at the beginning of the treatment. Primary endpoint is severe toxicity defined as treatment-related death, persistant or significant disability/incapacity, hospitalization or discontinuation of treatment for more than three weeks. Predictive factors of severe toxicity were first identified in a training retrospective cohort by multivariate analysis. Two independent cohorts (retrospective and prospective) will be used for external validation. Results: 371 patients entered the study (training retrospective cohort n = 171, 46.1 %; validation retrospective cohort: n = 160, 43.1%, validation prospective cohort: n = 40, 10.8%). Median age was 74.0 (range 70.0-88.0) in the training retrospective cohort. 73 patients (42.7%) were male. The most frequent solid tumors were lung 64 (37.4%), breast 50 (29.2%), sarcomas 27 (15.8%), colon 10 (5.8%) and kidney 8 (4.7%). The five most frequent prescribed TKIs were everolimus 51 (29.8%), erlotinib 43 (25.1%), pazopanib 18 (10.5%), gefitinib 17 (9.9%) and regorafenib 14 (8.2%). The prescribed dose was lower than that everolimus 51 (29.8%), erlotinib 43 (25.1%), pazopanib 18 (10.5%), gefitinib 17 (9.9%) and regorafenib 14 (8.2%). On multivariate analysis, female gender, ≥3 comorbidities and anti-angiogenic activity of TKI were independent predictive factors of severe toxicity. External validation on the other two independent cohorts (retrospective and prospective) will be presented at the meeting. Conclusions: One in four cancer patient ≥ 70 years old and treated with a TKI has severe toxicity impacting treatment outcome. The role of geriatric interventions to prevent such toxicities should be considered particularly in female patients, patients with ≥3 comorbid medications or when the TKI targets the VEGF receptors family. Clinical trial information: NCT02751827.

11551 Poster Session (Board #243), Mon, 1:15 PM-4:15 PM
Prognostic value of routine biomarkers in older patients with cancer: Pooled analysis of three prospective cohorts. First Author: Elena Paillaud, Hopital Européen Georges Pompidou, Paris, France

Background: To assess prognostic value of routine biomarkers in older patients with cancer. Methods: A pooled analysis of three prospective multicentre cohorts, ELCAPA, PHRC Aquitaine and ONCODAGE was conducted. Patients aged 70 years or older, with cancer were included. Biomarkers collected were plasmatic C-reactive protein, albumin and a combined score: Glasgow Prognostic Score (GPS). The GPS comprised three categories (0: CRP<10 mg/L, albumin≥35 g/L; 1: CRP≥10 mg/L and albumin<35 g/L, or CRP > 10 mg/L and albumin≥35 g/L; 2: CRP > 10 mg/L and albumin < 35 g/L). The primary endpoint was overall survival at 12 months. Multivariable Cox models were used, adjusting for age, sex, localisation, metastatic status, performance status, frailty screening index, the GPS. Discriminative properties were assessed using Harrell C index and NRI (Net Reclassification Improvement). Results: Overall 1800 patients were analyzed (ELCAPA: N = 543, PHRC Aquitaine: N = 253, ONCODAGE: N = 1004; mean age: 78.5±5.5 years; 61.7% of men; 37% metastatic; most frequent localisations: breast (34.9%) and colon-rectum (17.7%); 70.7% of patients screened at risk of frailty by G8). Overall survival was 71.1%. GPS was independently associated with death (among normal G8: GPS 1: Hazard Ratio (HR) = 4.48; 95% Confidence Interval (95% CI) = [2.03; 9.89], GPS 2: 11.64 [4.54; 29.81], among abnormal G8: GPS 1: 2.45 [1.79; 3.34], GPS 2: 3.97 [2.93; 5.37]. The addition of GPS to the clinical model (Harel C: 0.82 [0.80; 0.83) improved discrimination (Harel C: 0.84 [0.82; 0.85], NRI: 11% [5; 191]. Conclusions: GPS could be used in older patients with cancer to help decision-making and prognosis assessment.

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Role of the oncologic-multidimensional prognostic index in older patients with metastatic colorectal cancer treated in a real-world setting. First Author: Letizia Paesaccio. Department of Clinical and Experimental Oncology, Medical Oncology 1 Unit, Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy

Background: About 50% of diagnoses of colorectal cancer (CRC) occur in patients (pts) older than 70 years. Though a comprehensive geriatric assessment (CGA) is recommended for proper management of older cancer pts, there is still no consensus on the best form of geriatric assessment. We investigated possible prognostic factors in elderly metastatic (mCRC) pts in a real-world setting, focusing on the role of the oncologic-multidimensional prognostic index (onco-MPI).

Methods: Pts aged ≥70 years with mCRC referred to the Medical Oncology 1 Unit from May 2010 to May 2017 were assessed by a multidisciplinary team and received a basal CGA. Onco-MPI was calculated by a validated algorithm as a weighted linear combination of the CGA domains, as previously described. The following 3 different prognostic groups were identified: low (scores 0.0-0.46), medium (scores 0.47-0.63) and high risk (scores 0.64-1.0).

Results: A total of 206 mCRC pts were included, 123 males. Mean age was 76.1 years (69.2-90.8). ECOG PS was <2 in 90% and mini-mental state examination was ≥24 in 85% of pts. Primary tumor was located in rectum, left and right side in 18%, 42% and 40% of pts, respectively. RAS and BRAF mutations were detected in 44% and 9% of pts, respectively. According to onco-MPI score, 32%, 39% and 29% of pts were classified as fit, 56% of pts were classified as fit, 31% vulnerable and 13% frail. Median overall survival (OS) was 26 months (95% CI 19.7-32.4). The following factors were significantly associated with OS: ECOG PS (0-1 vs >1, 31% vs 15%, p = 0.004); onco-MPI score (low vs medium vs high risk, 29% vs 38% vs 19%, p = 0.005), treatment (monotherapy vs doublet/triple therapy, 31% vs 30%, p = 0.01). No significant difference in OS was observed in CGA-based groups (p = 0.15). In high onco-MPI score, doublet-regimen correlated with higher OS compared to monotherapy (79% vs 51%, p = 0.03).

Conclusions: Onco-MPI emerged as a significant prognosticator in mCRC elderly pts. It may be useful in daily clinical practice for driving decision-makin in this age group. Thanks to its marked standardization it may be also applied in clinical trials.

Functional impairment on admission and associated symptom burden and health outcomes among hospitalized patients with advanced cancer. First Author: Daniel E Lage, Massachusetts General Hospital, Boston, MA

Background: Hospitalized patients with cancer often have impaired function, as measured by activities of daily living (ADLs), related to age, comorbidities, and both cancer and treatment-related morbidity. However, the relationship between functional impairment and patients’ symptom burden and clinical outcomes has not been well described. Methods: We prospectively enrolled patients with advanced cancer, with unplanned admission at a tertiary academic medical center. Upon admission, nurses assessed patients’ ADLs (mobility, feeding, bathing, dressing, and grooming). We used the Edmonton Symptom Assessment Scale (ESAS) and Patient Health Questionnaire-4 to assess physical and psychological symptoms, comparing symptom burden between patients with and without ADL impairment. We used regression models adjusted for age, sex, education, Charlson comorbidity index, months since advanced cancer diagnosis, and cancer type to assess the relationship between any ADL impairment on admission and hospital length of stay, the composite outcome of death or readmission within 90 days of discharge, and survival. Results: Among 932 patients, 40.2% had at least one ADL impairment. Patients with ADL impairment were older (Mean = 67.2 vs 60.8 years, p < 0.001), had higher Charlson comorbidity index (Mean = 1.1 vs 0.7, p < 0.001), and higher physical symptom burden (ESAS Physical Mean = 35.2 vs 30.9, p < 0.001). Those with ADL impairment were more likely to have moderate to severe constipation (46.7% vs. 36.0%, p < 0.01), pain (74.9% vs. 63.1%, p < 0.01), drowsiness (76.6% vs. 68.3%, p < 0.01), as well as symptoms of depression (38.3% vs. 23.6%, p < 0.01) and anxiety (35.9% vs. 22.4%, p < 0.01). In adjusted models, ADL impairment was associated with longer hospital length of stay (B = 1.30, p < 0.01), higher odds of death or readmission within 90 days (odds ratio = 2.26, p < 0.01), and higher mortality (hazard ratio = 1.73, p < 0.01).

Conclusions: Hospitalized patients with advanced cancer who have functional impairment experience a significantly higher symptom burden and worse health outcomes compared to those without functional impairment. These findings highlight the need to assess and address functional impairment among this population to enhance their quality of life and care.

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<td>PTD 300</td>
<td>44 (20.37)</td>
<td>1.33 (0.80 to 2.18)</td>
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<td>TTI 573</td>
<td>73 (34.72)</td>
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| PTD 300 | 44 (20.37) | 1.33 (0.80 to 2.18) | 625 (33.26) | 1.15 (0.77 to 1.71) |
| TTI 573 | 73 (34.72) | 1.09 (0.60 to 1.96) | 1176 (57.70) | 1.72 (1.09 to 2.69) |

Multivariate analysis includes comorbidity, polypharmacy, type and timing of chemotherapy.

Obesity paradox in older cancer patients for middle and long-term mortality: A prospective multicenter cohort study of 2,071 patients. First Author: Claudia Martinez-Tapia, EA 7376 CEpiA (Clinical Epidemiology and Ageing Unit), Crétel, France

Background: Overweight and obesity are associated with numerous adverse health outcomes. However, among older adults, substantial literature suggests an improved survival among overweight and obese patients. This phenomenon, referred to as the “obesity paradox” remains controversial. In the context of cancer, the association between obesity and mortality is complex due to the concomitant weight loss and cachexia. We aim to assess the impact of high Body Mass Index (BMI) on mortality in a large population of older cancer patients. Methods: We studied patients aged ≥70 from the ELCAPA prospective cohort (2007-2016; 10 geriatric oncology clinics, Great Paris urban area). Endpoints were 12- and 48-months mortality. A variable combining BMI at cancer diagnosis and weight loss (in the 6 months preceding the diagnosis) was created. BMI categories considered: underweight (BMI < 22.4kg/m²), normal weight (BMI 22.5-24.9), overweight (BMI 25-29.9), and obese (BMI ≥30); weight loss (WL) categories; < 5%, 5-<10%, ≥10%. Univariate and multivariate Cox proportional-hazards analysis were conducted in males and females. Results: A total of 2071 patients were included (mean age, 81; female, 48%; metastases, 49%; main localizations: digestive (37%), urinary (26%), breast (16%); underweight (30%), normal weight (23%), overweight (20%) and obese (27%). Overweight or obese elderly women and men had no reduced risk of mortality compared to normal weight women and men. Overweight and obese men had no reduced risk of mortality irrespective of weight loss. Conclusions: By taking into account initial weight loss, we did not find evidence for obesity paradox in older patients with cancer except in the subgroup of women with minimal weight loss. Clinical trial information: NCT02884375.
Identifying patient-reported anxiety and depression in older adults with cancer.

First Author: Reena Jayani, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Anxiety and depression are associated with decreased quality of life, treatment adherence, and survival in patients with cancer. Mental Health Inventory (MHI-17) is a validated screening tool for psychological well-being, but cut points for older adults with cancer are unknown. The goal of this study is to identify cut points on MHI-17 Anxiety (MHI-A) and Depression (MHI-D) subscales which correlate with patient-reported anxiety and depression in older adults with cancer.

Methods: This is a secondary analysis of baseline data from a randomized controlled trial in adults aged 65+ with solid tumors starting chemotherapy. At baseline, patients completed MHI-17. MHI-A and MHI-D were calculated (range 0-100; higher scores represent better mental health). Self-reported anxiety was obtained from single-item Linear Analog Scale Assessment (0-5 = low, 6-10 = high). Self-reported depression was obtained from Yale Depression Screen, “Do you often feel sad or depressed?” The association of MHI-A and MHI-D with the patient-reported outcomes was analyzed using logistic regression. Youden’s index was used to determine the optimal cut points for MHI-A and MHI-D for identifying patients with high anxiety and depression.

Results: Of 10,702 titles, 26 studies (108,793 patients) were included. Pooled HR for DFS for obese vs non-obese were (i) ER/PgR+ve HER2-ve 1.21 (95% CI: 1.12-1.31, p < 0.0001), (ii) HER2+ve any ER/PgR 1.16 (95% CI: 1.06-1.26, p = 0.0006) and (iii) TN 1.13 (95% CI: 1.05-1.22 = 0.0022). Pooled HRs for OS were (i) ER/PgR+ve HER2-ve 1.45 (95% CI: 1.30-1.62, p < 0.00001), (ii) HER2+ve any ER/PgR 1.21 (95% CI: 1.10-1.34, p = 0.0001) and (iii) TN 1.13 (95% CI: 1.04-1.23, p = 0.0033). Pooled HR for OS (but not DFS) were somewhat higher in observational vs interventional studies in (i) ER/PgR+ve, HER2-ve 1.57 vs 1.36, HER2+ve any ER/PgR (i) 1.37 vs 1.09 and (ii) TN 1.2 vs 1.22 (p = 0.21, 0.03 and 0.48, respectively). Conclusions: Obesity was associated with a worse outcome in all BC subtypes. Higher HR for OS in observational studies in (i) ER/PgR+ve, HER2- and (ii) HER2+ve any ER/PgR may reflect selection of healthier patients for intervention trials.

Physiological and psychosocial effects of a highly structured exercise program in breast cancer survivors.

First Author: Judy A. Tjo, TORQUE, Aurora Health Care/ECOG/ACRIN, Milwaukee, WI

Background: Exercise after breast cancer treatment improves cancer-related outcomes, although the mechanism of action is unclear. Engagement in healthy active lifestyles after cancer treatment may also impact overall survival. We aimed to determine effectiveness of a highly structured, clinically overseen, goal oriented, group triathlon training program on improving physiological and psychosocial outcomes in female breast cancer survivors (BCS).

Methods: After stage appropriate local and systemic breast cancer treatment, 53 female BCS were recruited to participate in this study. The 14-week group triathlon training program was individually adjusted for treatment side effects. 28 similar BCS who did not participate in the training served as controls. Pre- and post-exercise training measures included: Functional endurance (Timed 6MWT), quality of life (QOL, FACT-B), cancer-related fatigue (CRF, FACIT-F), exercise self-efficacy (ESE) via questionnaires, estradiol, and inflammatory biomarkers (C-reactive protein, TNF-β, leptin and adiponectin). Results: Complete data were obtained from 41 (mean age 51 (7) yr, mean BMI 29.5 (6.2) triathlon finishers and 16 (mean age 56 (10) yr, mean BMI 31.5 (8.0)) controls, 6MWT improved (26 m) more in the triathlon group (p < 0.05). FACT-B, FACT-F, and ESE all improved compared to controls (all p < 0.05). Body mass and BMI decreased in the training group compared to controls (p = 0.01, p = 0.04 respectively). Arm circumference decreased in the trained group but increased in controls (p < 0.05). Estradiol and leptin positively correlated with initial body weight in both groups but did not change after training. Adiponectin significantly decreased in the triathlon group (p = 0.01), perhaps due to selection bias of controls. No significant changes were seen in other serological markers. Conclusions: A highly structured, clinically overseen, moderate intensity exercise program can improve endurance, QOL, CRF, body mass, and possibly improve survival after breast cancer treatment. Furthermore, improvements in ESE may provide tools for patients to continue adherence to regular exercise guidelines that may lower obesity and its related comorbidities, including arm lymphedema.

Poster Session (Board #248), Mon, 1:15 PM-4:15 PM

Poster Session (Board #249), Mon, 1:15 PM-4:15 PM

Poster Session (Board #250), Mon, 1:15 PM-4:15 PM

Poster Session (Board #251), Mon, 1:15 PM-4:15 PM

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Analysis of health behavior change on health utility (HU) and financial toxicity in head and neck cancer (HNC) survivors. First Author: Lawson Eng, Division of Dental Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Health behavior changes including tobacco cessation and increasing physical activity (PA) are important aspects of cancer survivorship. Understanding how these behaviors impact on HU and financial toxicity will help when evaluating survivorship programs. We evaluated the impact of tobacco cessation and PA on HU, function and financial toxicity among HNC patients.

Methods: HNC pts from Princess Margaret Cancer Centre completed questionnaires at baseline (diagnosis) and 12 months between 2014-2018 evaluating tobacco use, PA with the Godin questionnaire, cancer related monthly out of pocket costs (OOPC), HU using HU Index Mark 3, function using Lawton Brody Scale (LBS) and lost annual income. Multivariable linear regression analyses evaluated the impact of health behavior change on OOPC, HU, LBS and lost income. Results: Among 296 pts, mean age 61, 76% male; 29% smoked at diagnosis, 60% quit 1 year after; 26% met PA guidelines at diagnosis, 52% continued to meet guidelines at 1 year. 19% of those not meeting PA guidelines at diagnosis, met them at 1 year. Among all, mean monthly OOPC (SEM) was $171 (27) (12 months); mean monthly individual income was $25897 (2945). Among smokers at diagnosis, those continuing to smoke at 1 year lost a mean of $21272 (95% CI [$2783-39761] P = 0.03) more in individual annual income compared to pts who quit, adjusted for baseline income and education. Current smokers who quit at 1 year had an adjusted mean increase in HU of 0.15 (0.00-0.30) P = 0.05 greater than pts continuing to smoke. Pts who continued meeting PA guidelines at 1 year had an adjusted mean increase in HU scores of 0.11 (0.02-0.20) compared to those reducing PA levels after diagnosis. Comparison in PA and tobacco use was associated with changes in OOPC, improving to meet PA guidelines after diagnosis was not associated with HU or lost income (P> 0.05). Conclusions: Quitting smoking and maintaining PA levels after diagnosis were associated with improvements in HU scores; quitting smoking reduced lost income. Cancer survivors should be made aware of the potential economic impact of behaviour change.

Impact of overweight, obesity, and post-treatment weight changes on occupational reintegration of breast cancer (BC) survivors. First Author: Antonio Di Meglio, Institut Gustave Roussy, Villejuif, France

Background: Overweight and obesity are strongly linked to poorer BC-specific outcomes, quality of life and financial burden in cancer care. Weight loss interventions have the potential to improve such outcomes. Fewer data exist on whether excess weight and post-diagnosis weight changes impact the ability of BC survivors to return to work (RTW). Methods: CANTO (NCT01993498) is a multicenter prospective longitudinal study of 12000 patients (pts) with stage I-III BC that characterizes long-term toxicities of BC treatment. Of 5801 pts enrolled from 2012-2014 (last data lock), we identified 1874 pts who were professionally active at BC diagnosis, >5 years (yrs) younger than minimum legal retirement age (62 yrs) and with updated work status 2 yrs after diagnosis. Logistic regression models evaluated the impact of body mass index (BMI) at diagnosis and of weight changes over 2 yrs after diagnosis on odds of non-RTW, adjusting for age, education, income, BC treatment and recreational physical activity (PA). Results: 37% pts were overweight or obese at diagnosis (BMI ≥25 kg/m²); 34% of them gained ≥5% and 16% lost ≥5% weight after diagnosis. Rates of non-RTW at 2 yrs were significantly higher in overweight or obese vs under or normal weight pts (27% vs 18%, P<.001; adjusted odds ratio 1.37, 95% Confidence Interval [CI] 1.04-1.80, p = .017). Overweight and obese pts who did not RTW experienced higher increments in weight (mean [95% CI]: +3.6% [+2.3, +4.9] vs +1.5% [+0.8, +2.2]) and reported more modest changes in PA (mean [95% CI]: +1.0 [1.4, +3.5] vs +2.1 [+0.8, +3.3] METs/week) vs those who did RTW. Weight changes independently impacted odds of non-RTW in overweight and obese pts (p for interaction weight change*BMI = 0.001): a 5% weight gain was associated with 17% increase in adjusted odds of non-RTW (OR 2.35% CI 1.96-2.84; p = .024), whereas a loss ≥5% with 60% reduced odds of non-RTW vs weight gain (95% CI 18-82%, p = .013). Conclusions: Excess weight and weight changes are significantly associated with occupational reintegration after BC in overweight and obese pts. Randomized studies testing dedicated weight control interventions should also measure outcomes of social rehabilitation in this large subset of survivors. Clinical trial information: NCT01993498.
Overall, CT was strongly associated with neurotoxicity at all symptoms, sensory or motor neuropathy, paresthesia, headache, etc (all grades) proportion of patients presented neurological symptoms including cognitive intestinal, pulmonary and cardiac toxicities. Pain and joint/bone toxicity (stratified on endocrine therapy), gastrointestinal specific percentages for each considered side effect) for detailed neurological proportions of the 4 categories of pts in the CT and no CT groups. Furthermore, at neurological side effects changed between T0 and T12. The table shows the RTW 2 years after dx, with treatment (trastuzumab), clinical, psychological work. All models were adjusted for age, stage, marital status, socioeconomic status and comorbidities. Results: Two years after dx, 21% of pts did not work. Adjusted odds of non-RTW were increased among pts treated with combinations of chemotherapy (CT) and trastuzumab (TR) (e.g. OR of CT-TR = 2.20 [95% CI 1.24-3.88] and OR of CT-TR-hormonotherapy (HT) = 1.72 [1.13-2.63] vs. treated only with CT-HT), who had severe arm morbidity (OR = 1.87 [1.27-2.72] vs. no arm morbidity (OR = 1.13 [0.55-2.32] vs. no), anxiety (OR = 1.51 [1.02-2.23] vs. no), or depression (OR = 2.23 [1.27-3.94] vs no). In addition, we also found that the odds of non-RTW were increased among pts who had shift working hours (OR = 2.23 [1.32-3.76] vs. no), who did not work in a supportive environment before dx (OR = 2.50 [1.50-4.05] vs. supportive) and who perceived their job as non boring (OR = 3.57 [1.71-7.46] vs. not boring). Conclusions: More than 1/5 of pts did not RTW 2 years after dx, with treatment (trastuzumab), clinical, psychological and work-related factors being associated with job reintegration. Multidisciplinary strategies are needed to support BC survivors. Results: We analyzed 4684 patients with T0 and T12 consolidated data. Median age at diagnosis was 57y (22-90). Patients (pts) had HR=HER2+, HER2+ or triple negative tumors in 78.9%, 12.4% and 8.7% of cases, respectively. Overall, 2516 pts (53.7%) received CT. Most CT pts (81%) received a sequential antracyclines–taxanes schedule. As an example, a high proportion of patients presented neurological symptoms including cognitive symptoms, sensory or motor neuropathy, paresthesia, headache, etc (all grades) at either T0 or T12. Overall, CT was strongly associated with neurotoxicity at all times (OR = 2.27, p < 0.0001). However, proportions of patients with neurological side effects changed between T0 and T12. The table shows the proportions of the 4 categories of symptoms in the CT and no CT groups. Furthermore, at T12, neurological symptoms remained more frequent in the CT group, whether pts had symptoms at T0 (CT vs no CT, 81% vs 77%, p = 0.007) or not (CT vs no CT, 41% vs 36%, p = 0.03). Similar temporal trends were observed (with specific percentages for each considered side effect) for detailed neurological toxicities, pain and joint/bone toxicity (stratified on endocrine therapy), gastrointestinal, pulmonary and cardiac toxicities. Conclusions: Overall, symptoms burden is extremely high at T0 and T12 after treatment, and much higher in pts receiving CT. A high temporal variability was observed in all subsets, including a clinically meaningful delayed onset of e.g. neurological side effects. Clinical trial information: NCT01993498.
Effect of race/ethnicity on long-term cytopenias and major infections in adolescent young adult breast cancer survivors. First Author: Candice Sauder, Comprehensive Cancer Center, University of California, Davis, Sacramento, CA

Methods: Many Adolescent and Young Adult (AYA) Breast Cancer (BC) patients receive chemotherapy as part of their initial treatment. Long-term bone marrow suppression is a potential complication, but no studies have evaluated the impact of race/ethnicity on the development in AYA BC survivors. Methods: Female patients ages 15-39 diagnosed with BC during 1996-2012 and surviving ≥ 2 years were obtained from the California Cancer Registry and linked to statewide hospitalization data. We estimated the cumulative incidence of developing anemia, leukopenia, or major infection/sepsis (≥ 2 years after diagnosis), accounting for death as a competing risk, and examined the impact of race/ethnicity using multivariable Cox proportional hazards regression. Results: Of 14,729 patients, 48.8% were non-Hispanic white, 8.3% non-Hispanic black, 25.3% Hispanic, and 16.5% Asian/Pacific Islander. At diagnosis, 95.5% had local or regional disease (27.7% stage I, 49.4% stage II), and were mostly treated with surgery (96.2%) and chemotherapy (74.3%). The 10-year cumulative incidence of anemia (16.8% vs 11.7%), leukopenia (4.6% vs 2.1%), and major infection/sepsis (13.2% vs 7.9%) was greater following initial treatment with chemotherapy (p < 0.001 for all vs no chemotherapy). In multivariable analyses controlling for sociodemographic factors, baseline comorbidities, treatment and stage, Blacks had the highest risk (vs. non-Hispanic whites) of medical late effects, including anemia (HR: 1.62, CI 1.41-1.86), leukopenia (HR: 1.53, CI 1.17-2.00), and major infection/sepsis (HR: 1.51, CI 1.36-1.67). Asian/Pacific Islanders had a higher risk of developing anemia (HR: 1.16, CI 1.04-1.29; HR: 1.17, CI 1.03-1.33) and trended toward developing more leuko- penia (HR: 1.24, CI 1.00-1.54; HR: 1.25, CI 0.98-1.61). Conclusions: AYAs of Black, Hispanic, and Asian/Pacific Islander race/ethnicity are at an increased risk of anemia, leukopenia, and infections after chemotherapy compared to non-Hispanic White patients. With improvements in prognostic testing resulting in potential decreased chemotherapy usage, there may be a decrease in long-term late effects for these young cancer survivors.

Temporal trends among survivors of rhabdomyosarcoma: A report from the Childhood Cancer Survivor Study (CCSS). First Author: Pooja Hingorani, Phoenix Children’s Hospital, Phoenix, AZ

Background: Intergroup Rhabdomyosarcoma Study Group (IRSG) protocols included treatment modifications, which may have ameliorated late health outcomes for rhabdomyosarcoma (RMS) survivors treated in more recent era. Methods: We evaluated chronic health conditions (CHCs) and late mor- tality (> 5 years from diagnosis) among survivors treated 1970-1990 (IRSG I- III) and 1991-1999 (IRSG IV), and associations with specific treatments to identify treatment-related factors for adverse outcomes. Associations between treatments and CHCs and mortality were evaluated using Fine and Gray’s proportional hazards method accounting for competing risks. Results: 856 survivors treated 1970-90 (median diagnosis age 5.4 years [0-20]) and 306 treated 1991-99 (median diagnosis age 5.5 years [0-20]) were included. Significant exposure differences between eras included higher percentage (53% vs. 17%, p = 0.01) receiving ≥ 20gm/m² cumulative alkylators in 1991-99, but more receiving platinum (13% vs 5%, p = 0.01) and abdomen/pelvis radiation (29% vs. 23%, p = 0.04) in 1990-20, 20-year cumulative incidence for any (40% vs. 28%, p < 0.01), ≥ 1% (16% vs. 7%, p = 0.01), and endocrine (8% vs. 2.5%, p = 0.01) grade 3-5 CHCs was higher in 1990-99 compared to 1991-99. The hazard ratio (HR) for any (HR 0.7, 95% Confidence Interval [CI] 0.55-0.9), ≥ 2 (HR 0.38, 95% CI 0.22-0.66) and endocrine (HR 0.25, 95% CI 0.09-0.67) grade 3-5 CHC was lower for 1991-99 survivors than 1970-90. The effect of era (1991-99 vs 1970-90, HR 0.73, 95% CI 0.59-0.91) on CHC was not attenuated when treatment variables were added to the multivariable model. Exposures with increased risk of grade 3-5 CHC included platinum (peaking, HR 2, 95% CI 1.07-3.8), anthracycline ≥ 250mg/m² (cardiovascular, HR 2.7, 95% CI 1.2-6) and abdomen/pelvis radiation (second malignancy neoplasms, HR 2.1, 95% CI 1.1-4, gastrointestinal, HR 7.4, 95% CI 3.5-16 and endocrine, HR 2.5, 95% CI 1.4-4.4). Gonadal dysfuction was the most common endocrine CHC. There was no difference in all cause or cause-specific mortality between the two cohorts. Conclusions: RMS survivors from the IRSG IV era are at reduced risk for late onset chronic health conditions compared to previous era.

Cardiovascular disease risk in survivors of 20 adult cancers. First Author: Helen Strongman, London School of Hygiene and Tropical Medicine, London, United Kingdom

Background: There are concerns about long-term cardiovascular disease (CVD) risk in cancer survivors, but few studies have quantified the risks for a wide range of cancers and specific CVD outcomes. Methods: Using UK electronic health records, we identified cohorts of adults alive one year after a cancer diagnosis at 20 different sites. Risks of a range of CVD outcomes were compared to age, sex and general practice matched cancer free controls using Cox regression; crude and adjusted models were compared to investigate the role of shared cancer/ CVD risk factors (e.g. smoking and diabetes). Results: 126 120 cancer survivors and 603 144 controls were followed over a median (IQR) 4.6 (2.5-8.1) and 5.6 (3.2-9.2) years. Crude and adjusted hazard ratios (HRs) were similar. In adjusted models, there was strong evidence (p<0.01) of increased risk of CVD among cancer survivors compared with controls: venous thromboembolism (VTE, 18 cancers), heart failure/cardiomyopathy (7 cancers), arrhythmia (4 cancers), and stroke (3 cancers). In stratified analyses HRs were higher in younger people and continued beyond 5 years post diagnosis. Conclusions: We found increased long term CVD risk among survivors of several cancers com- pared to the general population, which varied by cancer site and specific CVD outcome.

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Coronary artery disease</th>
<th>Stroke</th>
<th>Arthritis</th>
<th>Heart failure/cardiomyopathy</th>
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<td>Malignant skin melanoma</td>
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<td>Non Hodgkin lymphoma</td>
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<td>5.6 (4.1-7.6)</td>
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Total body irradiation (TBI) and risk of breast subsequent malignant neoplasm (SMN) after blood or marrow transplantation (BMT): A report from the BMT survivor study (BMTSS). First Author: Andrea M. McDonald, Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, AL

**Background:** The association between TBI and breast SMN in BMT recipients is not clearly defined. We address this limitation to develop evidence for screening guidelines for those at risk. **Methods:** Study participants were drawn from BMTSS – a multi-site retrospective cohort of patients who had received BMT between 1974 and 2014 and survived $\geq$2y post-BMT. Adjudicators completed the BMTSS survey that included sociodemographics and health conditions. Breast SMN was confirmed by pathology report review. Clinical characteristics, pre-BMT and BMT exposures were abstracted from medical records. Using multivariable Cox proportional hazards models, freedom from breast SMN was measured from birth and TBI was treated as a time-varying covariate in analyses stratified by type of BMT (allogeneic; autologous).

**Results:** 1546 female participants (allogeneic 808; autologous 738) received BMT at a mean age of 43.1 $\pm$ 17.6y and were followed for 9.4-77.7y; primary diagnoses: HL/NHL (28%), AML/MDS (27%), PCa (19%), other (28%). TBI was used in 671 patients (allogeneic 57%; autologous 30%). Patients with pre-BMT chest radiation ($n$ = 45) were excluded from the analysis. A total of 38 cases of breast SMN were identified (allogeneic 19; autologous 19). Allogeneic BMT: exposure to TBI (HR = 3.4; 95%CI 1.1-10.9, $p = 0.04$) and age at BMT $< 40y$ (HR = 4.0; 95%CI 1.3-12.8, $p = 0.02$) were associated with increased risk of breast SMN. Risk of breast SMN was highest for allogeneic BMT and was not observed in any patients receiving TBI after 40y. The risk of breast SMN was especially high and occurred at a $p = 0.07$.

**Conclusions:** Younger age, among those exposed at age $\geq$ 60 (95%CI 1.1-20.1, $p = 0.03$) of breast SMN. TBI was associated with $\geq$ 40y (8.7% vs. 0% by attained age 50; 10.6% vs. 5.8% by attained age 60, $p = 0.003$). Autologous BMT: Age $< 40y$ was associated with a 4.8-fold higher risk (95%CI 1.1-20.1, $p = 0.03$) of breast SMN. TBI was associated with an increased risk of breast SMN compared to BMT alone (HR = 1.21; 95%CI 0.88-1.67, $p = 0.21$). The current study confirmed the increased risk of breast SMN among those exposed to TBI at age $< 40y$ vs. age $\geq$ 40y was 5.1% vs. 2.4% by attained age 60 ($p = 0.07$). **Conclusions:** TBI is associated with breast SMN among allogeneic BMT recipients. The risk is especially high and occurs at a younger age, among those exposed at age $< 40y$. These findings provide evidence for initiating screening at a young age after exposure to TBI.

Body weight changes in young breast cancer survivors and associated predictors. First Author: Tai Sella, Dana Farber Cancer Institute, Boston, MA

**Background:** Weight gain after cancer diagnosis is common in cancer survivors and has been linked to increased treatment toxicity, poor quality of life, and increased risk of second cancers and overall mortality. Young breast cancer (BC) survivors may be especially susceptible to weight changes given the impact of treatments such as chemotherapy and hormonal therapy on weight. **Methods:** We identified women with Stage 0-II breast cancer diagnosed at $\leq$ 40 years (y) between 2006-2016 from a multi-center prospective cohort study. Clinical data including self-reported pre-diagnosis and follow-up weights were obtained using baseline and follow-up patient surveys. Participants missing baseline weight, pregnant at diagnosis/within 1y of diagnosis or with BC recurrence within 1y were excluded; those pregnant or with BC recurrence between 1-3y from diagnosis were excluded from the $p = 0.05$ analysis. Menopausal status at baseline and treatment-related amenorrhea (TRA) in follow-up were defined by self-reported last menstrual period. Factors associated with weight gain ($>5\%$) were evaluated using univariate two-sided Fisher’s exact test. **Results:** At baseline, 1y and 3y post diagnosis, 956, 899 and 687 women were eligible for analysis respectively. Median age at diagnosis was 37y (17 - 40), 65% received endocrine therapy and 74% chemotherapy. Premenopausal status was verified in 94% at baseline. Mean BMI at baseline was 24.4 (SD 5.3) kg/m2; 20% (187/956) were overweight and 12% (116/956) obese. At 1y and 3y, mean BMI increased modestly to 24.7 (SD 5.6) and 24.9 (SD 5.2), respectively with weight gain ($>5\%$) observed in 18% (164/899) and 13% (87/687) respectively. 37% (300/804) and 32% (196/615) of eligible premenopausal subjects experienced TRA at 1y and 3y, respectively. Receipt of chemotherapy, receipt of endocrine therapy and TRA were not associated with weight gain at any timepoint. **Conclusions:** In this large prospective cohort of young BC survivors, mean BMI increased only modestly over time. Self-reported weight gain was not associated with treatment and not exacerbated by TRA. Further analysis to understand the effects of physical activity and other predictors of weight gain in this population are ongoing.

Poster Session (Board #265), Mon, 1:15 PM-4:15 PM

**Second solid (SMN) and hematologic malignant neoplasms (HMN) among 24,900 United States testicular cancer survivors (TCS) after chemotherapy (CHEM).** First Author: Mohammad Issam Abu Zaid, Indiana University School of Medicine, Indianapolis, IN

**Background:** No large, population-based U.S. study has comprehensively examined SMN and HMN risks after TC, taking into account initial therapy and focusing on recent decades. **Methods:** Standardized incidence ratios (SIR) for SMN and HMN stratified by site and time since TC diagnosis were calculated for 23,900 TCS (median age, TC diagnosis: 33 y) reported to population-based cancer registries in the NCI SEER program (1973-2014). TCS were initially treated with CHEM (n=6,340), RT (n=9,058), or SURG (n=8,995), with each group accruing 800, 156,735, and 128,039 person-years (PY) of follow-up, respectively. **Results:** During 372,709 PY of follow-up, 1,625 TCS developed SMN and 228 developed HMN, including 107 lymphomas, 92 leukemias, and 29 plasma cell dyscrasias. Among all TCS, overall risk of SMN was increased by 1.06-fold (95% CI 1.01-1.1). Risks of SMN were increased after RT (SIR 1.1, 95% CI 1.06-1.2) and CHEM (SIR 1.3, 95% CI 1.1-1.4); but not after SURG (SIR 0.8). After CHEM, significant excesses of SMN of the pancreas (SIR 2.2), soft tissue (SIR 4.0), kidney (SIR 1.7), thyroid (SIR 3.3) occurred; after RT, significantly elevated risks for SMN of the stomach (SIR 1.7), rectum/sigmoid (SIR 1.4), pancreas (SIR 2.7), soft tissue (SIR 2.2), bladder (SIR 1.5), and thyroid (SIR 2.0) were observed. The 30 year cumulative incidence of SMN after CHEM, SURG, and RT was 8.8% (95% CI 7.8-9.9), 10.1% (95% CI 8.8-11.5), and 17.0% (95% CI 15.6-18.7), respectively. Risks of lymphoma and plasma cell dyscrasias were not elevated (SIR 1.2 and 1.2, respectively). The current study confirmed the increased risk of breast SMN after CHEM (SIR 2.7) and SURG (SIR 1.8) and were driven by increased risks for acute myeloid leukemia, with significant excesses restricted to 1-10y after TC diagnosis, respectively. Non-significant 2-fold excesses occurred 1-10y after RT. Risks for lymphoma and plasma cell dyscrasias were not elevated (SIR 1.0 and 1.0, respectively). In the largest population-based study of U.S. TCS to date, we report significant 6% excesses of SMN and 2-fold increased risks of leukemias. Efforts to minimize CHEM exposure and decrease doses/field size of RT in TC should continue. TCS should be educated about cancer prevention and screening.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Cardiorespiratory fitness and cardiovascular mortality after prolonged androgen deprivation therapy for prostate cancer. First Author: Jingyi Gong, Brigham and Women’s Hospital Heart and Vascular Center, Boston, MA.

Background: Androgen deprivation therapy (ADT) plays a pivotal role in management of prostate cancer (PC), with prolonged ADT favored over short-term use in the definitive treatment of high risk PC with radiation. Objectives: To compare cardiorespiratory fitness (CRF) and cardiovascular (CV) mortality among patients with PC with and without ADT exposure, and to explore how duration of ADT exposure influences CRF and CV mortality risk. Methods: This is a retrospective study of patients referred for exercise treadmill testing (ETT) after a diagnosis of PC. PC risk classification was based on Gleason score (GS) at diagnosis: high risk GS = 8, intermediate risk GS = 7, and low risk GS = 6. CRF was categorized according to metabolic equivalents (METs); METs < 8 defined as good CRF and METs < 8 as reduced CRF. ADT exposure was grouped as short-term (< 6 months) versus prolonged (>6 months).

Results: 616 patients underwent an ETT a median of 4.8 years (interquartile range: 2.0-7.9) after diagnosis of PC. 150 patients (24.3%) received ADT prior to ETT; 51 with short-term versus 99 with prolonged exposure. 524 (85.1%) patients had ≥ 2 CV risk factors, and 28 CV deaths occurred over 4.2 (interquartile range: 2.3-7.1) years following the ETT. Reduced CRF was more frequent among ADT-exposed versus ADT-naive patients (48.7 versus 32.6%, p<0.001). Prolonged ADT was associated with reduced CRF (odds ratio (OR): 2.71; 95% confidence interval (CI): 1.31-5.61; p=0.007) and increased CV mortality (hazard ratio (HR): 3.87; 95% CI: 1.16-12.96; p=0.03) in adjusted analyses. In contrast, short-term ADT exposure was not independently associated with either reduced CRF (OR 1.71; 95% CI: 1.00-2.94; p=0.05) or CV mortality (HR: 1.60; 95% CI: 0.51-5.01; p=0.42). Conclusions: Among patients with PC and high baseline CV risk, > 6 months ADT exposure but not less was associated with reduced CRF and increased CV mortality. Reduced CRF may in part mediate increased CV mortality risk. Exercise interventions concurrent with prolonged ADT warrants investigation to potentially offset risk.

Symptoms and Survivorship 601s

Cardiorespiratory fitness and cardiovascular mortality after prolonged androgen deprivation therapy for prostate cancer. First Author: Jingyi Gong, Brigham and Women’s Hospital Heart and Vascular Center, Boston, MA.

Background: Androgen deprivation therapy (ADT) plays a pivotal role in management of prostate cancer (PC), with prolonged ADT favored over short-term use in the definitive treatment of high risk PC with radiation. Objectives: To compare cardiorespiratory fitness (CRF) and cardiovascular (CV) mortality among patients with PC with and without ADT exposure, and to explore how duration of ADT exposure influences CRF and CV mortality risk. Methods: This is a retrospective study of patients referred for exercise treadmill testing (ETT) after a diagnosis of PC. PC risk classification was based on Gleason score (GS) at diagnosis: high risk GS = 8, intermediate risk GS = 7, and low risk GS = 6. CRF was categorized according to metabolic equivalents (METs); METs < 8 defined as good CRF and METs < 8 as reduced CRF. ADT exposure was grouped as short-term (< 6 months) versus prolonged (>6 months).

Results: 616 patients underwent an ETT a median of 4.8 years (interquartile range: 2.0-7.9) after diagnosis of PC. 150 patients (24.3%) received ADT prior to ETT; 51 with short-term versus 99 with prolonged exposure. 524 (85.1%) patients had ≥ 2 CV risk factors, and 28 CV deaths occurred over 4.2 (interquartile range: 2.3-7.1) years following the ETT. Reduced CRF was more frequent among ADT-exposed versus ADT-naive patients (48.7 versus 32.6%, p<0.001). Prolonged ADT was associated with reduced CRF (odds ratio (OR): 2.71; 95% confidence interval (CI): 1.31-5.61; p=0.007) and increased CV mortality (hazard ratio (HR): 3.87; 95% CI: 1.16-12.96; p=0.03) in adjusted analyses. In contrast, short-term ADT exposure was not independently associated with either reduced CRF (OR 1.71; 95% CI: 1.00-2.94; p=0.05) or CV mortality (HR: 1.60; 95% CI: 0.51-5.01; p=0.42). Conclusions: Among patients with PC and high baseline CV risk, > 6 months ADT exposure but not less was associated with reduced CRF and increased CV mortality. Reduced CRF may in part mediate increased CV mortality risk. Exercise interventions concurrent with prolonged ADT warrants investigation to potentially offset risk.

Combination of olanzapine and aprepitant in the prevention of chemotherapy-induced nausea and vomiting (CINV) in breast cancer patients. First Author: Navaneeth Shanthilal, Mysores Medical College and Research Institute, Mysore, India

Background: Olanzapine and Aprepitant have been shown to be a safe and effective agent for the prevention of CINV. This study aims to compare Olanzapine, Aprepitant and their combination in the prevention of CINV. Methods: Prospective randomized controlled study in breast cancer patients receiving doxorubicin 60mg/m2 and cyclophosphamide 600mg/m2 chemotherapy. Female patient; age ≥ 18; chemotherapy naive; not included. Patients with seizure disorder, brain metastases were excluded. Olanzapine group received Tablet Olanzapine 10 mg on day 1 to 3. Aprepitant group received Tablet. Aprepitant 125mg on day 1, 80mg on days 2-3. The combination group received Aprepitant 125mg on day 1, 80mg on days 2-3 and Olanzapine 10mg on day 1. 4 groups received Palonosetron 0.25mg and Dexamethasone 8mg on day 1. The primary end point of the study was complete response (CR) for nausea that is no nausea in the acute, delayed and overall periods. Secondary endpoint was CR for vomiting and no use of rescue drugs in all periods. Beginning with the first day of chemotherapy and daily throughout day 5, patients were asked to record daily episodes of nausea using a visual analogue scale from 0 to 10, with 0 indicating no nausea and 10 indicating a maximal level of nausea. They were asked to record daily episodes of vomiting (number and time) and the utilization of rescue therapy. Results: A total of 141 patients were evaluated and consented for the study. The median age of patients for nausea was 51.5 years; range 24-74 years. CR for nausea in the acute period (within 24 hours) was 83%, 63.8% and 78.7% (p=0.078); for the delayed period (days 2-5) 59.6%, 55.3% and 63.8% (p=0.702); for the overall period (0-120 hours) 94.5%, 53.2% and 59.6% (p=0.817) for the Olanzapine, Aprepitant and combination arm respectively. CR for vomiting in the acute period was 91.5%, 91.5% and 97.9% (p=0.344); for the delayed period 74.6%, 85.1% and 97.9% (p=0.005); for the overall period 70.2%, 85.1% and 97.9% (p=0.001) for the Olanzapine, Aprepitant and combination arm respectively. There were no Grade 3/4 toxicities. Conclusions: The combination strategy shows trend towards better prevention of CINV. Clinical trial information: CTRI/2017/12/010864.
Background: Naldemedine for opioid-induced constipation is safe and effective in a large Canadian province.

Conclusions: Adequate pain control, an essential part of cancer care remains a challenge in resource limited countries like Nepal. Early use of morphine for Moderate Cancer Pain (MCP) and not sequential World Health Organization (WHO) analgesic ladder seems reasonable in the setting of limited access to healthcare. The purpose of this study was to compare efficacy of oral Morphine (MOR) with oral Tramadol (TRM) in control of pain as well as physical wellbeing in patients (pts) with MCP using Edmonton Symptom Assessment Scale (ESAS). Methods: An IRB approved randomized phase II trial was performed in opioid-naive pts with MCP as defined by pain score in Numerical rating scale (NRS) of 4-6. Patients were randomized to receive MOR syrup 5 mg 4 hourly or TRM 50 mg four times a day. Titration of dose was done in both groups for 3 days as per standard recommendation for MOR or till maximum recommended daily dose for TRM. MOR was changed to prolonged release form at Day 4. The primary endpoint was number of early responders, defined as pts with at least 20% reduction in pain intensity on NRS on Day 3. Secondary outcome was number of patients with highly meaningful pain reduction, defined as decrease in pain intensity on NRS by ≥ 5 and improvement in physical well-being with ESAS at Day 7. Results: 68 pts consented and were randomized, 34 in each arm. The primary endpoint occurred in 94.1% pts in MOR and 55.9% in TRM (p < 0.001). Number of patients with highly meaningful pain reduction was significantly higher in MOR than in TRM (75% vs 32.35%; p < 0.001). Improvement in physical wellbeing as assessed by ESAS was better in morphine group. No difference in adverse effects was noted between the treatment arms. Conclusions: In this study Morphine was superior to Tramadol in the control of pain statistically significant difference in the primary and secondary endpoints. So, early use of morphine skipping the WHO sequential analgesic ladder for moderate cancer pain seems a higher value option in resource scarce country with limited access to healthcare.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild pain</td>
<td>1.0 (1.1-1.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Moderate pain</td>
<td>2.6 (1.4-4.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
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<tr>
<td>Opioid use pre-diagnosis</td>
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<tr>
<td>Naive</td>
<td>3.0 (2.5-3.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total</td>
<td>2.3 (1.8-2.9)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Number of prescribers (continuous)</td>
<td></td>
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</tbody>
</table>

Patient level factors associated with chronic opioid use in cancer patients.

Background: opioid prescribing in oncology is increasingly scrutinized given public health concerns about chronic opioid use, misuse, and harms. We aimed to evaluate patient reported pain scores, mental health indicators, prior opioid use, and number of opioid prescribers as potential risk factors for chronic opioid use in a large Canadian province. Methods: This was a population-based cohort study using administrative health data of patients in Alberta, Canada, diagnosed between Jan 2016 and Jan 2017, and complete prospective comprehensive symptom survey within <60 days of diagnosis. Patients were divided into two groups: chronic opioid use (COU) (defined as continuous prescriptions for opioids for at least 90 days post-diagnosis) and non-chronic opioid use (NCOU). Logistic regression models were used to evaluate factors associated with COU. Results: We included 694 patients. Most had breast (20%), colorectal (13%), and lung (33%) cancers. There were no differences in mean age (65 years) or gender (50% female) between the groups. In total, 32% had moderate to high pain scores at diagnosis. Of the 14% with COU, 79% were opioid naive (NCOU) (defined as 90 days of opioids). Logistic regression models were used to evaluate factors associated with COU. Results: Specific patient groups were at increased risk of COU and should be referred for opioid education. Conclusions: Specific patient groups were at increased risk of COU and should be referred for opioid education.

<table>
<thead>
<tr>
<th>Function and knowledge at time of referral choice</th>
<th>Chose Referral</th>
<th>Did Not Choose Referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>n=31 (Median, IQR)</td>
<td>n=80 (Median, IQR)</td>
</tr>
<tr>
<td>Did Not Choose Referral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional Well Being Sub-score</td>
<td>23.0 (17.0, 26.0)</td>
<td>24.0 (18.0, 26.0)</td>
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<tr>
<td>Physical Well Being Sub-score</td>
<td>25.8 (23.9, 28.0)</td>
<td>24.0 (18.0, 26.0)</td>
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<tr>
<td>Emotional Well Being Sub-score</td>
<td>20.0 (15.5, 22.0)</td>
<td>17.0 (14.0, 21.0)</td>
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<tr>
<td>Functional Well Being Sub-score</td>
<td>23.0 (17.0, 26.0)</td>
<td>17.0 (14.0, 21.0)</td>
</tr>
<tr>
<td>FACT-G Total Score</td>
<td>72.0 (74.0, 90.0)</td>
<td>74.0 (65.0, 80.0)</td>
</tr>
<tr>
<td>PaCKS Knowledge Score</td>
<td>12.0 (12.0, 13.0)</td>
<td>12.0 (12.0, 13.0)</td>
</tr>
</tbody>
</table>

Comparison of the effectiveness of oral morphine versus oral tramadol on early pain control in opioid-naive patients with moderate cancer pain. First Author: Ramila Shilpakar, Annapurna Cancer Hospital, Kathmandu, Nepal

Background: Adequate pain control, an essential part of cancer care remains a challenge in resource limited countries like Nepal. Early use of morphine for Moderate Cancer Pain (MCP) and not sequential World Health Organization (WHO) analgesic ladder seems reasonable in the setting of limited access to healthcare. The purpose of this study was to compare efficacy of oral Morphine (MOR) with oral Tramadol (TRM) in control of pain as well as physical wellbeing in patients (pts) with MCP using Edmonton Symptom Assessment Scale (ESAS). Methods: An IRB approved randomized phase II trial was performed in opioid-naive pts with MCP as defined by pain score in Numerical rating scale (NRS) of 4-6. Patients were randomized to receive MOR syrup 5 mg 4 hourly or TRM 50 mg four times a day. Titration of dose was done in both groups for 3 days as per standard recommendation for MOR or till maximum recommended daily dose for TRM. MOR was changed to prolonged release form at Day 4. The primary endpoint was number of early responders, defined as pts with at least 20% reduction in pain intensity on NRS on Day 3. Secondary outcome was number of patients with highly meaningful pain reduction, defined as decrease in pain intensity on NRS by ≥ 5 and improvement in physical well-being with ESAS at Day 7. Results: 68 pts consented and were randomized, 34 in each arm. The primary endpoint occurred in 94.1% pts in MOR and 55.9% in TRM (p < 0.001). Number of patients with highly meaningful pain reduction was significantly higher in MOR than in TRM (75% vs 32.35%; p < 0.001). Improvement in physical wellbeing as assessed by ESAS was better in morphine group. No difference in adverse effects was noted between the treatment arms. Conclusions: In this study Morphine was superior to Tramadol in the control of pain statistically significant difference in the primary and secondary endpoints. So, early use of morphine skipping the WHO sequential analgesic ladder for moderate cancer pain seems a higher value option in resource scarce country with limited access to healthcare.

Effect of patient education on palliative care knowledge and acceptability of outpatient palliative care service among gynecologic oncology patients. First Author: Ashley Graul, University of Pennsylvania, Philadelphia, PA

Background: This was a randomized control trial to estimate the effect of an interventional video on improving palliative care knowledge and acceptability of outpatient services in gynecologic oncology patients. Methods: Women receiving active treatment for gynecologic malignancy (persistent or progressive disease despite primary treatment) were recruited at an academic tertiary care center from 2/2018 to 12/2019 and randomized to palliative care educational video or non-directive cancer center informational video (control). The primary outcome was desire for referral to palliative care. Function and knowledge were assessed using the Functional Assessment of Cancer Therapy (FACT-G) and the Palliative Care Knowledge Scales. Data analyses were performed using t-tests, Wilcoxon rank sum or Fisher’s exact tests with significance level of α=0.05. Results: 111 women were enrolled. Demographic characteristics were equally distributed between groups (mean age 63.4 vs 65.4 years; 78% vs 82% Caucasian, 58% vs 68% stage III, 71% vs 64% ovarian cancer, 65% vs 72% platinum-sensitive). There was no statistical difference in knowledge scores or in desire for referral to palliative care (29% vs 27%; p=0.79). Secondary analysis showed a statistically significant increase in utilization of palliative care services compared to historic institutional data (8.8% to 29.7%; p<0.001). Further, those that desired referral had significantly worse FACT-G scores at time of referral choice (table). Conclusions: Use of a palliative care educational video did not increase knowledge or acceptability of palliative care services within this RCT. However, the rate of patients seeking palliative care referral tripled compared to historic rates. Further studies should investigate whether discussion regarding palliative care services alone may increase desire for referral, and if use of Fact-G scores may identify patients in greatest need of services.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Cognitive function in chronic lymphocytic leukemia (CLL): Examining effects of disease, treatment, and inflammation. First Author: Anna Lynn Williams, University of Rochester Medical Center, Rochester, NY

Background: Cancer-related cognitive impairment (CRCI) is an important clinical problem that may occur through pro-inflammatory pathways, cancer-related pathology, or cancer treatment. However, their relative contribution to CRCI is unknown. We used CLL, an indolent cancer of the immune system, as a novel model to study differential roles of disease, treatment, and inflammation in CRCI. Methods: We assessed cognitive function and serum pro-inflammatory marker levels in 150 CLL patients (100 treatment naive and 50 chemotherapy treated) including 84 patients with high risk of CLL progression (deletion 17p, deletion 11q, unmutated IGHV, ZAP70+, or CD38+). Objective neuropsychological tests assessed global cognition, processing speed, attention, memory, and executive function (NIH Toolbox Cognition, Hopkins Verbal Learning Test Revised (HVLT), Trail Making Test (TMTA/B)). Linear regression models examined cognitive outcomes in relation to risk, treatment, and pro-inflammatory markers while adjusting for sociodemographic covariates. Results: High risk patients recalled almost 2 fewer words on a memory task (HVLT immediate recall β = -1.8, 95%CI -3.3, -0.3) and took 15 seconds longer on an executive function task (TMTB β = 15.4, 95%CI 3.1, 27.6) than low risk patients, independent of treatment status. Treated patients reported significantly greater cognitive difficulties than treatment naive patients (FACT-Cog β = -5.2, 95%CI -8.7, -1.6) but did not perform worse on objective cognitive measures. Higher CRP was significantly associated with more self-reported difficulties, but higher levels of interleukin-6 and interferon-γ were specifically associated with better performance on objective measures of global cognition, attention, and executive function. Conclusions: High risk patients experienced impairments in executive function and memory suggesting that disease biology contributes to CRCI independent of treatment. Increasing levels of pro-inflammatory cytokines were associated with better cognitive performance indicating that the role of inflammation with respect to CRCI in CLL may be complex, possibly due to tumor-related immune deficiencies.

Preemptive versus reactive topical clobetasol for regorafenib-induced hand-foot reactions: Results from the ReDOS trial. First Author: Aminah Jatoi, Mayo Clinic, Rochester, MN

Background: Hand-foot skin reaction (HFSR) is the most common regorafenib-induced skin reaction: Results from the ReDOS trial. Preemptive versus reactive topical clobetasol for regorafenib-induced hand-foot reactions: Results from the ReDOS trial. First Author: Aminah Jatoi, Mayo Clinic, Rochester, MN

Methods: The ReDOS trial was a randomized trial (https://clinicaltrials.gov/ct2/show/NCT02368886); here we describe an a priori secondary analysis of ReDOS with the goal of assessing whether clobetasol 0.05% cream (a potent corticosteroid) applied to the palms and soles twice per day is more effective when prescribed pre-emptively (before treatment starts) versus reactively (after the development of HFSR). Patients were assessed during the 1st and 2nd cycles of regorafenib. Results: Among 116 evaluable patients, 61 received pre-emptive clobetasol, and 55 reactive clobetasol. Baseline demographics were comparable between groups. During the 1st regorafenib cycle, 46% and 52% of patients developed HFSR with pre-emptive and reactive clobetasol, respectively (p = 0.52). However, during the 2nd cycle, 56% (of 47 total patients) and 80% (of 41 total patients), developed this toxicity with pre-emptive and reactive clobetasol, respectively (p = 0.02). Of note, during the 2nd cycle, rates of grade 1, 2, and 3 HFSR were 40%, 11%, and 5%, respectively. Patients reported outcomes showed HFSR compromised activities of daily living, including getting dressed, preparing meals, walking, and even driving, with seemingly worse descriptive outcomes in patients who received reactive therapy. No adverse events from clobetasol were reported. Conclusions: Compared to reactive therapy, pre-emptive topical clobetasol might lessen regorafenib-induced HFSR. Clinical trial registration: NCT02368886.

A community oncology palliative program: Early results for cost and quality measures within OCM program claims data. First Author: Adil Jamal Akhtar, Michigan Health Professionals, Sterling Heights, MI

Background: Oncology Care Model (OCM) is an initiative of the Centers for Medicare and Medicaid Innovation which aims to provide higher quality and more coordinated oncology care while lowering the costs. Oncology Division of Michigan Health Professionals (MHP) participates in OCM. Palliative and End of Life care was identified as one of the quality improvement areas. A community oncology Palliative care (PC) program was launched in October 2017. Methods: The multidisciplinary PC team was led by Board certified palliative care and hospice physicians. Patients appropriate for PC referral were identified by practicing medical oncologists. Patients were contacted by the PC team. If the patients agreed a Nurse Practitioner (NP) would assess and follow the patients at home. Care was coordinated by the NP’s in communication with the palliative care team and the primary medical oncologists. Last 30-day (limited by the OCM episode or patient death) OCM program claims data was analyzed by IntegraConnect. Results: From October 2017 to October 2018 a total of 273 patients were referred to the PC program. Fifty-eight patients were identified as having OCM episodes, of these 36 patients had claims data through June 30, 2018. Twenty patients accepted and were engaged with PC, 16 patients declined or were unable to reach for PC and formed the comparison group. Even when drug and office costs were excluded, PC engaged patients spent 17% less versus the comparison group (93k vs 112k) in last 30-day claims data. PC engaged patients had a lower acute care facility contact which accounted for 50% (46k) of reimbursement, compared with 95% (105k) for the comparison group. Fourteen OCM patients referred to Palliative program died within episode. 80% (8/10) of engaged patients met quality measure for OCM-3, at least 3 days in hospice vs. 0% (0/4) of patients who declined palliative care, before episode-death. Conclusions: Palliative engagement with OCM patients experienced more care at their homes at a lower cost. Palliative program improved practice performance in OCM-3 quality measure. MHP Palliative program is reaching patients in OCM episodes but the numbers are still small.
11588 Poster Session (Board #280), Mon, 1:15 PM-4:15 PM

Sex differences in adverse event reporting in SWOG chemotherapy, biologic/immunotherapy, and targeted agent cancer clinical trials. First Author: Joseph M. Unger, Fred Hutchinson Cancer Research Center, Seattle, WA.

Background: Women have more adverse events (AEs) from chemotherapy than men, but few studies have explored sex differences in biologic/immunotherapies (BIs) or targeted therapies. We examined subjective (symptomatic) and objective AEs by sex across different treatments. Methods: We analyzed drug-related severe (grade 3) or worse AEs by sex in SWOG phase II and III clinical trials conducted between 1980-2018, excluding sex-specific cancers. AE codes and grade were categorized using the Common Terminology Criteria for Adverse Events (CTCAE). Subjective or symptomatic toxicities were defined as those aligned with the NCI’s new Patient-Reported Outcome (PRO) CTCAE; lab-based or physician-determined AEs were designated as objective. Multivariable logistic regression was used, adjusting for age, race, and disease prognosis. Thirteen symptomatic and 19 objective AE categories were examined. Results: In total, 36,397 patients (women, 13,907 [38.2%]; men, 22,490 [61.8%]) experienced 522,835 AEs on 297 trials with 385 treatment arms were analyzed. Overall, 29.1% (n = 10,860) had severe or worse toxicity. Women experienced an increased risk of severe symptomatic AEs for BIs (OR = 1.53, 95% CI: 1.32-1.78, p < .0001), chemotherapy (OR = 1.31, 95% CI: 1.24-1.39, p < .0001), and targeted therapies (OR = 1.23, 95% CI: 1.06-1.43, p = .008). Women also had an increased risk of severe objective AEs for BIs (OR = 1.53, 95% CI: 1.32-1.78, p < .0001), chemotherapy (OR = 1.35, 95% CI: 1.28-1.43, p < .0001), but not targeted therapies (OR = 1.08, 95% CI: 0.94-1.25, p = .28). Across all treatments, sex difference in severe hematologic (OR = 1.29, 95% CI: 1.24-1.35, p < .0001) v. non-hematologic (OR = 1.13, 95% CI: 1.08-1.18, p < .0001) objective AEs. Conclusions: The greater severity of both symptomatic and objective – especially hematologic – AEs in women across multiple treatment paradigms indicates broad-based sex-differences exist. This could be due to AE reporting, pharmacogenomics of drug metabolism and disposition, total dose received, and/or adherence to therapy. Particularly large sex differences were observed for patients receiving BIs, suggesting studying AEs from these agents is a priority.

11589 Poster Session (Board #281), Mon, 1:15 PM-4:15 PM

Risk factors for opioid abuse/dependence in hospitalized cancer patients in the United States. First Author: Veli Bakalov, Allegheny Health Network, Department of Internal Medicine, Pittsburgh, PA.

Background: Opioid medications are the mainstay for treating cancer pain. Goal of this study was to identify risk factors for opioid abuse/dependence in patients hospitalized with cancer, explore whether risk of opioid abuse/dependence varies by cancer type and to assess whether opioid abuse/dependence in patients affects the outcomes of hospitalization. Methods: The Nationwide Inpatient Sample for the years of 2011-2015 was queried for the analysis. We used ICD-9-CM codes of solid tumors as a primary diagnosis for hospitalization, and opioid abuse/dependence as a secondary diagnosis of the hospitalization. We performed univariate and multivariate logistic regression analyses to examine the association between risk factors and opioid abuse/dependence. Data were analyzed using SAS v9.4 (SAS Institute, Cary, NC). Results: Total of 524,624 patients were included in our cohort. Rate of opioid abuse/dependence was highest in patients with liver cancer (1.77%). Opioid abuse/dependence was less associated with age (>65 years old: OR 0.29, 95% CI 0.21-0.39). Patients with Medicaid insurance associated with increased risk of opioid abuse/dependence comparing to other insurances (OR 5.29, 95% CI 4.78-5.86). Strongest association with opioid abuse/dependence were in patients with liver cancer (OR 6.07, 95% CI 5.11-7.20) followed by head and neck cancer (OR 3.20, 95% CI 2.67-3.84). Substance abuse (OR 9.9, 95% CI 9.04-10.84), mental disease (OR 2.87, 95% CI 2.64-3.13) and nutrition deficiency (OR 2.09, 95% CI 1.90-2.31) were highly associated with opioid abuse/dependence. Inhospital mortality rate was not associated with opioid abuse/dependence. Conclusions: We identified risk factors for opioid abuse/dependence in hospitalized patients with cancer and demonstrated that risk of opioid abuse varies by cancer type, and opioid abuse/dependence affects the outcomes of hospitalization. Inclusion of our findings in the development of screening tools will have serious potential for higher sensitivity and specificity for predicting the risk of opioid abuse/dependence in cancer patients.

11590 Poster Session (Board #282), Mon, 1:15 PM-4:15 PM

The effect of structured exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: A pilot study for interoceptive brain reorganization. First Author: Ian Kleckner, University of Rochester Medical Center, Rochester, NY.

Background: Over half of patients receiving “neurotoxic” taxane, platinum, or bortezomib chemotherapy experience CIPN—a dose-limiting toxicity involving numbness and pain in the extremities. There are no FDA-approved drugs for CIPN, but exercise may help. This randomized pilot study explored whether structured exercise during chemotherapy ameliorates CIPN symptoms and whether improvements involve changes in the brain’s sensory processing (interoceptive) circuitry. Methods: Nineteen patients scheduled to receive taxane, platinum, or bortezomib were randomized to exercise (home-based, low-moderate intensity, walking and resistance training, EXCAP) or nutrition education (control) for 12 weeks starting at their first infusion. At 0, 6, and 12 weeks, we assessed CIPN symptoms using the CIPN-20 questionnaire (sensory scale, ranges 9-36, higher is worse) and a finger tactile sensitivity test. Results: The 19 patients were 65 ± 6 years old: OR 0.29, 95% CI 0.18-0.44, p = .0001. Exercise during neurotoxic chemotherapy mitigated CIPN (ES = 1.03 and 0.07). Exercisers showed better neurotoxic recovery compared to 0.74). Conclusions: Exercise during neurotoxic chemotherapy mitigated CIPN symptoms, perhaps via improvements in interoceptive brain circuitry. Future work should test for replication with a larger sample. Clinical trial information: NCT03021174.

11591 Poster Session (Board #283), Mon, 1:15 PM-4:15 PM

Clinical impact of neutropenia and febrile neutropenia in mCRC pts treated with FOLFOXIRI/bevacizumab (bev): A pooled analysis of TRIBE and TRIBE2 studies. First Author: Daniela Rossiini, Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy.

Background: FOLLOWFOXIRI/bev is a valid option as first-line therapy for unresectable mCRC. TRIBE and TRIBE2 trials reported better activity and efficacy of the triplet/ bev when compared with doublets/bev at the price of a higher incidence of chemotherapy-related complications, including neutropenia. Our aim was to provide a detailed description of this adverse event, including the occurrence of febrile neutropenia (FN) and the use of granulocyte-colony stimulating factors (G-CSFs), in order to estimate the clinical relevance of N during FOLLOWFOXIRI/bev: Methods: Safety data of 1175 pts enrolled in the TRIBE and TRIBE2 studies were reviewed. The incidence of N, the incidence and severity of FN, and the use of G-CSF in the triplet/bev and in the doublets/ bev arms were compared using the Chi-square or the Fisher exact test as appropriate. Results: Out of 1175 pts included in the final analysis, 586 (49.8%) were treated with FOLLOWFOXIRI/bev. Five pts (0.8%) in the doublets/bev arms and 29 (4.9%) in the triplet/bev arms received a primary prophylaxis with G-CSF. Among other pts, 118 (20.2%) in the doublets/bev arms and 276 (49.9%) in the triplet/bev arms experienced ≥ 3N (p < 0.001). FN occurred in 25 (4.3%) and 41 (7.4%) cases respectively (p=0.041). Out of 78 FN episodes, 4 (13.3%) out of 30 in the doublets/bev arms and 13 out of 48 (27.1%) in the triplet/bev arms were associated with a poor MACCC score (p<0.01). G-CSF was used in 1069 (10.8%) cycles, 270 (5.3%) in doublets/bev and 799 (16.6%) in triplet/bev arms. In both arms, the majority of FN and FE episodes were observed in the first two months (318 ≥ G3 N episodes out of 675 (47.1%), and 54 FN episodes out of 78 (69.2%). Conclusions: FOLLOWFOXIRI/bev was associated with a higher risk of FN and N than doublets/bev. However, the risk of FN was lower than 10%, thus not requiring a systematic use of primary G-CSF prophylaxis. The majority of FN episodes was associated with a good MACCC score, thus having a limited clinical impact. The vast majority of FN episodes occurred in the first two months of treatment, suggesting a closer monitoring of this adverse event during the first courses of therapy.
11592  Poster Session (Board #284), Mon, 1:15 PM-4:15 PM
Supportive care medications (SCMs) and pharmacogenomics (PGx) relevance in 6,585 cancer patients (pts) undergoing distress screening. First Author: Jai Sarvendra Patel. Levine Cancer Institute, Charlotte, NC.

Background: SCMs are prescribed based on symptom burden, but response is variable, possibly due to PGx. We investigated the association between symptom burden, SCM prescribing, and frequency of SCMs with PGx evidence.

Methods: Cancer pts ≥ 18 years old and completing electronic distress screening within 90 days of intake between 1/1/2017-12/31/2017 were included. Anxiety was measured using the Generalized Anxiety Disorder 2-item (GAD-2) and depression using the Patient Health Questionnaire-2 (PHQ-2). Fatigue, nausea, neuropathy, pain and sleep were measured on a 0-10 scale. SCM prescribing within 90 days of intake was documented. Logistic regression compared symptom scores and SCM prescribing. Receiver Operating Characteristics analysis estimated sensitivity/specificity. Optimal symptom thresholds were selected according to Youden’s J statistic. SCMs with PGx evidence level A or B (according to Clinical Pharmacogenetics Implementation Consortium) were summarized.

Results: Of 6,585 pts, 65% were female, 75% Caucasian, 20% African American and median age was 60. 49% reported ≥ 1 severe symptom, which correlated with SCM prescribing (p < 0.001). 3208 (46%) were prescribed SCMs(s), mainly for pain (69%) or nausea (46%). Of these, 2759 (86%) received ≥ 1 SCM with PGx evidence and 2695 (84%) received a SCM metabolized by CYP2D6 - hydrocodone (47%), oxycodone (41%), and oxycodone (28%). Based on reported CYP2D6 allele frequencies conferring altered metabolism (~20%), 539 of the 2695 pts may have altered drug response. Threshold scores for each symptom are summarized in the table. Fatigue and nausea were not associated with SCM prescribing. Conclusion: Symptom burden is high in cancer pts and correlates with SCM prescribing. Many SCMs have PGx evidence, suggesting preemptive testing, particularly for CYP2D6, may have broad applicability in this population.

11595  Poster Session (Board #287), Mon, 1:15 PM-4:15 PM
Physician concordance with update to ASCO guidelines for antiemetic use with carboplatin AUC ≤ 4. First Author: Rudolph M. Navari, University of Alabama at Birmingham, Birmingham, AL.

Background: In 2017, NCCN (2/2017) and ASCO (8/2017) each amended antiemetic guidelines to classify carboplatin AUC ≤ 4 as highly emetogenic chemotherapy (HEC), recommending upfront triple prophylaxis with an NK1 receptor antagonist (RA) + 5HT3 RA + dexamethasone. Physician concordance with the new recommendations, and the consequences for avoidable post-chemotherapy acute care, merit study.

In a large electronic health record database (IBM Explorx), we identified carboplatin courses of therapy (≥14-day cycles as a proxy for AUC ≥ 4) and courses with ≥ 7-day cycles of other HEC and non-HEC therapy from 4Q 2012 through August 2018. Guideline concordance, defined as triple prophylaxis at HEC initiation, was evaluated. We also assessed 30-day post-chemotherapy acute care (inpatient or emergency department) associated with nausea or vomiting (NV) or eight other toxicities deemed avoidable in the US Centers for Medicare & Medicaid’s new oncology outcome measure OP-35. Results: 11,554 carboplatin courses were identified. Before the guideline change, rates of upfront triple prophylaxis grew from 14% in 2013 to 16% in mid-2017. Rates then rose to 26% by 1Q 2018 before dropping to 21% by 3Q 2018; quarterly rates averaged 20% (range 15%-26%) following the guideline change. In 31% of carboplatin courses we noted 30-day acute care use, of which 75% involved ≥ 1 of the ten OP-35 toxicities. NV (with or without acute care use) was reported in 24% of courses, and 27% of total OP-35 acute care events involved NV. Rates for NV, and for OP-35-related and NV-related acute care after carboplatin, were similar to rates for other HEC chemotherapy, and higher than rates after other non-HEC IV chemotherapy or oral HEC/MEC agents.

Conclusions: Use of upfront triple antiemetic prophylaxis has increased markedly in patients with carboplatin AUC ≤ 4 since the 2017 classification as HEC in national guidelines, perhaps due to low awareness of the change. Patients receiving carboplatin had similar rates of NV and related 30-day acute care events as seen for other HEC, confirming that the new HEC definition fits clinical experience. More triple prophylaxis use is needed to reduce NV and NV-related avoidable acute care seen with carboplatin AUC ≥ 4.

11596  Poster Session (Board #288), Mon, 1:15 PM-4:15 PM
Survival and safety of monosialotetrahexosylganglioside in GI cancer patients with oxaliplatin-induced peripheral neurotoxicity-result from TUMJCH-GI-001 trial. First Author: Zhou Likun, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin’s Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy Tianjin Medical University, Tianjin, China.

Background: TJMCH-GI-001 Trial was a randomized, double-blind, placebo-controlled phase III trial to study the efficacy of Monosialotetrahexosylganglioside (GM1) on the survival of patients with oxaliplatin-induced peripheral neurotoxicity (OIPN) in GI oncology patients. Majority patients (>80%) in both arms continued receiving oxaliplatin on the trial. The results showed GM1 effectively reduced OIPN in GI cancer patients. Here we report the survival and safety results of this trial. Methods: Patients were randomized in a 1:1 ratio to receive GM1 or placebo. Patients with OIPN ≥ 2 by CTCAE 4.03 persisting during or after oxaliplatin-based chemotherapy were eligible. The patients who remained on oxaliplatin after enrollment, received concurrent placebo or GM1 7 days with each chemotherapy cycle. The patients who stopped taking oxaliplatin, were treated with placebo or GM1 14 days every 3 weeks. GM1 was dosed at 60mg daily for every 3-week or 40mg daily for every 4-week schedule. Trial was continued until modified EORTC QLQ-CIPN20 (MCIPN) increased by 30% or stayed unchanged after two more treatments beyond completion of oxaliplatin. Survival data for the treatment arms were compared using a log-rank test and Chi-square tests were used for safety analysis. Results: From May 2015 to Dec 2017, 73 patients were enrolled in GM1 and 72 in placebo arm. The median follow-up was 16.6 months at Dec.2018. Four patients lost to follow up. There was no deleterious impact of GM1 on survival. As a matter of fact, receiving GM1 was associated with a trend toward improved PFS and OS (HR=0.74, 95% CI: 0.469 - 1.156 for PFS and HR=0.76, 95% CI: 0.469 - 1.156 for OS). The most frequent Grade 3 or 4 adverse events included neutropenia (8 patients in GM1 group VS. 4 in placebo group) and hypoleukemia (4 patients in GM1 group VS. 1 in placebo group). Other 3 or 4 adverse events (all less than 3 patients) included anorexia, hypercalcemia, nausea, vomiting, proteinuria, hyperbilirubinemia, hypokalemia, hypertension and appendicitis. All the 3 or 4 adverse events were related to chemotherapy, not to GM1. Conclusion: In a placebo-controlled phase III trial, GM1 showed acceptable toxicity with trends favorable PFS and OS in GI cancer patients. Clinical trial information: NCT02486198.
Poster Session (Board #289), Mon, 1:15 PM-4:15 PM
Validation of a new prognostic body composition parameter in cancer patients. First Author: Paolo Pedrazzoli, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Background: In cancer patients protein-calorie imbalances are responsible for decreased lean body mass and, in turn, for worse clinical outcome. We evaluated the prognostic value of a new body composition parameter (creatinine height index [CHI]) obtained from bioimpedance vectorial analysis-derived body cell mass and its association with nutritional and functional status. Methods: Data from Italian and German cancer patients based on information from previous prospective cohort studies was used. Nutritional status and functional status were evaluated with the MNA screener and the SF-36 questionnaire, respectively. Tumor stage was assessed with the American Joint Committee on Cancer (AJCC) staging system. Results: Overall, 1684 cancer patients were included (Italians, N=454; Germans, N=630). Low CHI was independently associated with mortality in both Italian and German cohorts (Table). Low FFMI and low SPA did not predict survival in the German cohort. In patients with low CHI, worse nutritional and functional status were observed in both study populations. Performance of models addressing the study endpoints showed substantial consistency with both cohorts, particularly of those including low CHI. Conclusions: We validated a new prognostic body composition parameter, which is easier to interpret than standard nutritional parameters and may be useful for identifying cancer patients at nutritional risk, requiring early nutritional support.

Poster Session (Board #290), Mon, 1:15 PM-4:15 PM
Effect of whey protein isolate supplementation on body composition, muscle strength, and treatment tolerance in malnourished advanced cancer patients undergoing chemotherapy. First Author: Paolo Pedrazzoli, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Background: Malnutrition is frequent in cancer pts, particularly in advanced disease, which requires appropriate multidisciplinary interventions. We evaluated the benefit of whey protein isolate (WPI) supplementation in addition to nutritional counseling in malnourished cancer pts undergoing chemotherapy (CT). Methods: In a single-center, randomized, pragmatic, parallel-group clinical trial (ClinicalTrials.gov: NCT02056726), 168 malnourished advanced cancer pts undergoing CT were randomly assigned to receive nutritional counseling with (N=82) or without (N=84) WPI supplementation (20 grams/daily) for 3 months. Primary endpoint was the change in phase angle (PhA). Secondary endpoints included changes in standardized PhA (SPA), fat-free mass index (FFMI), body weight, muscle strength, quality of life and CT toxicity. Results: In pts with the primary endpoint assessed (modified intention-to-treat population), counseling plus WPI (N=66) resulted in improved PhA compared to nutritional counseling alone (N=69): mean difference, 0.48% (95% CI, 0.05 to 0.90) (P=0.027). Imputation of missing outcomes yielded consistent findings. WPI supplementation resulted also in improved SPA (P=0.021), FFMI (P=0.041), body weight (P=0.023), muscle strength (P<0.001) and in reduced risk of CT toxicity, particularly of severe (grade ≥3) events (Table). Conclusions: In malnourished advanced cancer patients undergoing CT and receiving nutritional counseling, 3-month supplementation with WPI resulted in improved body composition, muscle strength, body weight and reduced CT toxicity. Further trials in newly diagnosed specific cancer types are warranted. Clinical trial information: NCT02056726.
Background: Outpatient PC facilitates timely referral and improved outcomes for cancer patients. We examined the change in outpatient PC services at US cancer centers over the past decade. Methods: Between April and August 2018, we surveyed all 62 National Cancer Institute designated cancer centers (NCI-CCs) and a random sample of 61 out of 1306 non-NCI-CCs. Two surveys previously used in a national study (Hui et al. JAMA 2010) were sent to each institution: a 22-question executive survey, asking about anxiety PC infrastructure and attitudes toward PC and an 82-question PC program provider survey inquiring about the PC structures, processes and outcomes in detail. Generalized linear mixed model and logistic regression were used to examine the change in availability of outpatient PC services between 2009 and 2018 among NCI-CCs and non-NCI-CCs, respectively. Results: Among NCI-CCs, 40/62 (65%) executives and 52/61 (85%) program leaders responded. Among non-NCI-CCs, 41/61 (67%) executives and 27/39 (69%) program leaders responded. For NCI-CCs, we observed a significant increase in outpatient PC clinic between 2009 and 2018 (59% v. 95%; OR 13.1, 95% CI 2.6–66.8; P = 0.004) but no significant change in inpatient consultation team (92% v. 90%), PC unit (26% v. 40), or institute-run hospice (31% v. 18%). For non-NCI-CCs, there was a significant increase in outpatient PC clinics (22% v. 42%; OR 2.51, 95% CI 1.01, 6.26; P = 0.05) and decrease in institute-run hospice (42% v. 22%; P = 0.05) over the past decade but no significant change in inpatient consultation team (56% v. 68%) and PC unit (20% v. 17%). The median (IQR) duration from outpatient referral to death increased from 90 (84, 120) days to 180 (131, 220) days for NCI-CCs and from 41 (28, 54) days to 84 (48, 120) days for non-NCI-CCs, respectively. We also observed significant growth in staffing, service hours, number of relationships with palliative care teams, and number of fellows, although research activity remains low. Conclusions: Cancer centers reported significant growth in outpatient PC clinics and overall PC infrastructure since 2009. However, major gaps in structures and processes exist, such as the lack of outpatient clinics at non-NCI-CCs, absence of PC units and limited research.

Background: Fatigue is one of the most common and distressing symptoms reported by patients with gynecological cancers, but few studies have empirically examined whether it resolves without intervention. The aim of this study was to identify: 1) clinically-distinct subgroups of patients with fatigue over time and 2) medical and psychological predictors of clinically-significant fatigue one-year post-diagnosis. Methods: Secondary analysis of a prospective cohort study. Symptoms of fatigue, depression, and anxiety were assessed at diagnosis, 6-months, and 12-months with the 10-item Fatigue Assessment Scale (FAS), and the Hospital Anxiety and Depression Scale (HADS), respectively. Group-based trajectory modeling was used to classify patients by their fatigue scores over time, and logistic regression models were fit to examine associations between clinically-significant fatigue and demographic, clinical, and psychosocial characteristics. Patients with recurrent or primary progressive cancers were excluded from the primary analysis. Results: Among 312 participants with newly diagnosed ovarian (n = 112) or endometrial (n = 200) cancers, the median age was 66 years (IQR = 60–72 years), 36% had ovarian cancer, and 79% had early stage disease. At baseline, 49% reported clinically significant fatigue and one year later, 42% had persistent fatigue. During the year after diagnosis, there were three distinct trajectories of fatigue that persisted: (1) severe fatigue (15%), (2) moderate fatigue (45%), and (3) no fatigue (41%). Patients with ≥2 comorbid conditions (odds ratio [OR] 2.52, 95% confidence interval [CI] = 1.21–5.27, P = 0.01), clinically significant fatigue at baseline (OR 5.47, 95% CI = 2.71–11.03, P < 0.0001), and those reporting depressive symptoms at baseline (OR 3.45, 95% CI = 1.13–10.55, P = 0.03) were more likely to report clinically-significant fatigue at 12 months. Conclusions: Half of women with gynecological cancers have clinically-significant fatigue at diagnosis and 42% of survivors have persistent fatigue one year later, suggesting spontaneous regression of symptoms is rare. Importantly, depressive symptoms contribute to persistent fatigue and are modifiable with psychological interventions. Future studies should test scalable psychological interventions that address depressive symptoms, reduce fatigue, and improve quality of life for women with gynecologic cancers.

Background: Non-Medical opioid use is a growing crisis. Cancer patients at risk of harmful use of prescribed opioids are frequently underdiagnosed. The aim was to develop a nomogram to predict the probability of occurrence of inappropriate opioid use that is, presence of SOAPP ≥ 7) among patients receiving outpatient supportive care consultation at a comprehensive cancer center. Methods: 3588 consecutive cancer patients referred to a supportive care clinic from March 1, 2016 to July 15, 2018 were reviewed. Patients were eligible if they had diagnosis of cancer, and were on opioids for pain for at least a week. All patients were assessed using Edmonton Symptom Assessment Scale with spiritual pain and financial distress (ESAS-FS), MDED (morphine equivalent daily dose), SOAPP-14 (validated questionnaire for assessment of risk of inappropriate opioid use, and CAGE-AID (screening questionnaire for alcoholism/substance use disorder). Patients at with SOAPP+ were defined by SOAPP score ≥ 7. A nomogram was devised based on the risk factors determined in the multivariable logistic regression model and it can be used to estimate the probability of inappropriate opioid use.

Results: Median age was 62yrs. Median ESAS pain item score on consultation was 5, Median ECOG was 2.20.4% were SOAPP+ and 10.1% were CAGE- AID+. SOAPP+ was significantly associated with gender, race, marital status, smoking status, depression, anxiety, financial distress, MDED and CAGE score. The c-index is 0.861 (95% CI 0.840-0.883). For example, for a male Hispanic patient, who is married, never smoked, with the following ESAS scores: (depression = 3, anxiety = 3, financial distress = 8), CAGE score of 0, and MDED of 20, the total score is 9+4+0+6+10+26+0+1 = 61. In the nomogram a score of 58 indicates the probability of inappropriate opioid use between 10% to 20% (close to 10%). Conclusions: A nomogram can predict the risk of inappropriate opioid use in cancer patients.
Methods: The effectiveness of enterade to reduce GI toxicities after high-dose melphalan improved body weight following irradiation. The goal was to investigate the rebuilding of villi and reduce antigenic translocation by tightening the mucosa that can facilitate retention of the absorbing capacity of the small intestine by a mixture as diarrhea prevention in patients undergoing autologous stem cell transplantation (HSCT) in multiple myeloma (MM) and non-Hodgkin lymphoma (NHL) patients. Gastrointestinal symptoms were assessed for safety and tolerability of BPM31543. Patients with a diagnosis of breast cancer, gynecologic cancer or sarcomas receiving a taxane-based chemotherapy regimen applied 1 mL of the formulation to the scalp 8ID, 5 days prior to starting chemotherapy for at least 3 months or until treatment completed. Safety and efficacy assessments included AE, monitoring, PK analysis, blinded photographic assessments and patient self-assessment. Results: 22/23 (95.7%) female patients receiving treatment and included in the safety population experienced at least one TEAE. The most frequently experienced TEAEs were alopecia (14 pts; 60.9%), fatigue (11 pts; 47.8%), nausea (9 pts; 39.1%), peripheral sensory neuropathy (7 pts; 30.4%), and maculopapular rash and vitamin D increased each in six patients (26.1%). Of these, elevated vitamin D and rash were possibly or probably related to treatment. Fatigue, nausea, and neuropathy were likely due to chemotherapy. In 18 patients included in the post-dose versus pre-treatment comparison, there was no dose-dependency on systemic levels of calcium. Hair loss < 50% from baseline was observed in 8 patients at week 7 that was maintained at week 15 in 2 patients. Conclusions: Study results showed BPM31543 applied topically twice daily to the scalp in patients receiving taxane-based chemotherapy was safe and well-tolerated. No DLT was observed up to 80 μg/mL dose and no MTD level was reached. There was a signal of potential efficacy detected at each dose level. A seamless Phase 2/3 trial strategy for clinical development is planned. Clinical trial information: NCT01588522.

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Lower costs of care, improved discharge disposition, and improved survival of advanced cancer patients (ACP) receiving early inpatient palliative care (PC) compared to standard oncologic care (SOC). First Author: Christopher Daugherty, University of Chicago, Chicago, IL

Background: Outpatient PC improves ACP symptom burdens, end-of-life care transitions, and mortality thereby enhancing quality of life. Yet, the financial implications, discharge disposition, and survival benefits of early, inpatient PC compared to SOC remains less understood. Methods: Retrospective cohort analysis of ACP receiving either PC or SOC between Jan 2015-Dec 2015 (N = 810). ACP cohorts were compared for demographics, costs, disposition, and survival. Financial costs collected included: fixed (overhead expenditures, facility maintenance, hospital property); variable (patient care supplies, diagnostic/therapeutic supplies, medications); operating (fixed, variable, breaking-even costs); direct (labor, materials, commissions, piece-rate wages, manufacturing supplies); indirect (production-supervision salaries, quality control, insurance, depreciation). Univariate and multivariate analyses were completed. Results: 468 were admitted to PC and 342 to SOC. Compared with SOC, PC were more likely to be: younger (61.1 ± 13.2 v. 62.5 ± 13.0, p = 0.02); African American (40% v. 36%, p = 0.0045); female (50% v. 40%, p = 0.005); and have shorter length of stay (6.7 ± 4.9 v. 6.2 ± 6.5, p = 0.01). PC had significantly less 30-day readmissions (16% v. 23%, p = 0.03) and lower costs: direct ($9,478 v. $10,416, p = 0.01); indirect ($9,538 v. $10,999, p = 0.002); fixed ($10,308 v. $12,076, p = 0.001); variable ($8,709 v. $9,339, p = 0.02); operating ($19,017 v. $21,416, p = 0.03). Compared with SOC, ACP receiving PC were more likely to be discharged to: home (56% v. 45%, p = 0.01); healthcare facilities (e.g. skilled nursing, inpatient rehabilitation) (36.1% v. 20%, p = 0.04); and hospice (home and inpatient) (7.7% v. 5.8%, p = 0.02). PC had overall greater median survival from the time of discharge (106.8 v. 99.95 v. 73.8 ± 61.93, p = 0.03) compared to SOC. Conclusions: Early PC results in less financial strain, greater cost savings, and improved outcomes for younger and underserved inpatient ACP. Our results provide additional evidence for policies supporting that ACP access to routine PC must become a healthcare priority.

Therapy discontinuation processes in a gynecologic oncology population. First Author: Catherine H. Watson, Duke University, Durham, NC

Background: The decision to discontinue anti-cancer therapies in oncology patients is a complex one and may occur in several unique ways. We sought to understand the processes of therapy discontinuation in a gynecologic oncology population and to discern possible changes in the distribution of these processes after implementation of a palliative care (PC) quality improvement project. Methods: Women with incurable gynecologic malignancies seen in the outpatient setting at an academic center were identified with the recommendation for ‘goals of care’ discussion within 3 visits following identification. Processes of discontinuing chemotherapy for this population were assessed and categorized into 1 of 4 categories: definitive outpatient decision, definitive inpatient decision, interruption by hospitalization, treatment holiday, and “no decision.” Retrospective chart review identified a similar cohort of women prior to the implementation of our PC intervention. Univariate analyses were conducted to determine associations between characteristics and binary outcome of definitive outpatient decision versus all other decision processes. Results: 90/102 (88%) pre-intervention subjects and 83/157 (53%) post-intervention subjects had died at time of analysis. Of the total deceased cohort, 59/173 (34%) made a definitive decision to stop therapy in the outpatient setting. After implementation of the PC initiative, there was a trend towards fewer women identified as having made “no decision” (28.1% vs 30%). Those who made a definitive outpatient decision were less likely to die within 30 days of hospitalization than those who did not (OR 0.16 [95% CI 0.07-0.39], p < 0.0001). Conclusions: Discontinuation of therapy is a nuanced concept in gynecologic oncology patients that can be stratified into several processes. While our data demonstrates a possible increase in active decision-making with the PC initiative, a majority of patients near the end of life still did not make definitive therapy cessation decisions. This reveals an urgent need for the development of initiatives to enhance patient engagement and shared decision-making for women near the end of life.

Learning from best scalp cooling practices in a registry: Differences in results from n=7000 patients with solid tumors. First Author: Corina van den Hurk, Netherlands Comprehensive Cancer Organisation, Utrecht, Netherlands

Background: Hair loss is a frequently occurring and stigmatizing side effect of chemotherapy. Worldwide scalp cooling is being introduced to prevent chemotherapy-induced alopecia (CIA). In the Netherlands scalp cooling is implemented in many hospitals since 2005. FDA clearance has been approved for scalp cooling among breast cancer patients in the USA in 2016. Recently approval has been expended for solid tumors. Methods: In a prospective, longitudinal registry data have been collected between 2006 and 2017. Patients could be included if they received chemotherapy that induced severe alopecia, regardless type of solid tumor, stage of disease, age, gender or receiving adjuvant or palliative treatment. Patients were eligible for evaluation of hair loss after they received at least 2 cycles of chemotherapy or if they ceased scalp cooling because of severe hair loss after the first cycle. Failure was defined as feeling the need to use a wig or head cover. Data will be presented using descriptive statistics and multivariate regression analysis to explore determinants of scalp cooling efficacy per largest groups of chemotherapy regimen, and evaluate variation between hospitals. Results: Preliminary results show data of 7378 patients from 68 hospital locations of whom 75% had breast cancer and 8% prostate cancer. Overall 57% of patients did not feel the need to wear a wig or head cover. Variation was observed between hospitals in scalp cooling procedures: e.g. wetting the hair (0-100% of patient) and cooling- and infusion times that varied per type of chemotherapy. Also results varied between hospitals per type and dose of chemotherapy (n > 10 patients), e.g. minimal 37% and maximal 86% success rates between hospitals for paclitaxel-carboplatin (n = 498), 17-54% success for irinotekan monotherapy (n = 275), 29-79% success for 5FU/epirubicin/ cyclophosphamide-docetaxel (n = 843) and 79-94% for docetaxel monotherapy (n = 824). Also variation in satisfaction with information about scalp cooling and nursing expertise was observed. Results from the regression analyses will be presented at the conference. Conclusions: Scalp cooling efficacy varied enormously between hospitals. A registry is a useful tool to identify best practices and to provide guidance to further improve results. An international registry has been set up to also collect data on CIA among scalp cooled and non-scalp cooled patients in the USA, Australia and the UK.
Background: Family is often overlooked in cancer care. Little is known about the patient preferences for involving family in communication, whether preferences may be elicited and supported at the point of care, and impact on care quality. Methods: We conducted a two-group pilot randomized controlled trial (NCT03283553) of patients on active treatment for breast cancer and the “care partner” who accompanies them to routine visits (n = 13 dyads). Intervention dyads (n = 69) completed a self-developed checklist to clarify the care partner role, establish a shared visit agenda, and facilitate access to the electronic health record (MyChart) patient portal. Control dyads (n = 63) received usual care. Intervention acceptability and short-term effects were assessed from post-visit surveys and MyChart utilization at 6 weeks. Results: At baseline, most patients (89.4%) but few care partners (1.5%) were registered for MyChart. Most patients (79.4%) wanted their care partner to have access to their records and 39.4% of care partners reported accessing it in the past year using the patient’s account login/password. In completing the checklist, intervention patients and care partners identified an active communication role for the care partner and similar issues for the visit agenda: topics most frequently selected were treatment goals/expectations (75.4% & 66.7%, respectively), symptoms/side effects (73.9% & 62.3%) and chances of cancer recurrence/spread (49.3% & 44.9%). More than 50% of intervention participants reported completing the checklist was easy, useful, and most memorable. At 6 weeks, intervention (vs control) care partners were more likely to be registered for MyChart (75.4 % vs 1.6%; p = 0.001), to have logged in (43.5% vs 0%; p < 0.001) and viewed clinical visit notes (30.4% vs 0%; p = 0.001), but no more likely to have exchanged direct messages with the clinical team (1.7% vs 0.1%; p = 0.176). No intervention effect was noted on MyChart registration, use, or messaging was found at 6 weeks, but intervention patients more often viewed clinical visit notes (50.7% vs 9.5%; p < 0.001). Conclusions: A self-administered patient-family communication intervention affected online practices of patients and cancer care partners. Follow-up continues. Clinical trial information: NCT03283553.
11618 Poster Session (Board #310), Mon, 1:15 PM-4:15 PM
After cancer, what's more important? The survivorship care plan or the survivorship care visit? First Author: Harish Sagaranesh, Lifespan Cancer Institute, Providence, RI

Background: The Commission on Cancer has made the provision of survivorship care plans (SCPs) a prerequisite for accreditation of cancer programs. However, whether all patients desire or derive benefits from an SCP is not established. This study sought to characterize the provision of survivorship care at the Lifespan Cancer Institute (LCI) to (1) determine clinical and distress characteristics at first visit to the LCI among patients treated with curative intent for a solid tumor diagnosis; (2) characterize which factors were associated with receipt of an SCP with or without a survivorship care visit (SCV); and (3) determine referral patterns and outcomes among patients with an SCP with or without an SCV. Methods: We have retrospectively reviewed 650 patients at Lifespan Cancer Institute so far, all of whom were initially seen between the years 2014-2017. As part of routine practice, all new patients are screened with the NCCN Distress Thermometer (DT). Data related to demographics, treatment variables, and presenting distress score were gathered using our electronic medical records. Categorical data were analyzed using Fisher's Exact Test or Chi-Square. Multinomial logistic regression was performed for multivariable analysis. All analyses were performed in STATA 13.0.

Results: The median age was 63 (range 29 to 90), 74.8% were female, and 39.5% were married or partnered. The major cancers represented included breast (52.2%), lung (16.6%), and prostate (6%) cancers. Severe distress (DT≥4) was reported in 49.5% of patients at their first visit with top concerns being anxiety (54.3%), fatigue (46.6%), and sleep disturbance (37.3%). An SCP was documented in 461 patients (71.1%) and of these, 267 (57.9%) were seen in an SCV as well. On multivariate analysis, gender, marital status, and stage were significantly associated with the receipt of an SCP. However, only disease site was significantly associated with being seen in an SCV. Compared to those with an SCV, patients not seen in an SCV were significantly more likely (p < 0.005) to be referred for post-treatment evaluation, including psychological counseling (15.7% vs 6.7%), physical therapy (56.9 vs 22.7%), and nutrition (26.6 vs 8.2%). The majority of patients followed up with referrals, though it was significantly higher among those with an SCV (95% vs 87%, p = 0.015). Survival rates were highest among patients with gynecologic and GI cancers. Referral to other resources is significantly higher among those seen in visits, and those who are referred will follow up.

11620 Poster Session (Board #312), Mon, 1:15 PM-4:15 PM
Differences among Asian/Asian American, and Caucasian breast and gynecologic cancer patients: representation needs, symptom mindsets (N=220). First Author: Lidia Schapira, Stanford Cancer Center, Palo Alto, CA

Background: Cancer experiences are mediated by host and disease factors and affected by social and cultural determinants of health. We sought to characterize perceived supportive care needs and domains of psychosocial functioning among a diverse group of women attending routine appointment for treatment of breast and gynecologic cancers. Methods: The Stanford Distress in Cancer Questionnaire (SDCQ) is an electronic survey on their supportive care needs assessment (The Short-form Supportive Care Needs Survey Questionnaire) which contains physical, social, information, sexual and psychological scales, anxiety and depression (Patient Health Questionnaire-4) and mindsets about illness and the body (Supportive Care Needs Survey Questionnaire) which contains physical, nutritional, and psychological domains of distress. Participants were approached to participate. 220 cancer patients were recruited from July 2018 until January 2019, all patients seen at the Stanford Women’s Cancers Program (serving women treated for breast and gynecologic cancers) were approached to participate. 220 cancer patients (78% breast and 22% gynecologic) were approached (SD = 12) completed an online survey on their supportive care needs assessment (The Short-form Supportive Care Needs Survey Questionnaire) which contains physical, social, information, sexual and psychological scales, anxiety and depression (Patient Health Questionnaire-4) and mindsets about illness and the body (Supportive Care Needs Survey Questionnaire) which contains physical, nutritional, and psychological domains of distress. Participants were recruited from July 2018 until January 2019, all patients seen at the Stanford Women’s Cancers Program (serving women treated for breast and gynecologic cancers) were approached to participate. 220 cancer patients were recruited from July 2018 until January 2019, all patients seen at the Stanford Women’s Cancers Program (serving women treated for breast and gynecologic cancers) were approached to participate. 220 cancer patients (78% breast and 22% gynecologic) were approached to participate.

Results: The median age was 63 (range 29 to 90), 74.8% were female, and 39.5% were married or partnered. The major cancers represented included breast (52.2%), lung (16.6%), and prostate (6%) cancers. Severe distress (DT≥4) was reported in 49.5% of patients at their first visit with top concerns being anxiety (54.3%), fatigue (46.6%), and sleep disturbance (37.3%). An SCP was documented in 461 patients (71.1%) and of these, 267 (57.9%) were seen in an SCV as well. On multivariate analysis, gender, marital status, and stage were significantly associated with the receipt of an SCP. However, only disease site was significantly associated with being seen in an SCV. Compared to those with an SCV, patients not seen in an SCV were significantly more likely (p < 0.005) to be referred for post-treatment evaluation, including psychological counseling (15.7% vs 6.7%), physical therapy (56.9 vs 22.7%), and nutrition (26.6 vs 8.2%). The majority of patients followed up with referrals, though it was significantly higher among those with an SCV (95% vs 87%, p = 0.015). Survival rates were highest among patients with gynecologic and GI cancers. Referral to other resources is significantly higher among those seen in visits, and those who are referred will follow up.

11619 Poster Session (Board #311), Mon, 1:15 PM-4:15 PM
Lung cancer stigma: A ten-year look at patient and oncologist attitudes about lung cancer. First Author: Jennifer C. King, Lung Cancer Alliance, Washington, DC

Background: The presence of lung cancer stigma is well documented and has been shown to impact the care and treatment of lung cancer survivors (Tod et al. 2008; Carter-Harris et al. 2014). In the past decade, there has been considerable research progress in lung cancer but it is unknown if the level of stigma has changed and how that affects patient care. Methods: 205 oncologists who treat lung cancer, 208 patients with lung cancer, and 1001 members of the general public were surveyed with the same survey instrument from a 2008 survey (Weiss et al. 2014) plus 5-15 additional questions at the end. The survey was carried out with identical methodology by phone and online between June 6 and July 26, 2018. Statistical analysis was performed comparing 2008 and 2018 datasets using paired t-tests if normally distributed or Mann-Whitney U tests for continuous data and Chi-squared or Fisher’s exact test for categorical data. Results: In 2018, significantly more oncologists feel they have adequate treatment options for metastatic lung cancer (67% vs 63%, p < 0.001) and the majority of patients report being satisfied with their medical care (87% vs 86% in 2008) and that patients blame themselves (67% vs 57%). Significantly more patients felt that there was a stigma associated with having lung cancer (70% vs. 54%, p < 0.001). In addition, 57% of oncologists indicated that patients with different cancers are thought about, approached, or handled differently, similar to 2008. Lung cancer patients were most frequently cited as treated differently. In 2018, 40% of patients agreed with the statement “patients with lung cancer are treated differently by doctors and nurses” compared to 26% a decade ago (p = .01). Both groups felt the most common way patients were treated differently was “received as much medical care from medical specialty services” After a decade of research progress in lung cancer, stigma surrounding the disease remains a critical problem even in a healthcare setting. Patients are perceiving stigma at higher levels and oncologists are not reporting any improvement. This work underscores the need to address stigma with proactive multilevel approaches including the need for medical providers to practice empathic communication.

11621 Poster Session (Board #313), Mon, 1:15 PM-4:15 PM
Relationship between perceptions of treatment goals and psychological distress in patients with advanced cancer. First Author: Amanda L. Jankowski, Massachusetts General Hospital, Boston, MA

Background: Several studies have demonstrated discordance between how patients perceive their goal of treatment versus how they perceive their oncologist’s goal. Studies evaluating the extent and risk factors of this discordance are lacking. Methods: We conducted a cross-sectional study of 559 patients with incurable lung, gastrointestinal, breast, and brain cancers. We used the Perception of Treatment and Prognosis Questionnaire to assess patients’ perceptions of both their treatment goal and their oncologist’s goal and categorized responses: 1) patients who reported that both their goal and their oncologist’s goal was concordant (either to cure or not to cure); and 2) patients who reported discordant perceptions of their goal and their oncologist’s goal. We assessed patients’ psychological distress using the Hospital-Anxiety-Depression-Scale and used linear regression to assess the relationship between patients’ perceptions of their treatment goal and psychological outcomes. Results: 61.7% of patients reported that both their goal and their oncologist’s goal was non-curative; 19.3% reported that both their goal and their oncologist’s goal was to cure their cancer; and 19.0% reported discordance between their goal and their perception of the oncologist’s goal. Older age (OR = 0.98, P = 0.01), non-Hispanic ethnicity (OR = 0.31, P = 0.049), and higher education (OR = 0.62, P = 0.042) were associated with lower likelihood of reporting discordant goals. Patients with discordant perceptions of their goal and their oncologist’s goal reported higher anxiety (B = 1.56, P = 0.003) compared to those who reported that both their goal and their oncologist’s goal was curative. Patients who reported both their goal and the oncologist’s goal was non-curative had higher depression symptoms (B = 1.06, P = 0.001) compared to those who reported that both their goal and the oncologist’s goal was curative. Conclusions: A fifth of patients with advanced cancer report discrepancies between their perceptions of their own and their oncologists’ treatment goal which is associated with psychological distress. Tools are needed to identify patients at risk of cognitive dissonance about their prognosis.

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11622 Poster Session (Board #314), Mon, 1:15 PM-4:15 PM
The individualized Goals of Care Discussion Guide: A simple tool to empower patients with metastatic breast cancer. First Author: Jeffrey M. Peppercorn, Massachusetts General Hospital, Boston, MA, USA

Background: Individualized treatment planning is a critical part of quality cancer care, but how best to achieve this for patients with metastatic breast cancer (MBC) is unclear. We evaluated the feasibility, acceptability and impact of using a simple and scalable “Individualized Goals of Care Discussion Guide” (IGCDG) to facilitate patient-provider communication at the time of decision making. Methods: We developed the IGCDG based on structured interviews with MBC patients and input from experts in cancer care, decision sciences, psychology and palliative care. We then conducted a single arm feasibility trial among patients with newly diagnosed or progressive MBC. Prior to clinic, patients received the IGCDG, an 8-page MBC informational brochure and 1-page questionnaire regarding treatment preferences, personal goals and priorities for care planning. The completed questionnaire was provided to the oncology team at the patient’s visit. Pre and post assessment included the Distress Thermometer (DT), Patient Satisfaction with Cancer Care Scale and the Control Preferences Scale. Feasibility was defined as: 1) accrual of >50%, 2) attrition rate <32%, and 3> 50% of patients experiencing increased distress following the intervention. Results: Among 60 eligible patients, 41 participated (70% accrual), 40 completed all surveys (2% attrition), and only 7 (18%) reported increased distress. Mean age was 57 (range 31 – 79), 85% were white, 7% black, 5% Hispanic, 66% were college graduates, and 40% reported high baseline distress (DT > 4). Patient priorities for discussion included cancer directed therapy (70%), symptom management (66%), psychological distress (50%), and decision roles planning ahead (60%). At 2-month follow-up, 53% reported decreased distress compared to baseline. Satisfaction with cancer care was high at baseline and follow-up. Most patients preferred shared decision making (77%), and 79% reported decision roles concordant with preferences. Overall, 72% of participants found the IGCDG helpful, 93% found it easy to complete, and 44% felt it improved communication with their doctor (49% unsure). Conclusions: Administration of the Individualized Goals of Care Discussion Guide is feasible and provides patients with MBC an opportunity to define their goals of care and priorities for discussion in clinic. Clinical trial information: NCT03375827.

11623 Poster Session (Board #315), Mon, 1:15 PM-4:15 PM
Depression and anxiety symptoms in bereaved caregivers of patients with advanced cancer. First Author: Olivia Vanbenschoten, Massachusetts General Hospital, Boston, MA, USA

Background: Caregivers of patients with advanced cancer experience substantial caregiving burden and psychological distress during the illness course. However, data on depression and anxiety symptoms in bereaved caregivers and factors associated with their psychological distress are lacking. Methods: We conducted a secondary analysis of 168 caregivers enrolled in a randomized trial of early palliative care integrated with oncology care for patients with newly-diagnosed with incurable lung and non-colorectal gastrointestinal cancers and their caregivers who completed bereavement assessments at 3 months after their loved one’s death. We used the Hospital Anxiety and Depression Scale (HADS) to assess patients’ and caregivers’ depression and anxiety symptoms at baseline in 8 weeks of diagnosis, and at 3-4 months after the patient’s death (for caregivers). We asked caregivers to rate patient’s physical and psychological distress in the last week of life on a 10-point scale. We used linear regression adjusting for randomization and cancer type to explore associations between patient and caregiver factors and bereaved caregivers’ depression and anxiety symptoms. Results: 30.4% (51/168) and 43.4% (73/168) of bereaved caregivers reported clinically significant depression and anxiety symptoms, respectively. Younger patient age (B = -0.06, P = 0.041), higher patient baseline anxiety (B = 0.28, P = 0.002), and caregiver rating of worse physical (B = 0.28, P = 0.035) and psychological (B = 0.41, P < 0.001) distress experienced by the patient at the EOL (B = 0.42, P = 0.001) were associated with worse bereaved caregivers’ depression and anxiety symptoms. Conclusions: Caregivers of patients with advanced cancer experience substantial psychological distress which is associated with their perceptions of their loved one’s distress at the EOL. Interventions to optimize EOL care for patients and reduce bereaved caregivers’ psychological distress are needed.

11624 Poster Session (Board #316), Mon, 1:15 PM-4:15 PM
Effectiveness of psychological distress reduction with cognitive behavioral therapy for oncological patients: A one-year follow-up study. First Author: Alessandro Rossi, Department of Philosophy, Sociology, Education, and Applied Psychology, Section of Applied Psychology, University of Padova, Padova, Italy

Background: Distress has a negative impact on medical treatment (Di Matteo, Lepper & Croghan, 2006) and it is considered one of the most important indexes of psychological suffering in oncological patients (NCCN, 2015). Thus, the purpose of this study was to determine the long term effectiveness of brief Cognitive Behavioral Therapy for patients with cancer (CBT-C) compared with a control group (CG) of oncological patients without any psychotherapy intervention - at one year after a chemotherapy treatment. Methods: Participants (n = 80; mean age = 63.3, SD = 13.4; 54 female) enrolled at the Oncology Day Hospital at the “Presidio Ospedaliero” of Sarorno, ASST Valle Oltona, Italy who undertook (CBT-C: n = 40) or non-undertook (CG: n = 40) a psychotherapy intervention. Individual psychotherapy sessions strictly followed the IPOS guidelines (Watson & Kissane, 2017). Participants were tested with the Psychological distress Inventory (PDI) at the baseline (T1; Cronbach α = .88) at the end of the chemotherapy treatment (T2; Cronbach α = .87), at the end of the psychotherapy intervention (T3; Cronbach α = .88), 6-month follow-up (T4; Cronbach α = .85), and 1-year follow-up (T5; Cronbach α = .84). Results: Multilevel growth curve modeling – controlling for age, number of sessions, type and localization of tumor - showed a sharp reduction of distress for CBT-C participants that continue after posttreatment until 1-year follow-up (p < .001); whereas for CG participants it reduced more gradually from pre-treatment to 1-year follow-up (p < .001). The results revealed a significant difference between the linear slopes for each treatment condition (p < .001). The overall Hedges’ g comparing the two groups for distress reduction between pretreatment and 1-year follow-up was 2.14 (p < .001) in favor of CBT-C. Conclusions: Given that psychological distress occurs frequently among oncological patients this study is into an important area of study. Results suggest that CBT-C is statistically and clinically effective in treating psychological distress 1 year after the chemotherapy treatment. These findings revealed a kind of long-term effectiveness, psychological distress reduction can improve better quality of life in oncological settings.

11625 Poster Session (Board #317), Mon, 1:15 PM-4:15 PM
Evaluating the effects of a structured exercise intervention on physical self-worth in prostate cancer: Addressing an unmet need. First Author: Richard Francis Dunne, University of Rochester James P. Wilmot Cancer Institute, Strong Memorial Hospital, Rochester, NY

Background: Improving body image and self-esteem are top ASCO priorities in the survivorship care of men with prostate cancer (PCa). Body image and global self-esteem, influenced by physical self-worth, are negatively affected by PCa treatment. We investigate whether exercise can improve physical self-worth in men treated for PCa and if improving self-worth is associated with changes in quality of life (QoL) and mental health. Methods: We performed a secondary analysis of a phase II randomized controlled trial comparing the effects of Exercise for Cancer Patients (EXCAP), a structured, 6-week, home-based exercise intervention, to usual care (UC) in men with non-metastatic PCa receiving radiation or Androgen Deprivation Therapy (ADT). The Physical Self-Perception Profile (PSPP), a valid 30-item questionnaire where higher scores indicate greater physical self-worth, was assessed at pre- and post-intervention. Changes between arms were compared using ANCOVA. Spearman correlations were calculated for pre/post-intervention change scores for PSPP and QoL, depression, and anxiety as measured by the Functional Assessment of Cancer Therapy (FACT), Center of Epidemiologic Studies Depression (CES-D) scale, and State-Trait Anxiety Inventory (STAI), respectively. Results: Fifty-eight men were randomized; average age was 67.1 years. Physical self-worth at baseline moderated the effect of the intervention. Compared to UC, EXCAP improved physical self-worth in those with baseline PSPP scores above the median (p < 0.04). Exercisers with baseline PSPP scores in the top quartile demonstrated a more significant improvement over UC (p < 0.01). Improvements in physical self-worth were associated with improved QoL (r = 0.29, p < 0.04), depression (r = -0.28, p = 0.04) and anxiety (r = -0.30, p = 0.03). Conclusions: Exercise significantly improves physical self-worth in men with PCa on radiation or ADT, and greater physical self-worth is associated with improved QoL, depression and anxiety. Those with higher baseline physical self-worth derived the most benefit from exercise. Exercise should be prescribed to boost self-esteem and body image in men receiving radiation or ADT for PCa. Clinical trial information: NCT00815672.
The importance of altruism to biomarker development for pancreatic cancer.

First Author: Danny HJ Heo, Beth Israel Deaconess Medical Center, Boston, MA, USA

Background: Longitudinal donation of tissue and health information by patients with pancreatic ductal adenocarcinoma (PDAC) is critical to validating algorithms for precision treatment. Unlike therapeutic trials offering potential survival benefit, factors motivating long-term participation in biomarker studies are poorly understood. We hypothesized that long-term participation (PART) depends on identifiable factors motivating study volunteers at one-time, non-therapeutic biomarker studies. Methods: A prospective single-institution biomarker study was screened to identify participants with, or at elevated risk for, PDAC and peripancreatic cancer (Jul 2015-Dec 2018). Study consent precluded individual receipt of value or research benefit. Detailed biospecimen and clinical data (n = 294) were analyzed using multivariable modeling and Bayesian Ai (bAiCis) to characterize motivators of PART. Results: Of 294 participants, 185 had PDAC (63%); 89 had premanifest lesions (30%) or tumors (20%; 7%) mimicking PDAC. Mean age was 68 years, 54% male, 26% with prior cancers, and 18% family PDAC history. Treatment was not indicated (37% no cancer), potentially curative (27%), non-curative (35%); or refused (14%). Bayesian analysis characterized the leading predictor of PART as being the leading predictor of PART. Using multivariable modeling and adjusting for the competing risk of death, none of the following domains predicted PART: demographics, perceived personal/family cancer risk, health insurance type, median income, housing price, travel time/distance or diagnosis to be the leading predictor of PART. Methods: A prospective ACP cohort enrolled in phase I trials was assessed at baseline (T1) and at one month (T2) utilizing psychosocial measures: state-trait anxiety (STAI-S/T), depression (CES-D), quality of life (QOL) (FACT-Pal), and global health (SF-36). Semi-structured interviews evaluated the ACP-SC-EL experience: cognitive awareness (e.g., death, terminal prognosis); and, emotions (physical isolation; emptiness; abandonment). Results: To date, 160 participants (80 Phase I ACP and 80 SC) have been separately interviewed at T1 and T2. Total population demographics include: median age 62 (28-78y); 50% male; 100% married; 89% Ca; 68% Black; 58% GI dx; ACP median survival 8.3 months (518-19.9) 55% income < $65,000 yr. At T1, 77% of ACP acknowledged a cognitive awareness of death; 89% felt isolated; 65% recognized a cognitive awareness of death; 89% felt isolated; and 82% sensed emotional abandonment. Over time, rates of EL remained consistent for ACP-SC with the exception of increased self-reported isolation at 79% and 92% respectively at T2. At T2, ACP with death cognitions had higher STAI-S anxiety (39±17 v. 35±13, p = 0.03) at T2. Regression analyses revealed ACP with EL death cognitions had poorer FACT-Pal QOL over time. Moreover, SC with self-reported physical isolation at T2 was negatively associated with SF-36 scores. ACP with EL had shorter overall survival compared to ACP without EL (4.1 v. 6.9 months, p = 0.02). ACP and SC qualitative inquiry re EL exposed unique themes: difficulty articulating EL experience; acceptance of death; finding meaning within crisis. Conclusions: EL is negatively associated with QOL for ACP participating in Phase I Trials. Supportive couples-based, dyadic psychological interventions at the end-of-life to assist with coping are indicated.
TPS11630  Poster Session (Board #321b), Mon, 1:15 PM-4:15 PM
Implementation of complex perioperative intervention in older patients with cancer (IMPROVED program). First Author: Elena Paillault, Hospital European Georges Pompidou, Paris, France

Background: Nearly 50% of patients are older than 70 years at diagnosis of digestive cancer. Surgical resection is the first line strategy of treatment. Despite improvement in surgical techniques and development of rehabilitation programs, the rate of postoperative complications remains high. Peri-operative involvement of geriatricians may improve care management older cancer patients.

Methods: During a 6 months run-up period (emerging project), we structured a multi-professional network (digestive surgeons, anesthetists, geriatricians, digestive oncologists, epidemiologists), we elaborated an innovative peri-operative geriatric intervention (Improved program) in digestive surgery setting based on evidence-based data. We build a dedicated evaluation plan by determinate the best design for assessing geriatric intervention in this complex context and choose the more appropriate endpoints.

Results: We will include 554 patients aged 75 or more with resectable digestive cancer in a stepped wedge cluster randomized trial. The intervention is based on 1/ a preoperative geriatric assessment, focusing on frailty parameters and developing a coordinated program of tailored geriatric interventions 2/ a postoperative shared care with an integrated care model where both surgeon and geriatrician share responsibility for the patient management in surgical ward. This geriatric postoperative management will focus on prevention and correction of complications, early mobilization, optimal nutritional support. The main endpoint is is Grade I or high post-surgical complications rate according Clavien-Dindo classification within 30 days after the surgical procedure. Conclusion: We expected to demonstrate a benefit of a peri-operative shared management model to decrease the risk of post-surgical complications in older patients with digestive cancer.

TPS11631  Poster Session (Board #322a), Mon, 1:15 PM-4:15 PM
eMouvoir: Randomized study estimating the impact of a personalized and remote support centered on physical activity (PA) for patients (pts) after breast cancer (BC). First Author: Laurence Vanlemmens, Centre Oscar Lambret, Lille, France

Background: BC pts can reduce their health-related quality of life (HRQoL) encompassing physical, psychological and social components due to cancer and treatments (trts). Despite the strong evidence of the beneficial effects of EPA for BC pts on HRQoL, the cancer pts’ EPA levels most often decline after diagnosis and trts due to physical and psychological components, accessibility to exercise programs, time constraints. Connected watches can now contribute to pts’ deeper commitment to their program by providing reliable trends of their EPA metrics. Notwithstanding this recent progress, cancer pts keep facing challenges to maintain a regular EPA. We aim at evaluating a holistic intervention including a physical activity educator, coaching pts remotely for 4 months (mo), to improve HRQoL after BC. Methods: eMouvoir is a multicenter randomized, controlled phase 3 trial started 4-6 mo after the end of trt among non-metastatic BC pts. It assesses the benefit of a personalized remote EPA coaching, including a connected watch, access to a digital platform, personalized objectives, ≥ 2 messages per week, weekly learning sessions for 4-6 mo duration compared to the standard supportive approach (recommendations for EPA made during visits with the oncologist) in terms of HRQoL. The randomization is balanced 1:1 and controlled for HRQoL at inclusion, trts, exercise practice, age, access to the Internet and center. Main eligibility criteria are: age ≥18; adjuvant or neoadjuvant trt for non-metastatic BC; medical certificate for sports practice. Patients without a connected device are eligible. HRQoL is evaluated using the SF-36 questionnaire, at 4, 8 and 12 mo. Both components (physical and mental summary) at 12 mo are used as co-primary endpoints. The study includes a health-economics evaluation, using EQ-SD and EQ VAS, to estimate the incremental cost-utility ratio. Based on the following assumptions: expected mean difference for each SF-36 component at 12 mo ≥3 points, standard deviation=15, power=90%, 2-sided alpha=2.5%, 10% drop-outs, 1242 evaluable pts are required, leading to 1380 pts. The trial is funded by the French ministry of health and should open enrollment soon.

TPS11632  Poster Session (Board #322b), Mon, 1:15 PM-4:15 PM
Physical activity platform to improve bone health in cancer survivors. First Author: Cathy Skinner, Thrivors Inc., Saint Paul, MN

Background: Cancer treatment-induced bone loss and the subsequent risk of fractures in both men and women is a significant burden on national health care. US cancer survivors will reach 18 million by 2022 and by 2025 and the projected burden of osteoporosis is $25.3B. Cancer patients treated with medications that lower hormone levels face an increased risk of fractures. Several factors account for the increased risk of osteoporosis and fractures in cancer patients: treatment-induced bone loss, adjuvant chemotherapy and endocrine therapy adherence rate in women with breast cancer: The Lifestyle Exercise and Nutrition Early After Diagnosis (LEANER) Study. First Author: Tara B. Sant, Yale School of Medicine, New Haven, CT

Background: The World Cancer Research Fund and the American Cancer Society provide diet and exercise guidelines for cancer survivors. Many women with breast cancer do not follow these guidelines. Adoption of recommended lifestyle behaviors soon after diagnosis may prevent adverse changes in body composition, breast cancer biomarkers, and may improve adherence to treatment thereby improving breast cancer prognosis. The Lifestyle, Exercise, and Nutrition Early after Diagnosis (LEANER) study is testing the impact of a healthy lifestyle intervention on chemotherapy completion and endocrine therapy adherence. Secondary endpoints include changes in inflammatory and metabolic biomarkers, body composition, and patient reported outcomes.

Methods: Eligible participants are women with stage I-III breast cancer undergoing chemotherapy. 250 participants are being recruited and randomized 1:1 to a yearlong, 16 session, healthy diet and exercise counseling intervention versus usual care. The primary endpoint is adherence to exercise (primary outcome) and platform usage will be measured by platform software, while user engagement (secondary outcomes) will be assessed by surveys. Differences between primary and secondary outcomes for the control and intervention groups will be evaluated. Usage statistics, motivational responses and user feedback will be used to further refine platform features and content. Clinical trial information: NCT03314688.

TPS11633  Poster Session (Board #323a), Mon, 1:15 PM-4:15 PM
A randomized trial of a healthy lifestyle intervention versus usual care on chemotherapy and endocrine therapy adherence rate in women with breast cancer: The Lifestyle Exercise and Nutrition Early After Diagnosis (LEANER) Study. First Author: Tara B. Sant, Yale School of Medicine, New Haven, CT

Background: BC pts can reduce their health-related quality of life (HRQoL) encompassing physical, psychological and social components due to cancer and treatments (trts). Despite the strong evidence of the beneficial effects of EPA for BC pts on HRQoL, the cancer pts’ EPA levels most often decline after diagnosis and trts due to physical and psychological components, accessibility to exercise programs, time constraints. Connected watches can now contribute to pts’ deeper commitment to their program by providing reliable trends of their EPA metrics. Notwithstanding this recent progress, cancer pts keep facing challenges to maintain a regular EPA. We aim at evaluating a holistic intervention including a physical activity educator, coaching pts remotely for 4 months (mo), to improve HRQoL after BC. Methods: eMouvoir is a multicenter randomized, controlled phase 3 trial started 4-6 mo after the end of trt among non-metastatic BC pts. It assesses the benefit of a personalized remote EPA coaching, including a connected watch, access to a digital platform, personalized objectives, ≥ 2 messages per week, weekly learning sessions for 4-6 mo duration compared to the standard supportive approach (recommendations for EPA made during visits with the oncologist) in terms of HRQoL. The randomization is balanced 1:1 and controlled for HRQoL at inclusion, trts, exercise practice, age, access to the Internet and center. Main eligibility criteria are: age ≥18; adjuvant or neoadjuvant trt for non-metastatic BC; medical certificate for sports practice. Patients without a connected device are eligible. HRQoL is evaluated using the SF-36 questionnaire, at 4, 8 and 12 mo. Both components (physical and mental summary) at 12 mo are used as co-primary endpoints. The study includes a health-economics evaluation, using EQ-SD and EQ VAS, to estimate the incremental cost-utility ratio. Based on the following assumptions: expected mean difference for each SF-36 component at 12 mo ≥3 points, standard deviation=15, power=90%, 2-sided alpha=2.5%, 10% drop-outs, 1242 evaluable pts are required, leading to 1380 pts. The trial is funded by the French ministry of health and should open enrollment soon.

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TPS11634 Poster Session (Board #323b), Mon, 1:15 PM-4:15 PM
Understanding and predicting fatigue, cardiovascular (CV) decline, and events after breast cancer treatment (UPBEAT): A prospective cardiology oncology study. First Author: Karryn Reynolds, Fred Hutchinson Cancer Research Center & University of Washington, School of Nursing, Seattle, WA

Background: Modern treatment for breast cancer (BC) has led to improved survival; however, this improvement can be offset by an increase in cancer therapy-related morbidity and mortality. Over one-third of early stage BC patients treated with cancer therapy experience CV injury, left ventricular (LV) dysfunction, exercise intolerance, or fatigue. CV disease is a leading cause of mortality in BC survivors. There is limited information on the time course and long-term CV health of BC survivors. UPBEAT, a multicenter study, will prospectively evaluate CV risk factors and outcomes in early stage BC patients, treated with modern cancer therapies. This will facilitate evaluation of primary CV prevention strategies in this patient population. Methods: This is a prospective cohort study of 840 patients with early stage (I-IIIA) BC treated with chemotherapy +/- radiation and 160 controls. Baseline and serial longitudinal measures will examine the influence of cancer treatment on CV function, exercise capacity and fatigue, and future development of CV events. The comprehensive assessment of factors includes ascertainment of cardiac biomarkers, CV risk factors, comorbidities, functional status (e.g., disability measures, Expanded SPPB), neurocognitive tests, behavioral risk factors, sociodemographics, and quality of life at baseline, 3-, 12-, and 24-mos. Outcomes measured at the same time points, include a deep phenotyping of CV dysfunction (via cardiac MRI assessing LV end diastolic volume, LV end systolic volume, LV ejection fraction, myocardial strain, strain rate, left atrial volumes and mass, and aortic stiffness), exercise intolerance (submaximal as 6-minute walk test and maximal as VO2peak via cardiopulmonary exercise test), fatigue (via FACT-F). Eligibility criteria are: age ≥18 years; ECOG 0-2, able to walk without symptoms; and for BC patients, treatment with chemotheraphy. 143 participants are accrued and currently enrolling through ECOG and NCORP sites. Participants will be followed for 9 years with active surveillance of CV events, i.e., heart failure, myocardial infarction, stroke, all-cause and CV death. Clinical trial information: NCT02791581.

TPS11635 Poster Session (Board #324a), Mon, 1:15 PM-4:15 PM
Patient controlled analgesia (PCA) versus non-PCA intravenous hydromorphone titration for severe cancer pain: A randomized, controlled, multicenter, phase III trial, HMORCT09-1. First Author: Rongbo Lin, Gastrointestinal Medical Oncology, Fujian Cancer Hospital, Fuzhou, China

Background: The opioid dose for an individual with cancer pain to provide adequate relief of pain with an acceptable degree of side effects is variable. Opioid titration is a process to obtain the tailored dose. Conventional titration is administered by a clinician or nurse. PCA is that patients control cancer pain by self-administration of intravenous opioids using programmable pump. The aim of our study is to evaluate the efficacy of PCA titration versus conventional titration intravenously for severe cancer pain (10-point numerical rating scale, NRS ≥ 7). Injectable Hydromorphone was selected as pharmaceutical analogues, which works as well as morphine and oxycodone and had similar side effects. Methods: This is currently enrolling patients (n=230) with severe cancer pain during previous 24 hours. Patients are randomized 1:1 and stratified by opioid intolerance or opioid tolerance into PCA or non-PCA titration. PCA titration using programmable pump: bolus hydromorphone at 0.5mg (for opioid intolerance) or hydromorphone dose equivalent to 10% to 20% of the total opioid taken in the previous 24 hours with a lockout time 15 minutes (for opioid tolerance) was administered by the patients educated. No basal infusion was set in the pump. Non-PCA titration administered by a nurse or clinician: Initial hydromorphone doses were same with PCA titration. Reassess pain at 15 minutes. Increased dose of hydromorphone by 50%-100% if pain unchanged or increased, or repeat same dose if pain decreased to NRS 4-6, or continue at current effective dose as needed over initial 24 hours. The primary endpoint is the time needed to successful titration was defined the time from the first dose of hydromorphone after randomization to achieve satisfied pain control. The satisfied pain control was defined NRS pain score ≤ 3 at rest in at least 2 consecutive assessment (15 minutes interval). The time needed to successful titration was extended to achieve satisfied pain control again if NRS pain score > 7 after satisfied pain control within 24 hours. The failure of successful titration was defined that satisfied pain control does not achieve within 24 hours. Secondary endpoints include the percentage of patients titrated successfully, the mean NRS pain score of 24 hours, the total dose of hydromorphone titrated, and adverse events. Clinical trial information: NCT03375515.

TPS11636 Poster Session (Board #324b), Mon, 1:15 PM-4:15 PM
Impact of a regular exercise program on amount of exercise and QOL metrics in patients on immune therapy. First Author: Nicole Brenna Quenelle, Univ of Connecticut, West Hartford, CT

Background: Studies show physical activity has a positive impact on fatigue and quality of life both during cancer treatment with chemotherapy and radiation and post-treatment (1, 2). There may also be a survival benefit to increasing physical activity both during and after treatment (3). To date there is no published research on the role of exercise in ameliorating the fatigue patients can experience during treatment with immune therapy. Our study proposes to use the existing framework of the LIVESTRONG at the YMCA program to objectively measure improvement in activity level and objective quality of life measurements. Methods: Randomized controlled prospective study evaluating patient participation in LIVESTRONG at YMCA program during active cancer treatment to assess change in minutes per week of self-reported physical activity over 12 weeks. Assessments will be done based on attendance of 12 week program, activity log, functional assessments of physical activity pre- and post-program (6 min walk test, % change in weight, % change in max weight lifted and flexibility), and questionnaires evaluating fatigue (PROMIS 13a FACIT-F), pain (PROMIS pain intensity scale, ASCQ-Me short form), quality of life (FACT-G), Godin Leisure Time Activity Questionnaire, and inflammatory markers (ESR, CRP). Data will be analyzed on an intention-to-treat analysis. A sample size of 150 participants per group will achieve 80% power to detect a 60 minute difference with a standard deviation of 150 minutes and with a significance level (alpha) of 0.050 using a two-sided two-sample t-test. Enrollment is targeted at 108 participants per arm to allow for 8% attrition, 216 total. Secondary endpoints will be assessed at a baseline functional assessment session for all participants and a follow up session after 12 weeks, including administration of questionnaires at both sessions. For physical activity measurements and survey completions, percent change in baseline and completion measurements will be calculated for each patient, then comparison using a chi-square test will be done to determine statistical significance. (Tomlinson et al. Effect of exercise on cancer-related fatigue: a meta-analysis. Am J Phys Med Rehabil. 2014;93:675-686; Irwin et al. Characteristics of the LIVESTRONG at the YMCA Exercise Program on Physical Activity, Fitness, Quality of Life, and Fatigue in Cancer Survivors. 2016 (published online October 28, 2016); Li T et al. The dose-response effect of physical activity on cancer mortality: findings from 71 prospective cohort studies. Br J Sports Med. 2016;50:339-345).
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