3000 **Oral Abstract Session**

A phase Ia/Ib study of CBP-1008, a bispecific ligand drug conjugate, in patients with advanced solid tumors.

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Background: Folate receptor α (FRα) and vanilloid subfamily member 6 of transient receptor potential channels (TRPV6) are overexpressed in many solid tumors hence could be promising therapeutic targets. CBP-1008 is a first-in-class bi-specific ligand drug targeting FRα and TRPV6 carrying monomethyl auristatin E (MMAE) as payload. Here we report the first-in-human, multicenter, phase Ia/Ib study designed to explore the safety, pharmacokinetics and efficacy of CBP-1008 in advanced solid tumors. **Methods:** CBP-1008 was administered by intravenous infusion. Phase Ia study included a dose-escalation period initiated by accelerated titration (0.015, 0.03mg/kg d1,15; q28d) and then switched to 3+3 scheme (0.12, 0.15, 0.17, 0.18mg/kg d1,15; q28d) and a dose expansion period. Phase Ib clinical expansion study included 3 cohorts, platinum-resistant ovarian cancer (OC), metastatic triple negative breast cancer (TNBC) and other solid tumors. The primary objective was to assess the safety and preliminary efficacy. **Results:** As of January 13, 2022, 106 patients received at least one dose of study drug were enrolled (phase Ia: n = 30; phase Ib: n = 76) and received median 3 prior regimens. Included tumor species were OC (n = 52), TNBC (n = 20), ER+/Her2+ breast cancer (BC) (n = 16), lung cancer (n = 3), pancreatic cancer (n = 2) and others (n = 13). In phase Ia study, DLTs were observed in 3 patients (0.12, 0.15, 0.18mg/kg, n = 1 each), including grade 4 hypophosphatemia, neutropenia, febrile neutropenia, and grade 3 hyperglycemia, alanine aminotransferase (ALT). MTD was not yet reached. Majority of adverse events were mild to moderate. The most common grade 3/4 treatment-emerging adverse events (TEAEs) were neutropenia (37.7%), AST elevation (6.6%), ALT elevation (5.7%), hyperglycemia (2.8%), hypohemoglobinemia (2.8%) and nausea (1.9%). Drug-related death was not observed. A total of 69 patients at dose of 0.15mg/kg or above were evaluable for efficacy assessment. There were 11 patients achieved partial response (PR) (OC n = 8, ER+/Her2+ BC n = 2, TNBC n = 1) and 30 patients achieved stable disease (SD). In 32 advanced platinum-resistant OC patients with FRα and/or TRPV6-positive expression, 6 PR and 16 SD were observed. Moreover, 6/18 PR (33.3%) and 8/18 SD (44.4%) were observed in enriched OC patients who showed high score of FRα/TRPV6 receptor. **Conclusions:** The preliminary results showed that CBP-1008 has manageable safety profile. Antitumor activity was observed in patients with FRα/TRPV6 receptor expression, especially in platinum-resistant OC cohort with high score of the two receptors. Clinical trial information: NCT04740398. Research Sponsor: Coherent Biopharma (Suzhou) Co., Ltd.

3001 **Oral Abstract Session**

Phase 1a/1b study of FOR46, an antibody drug conjugate (ADC), targeting CD46 in metastatic castration-resistant prostate cancer (mCRPC).

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Background: FOR46, a fully human antibody (ab) conjugated to monomethyl auristatin E (MMAE), targets a tumor selective epitope of CD46, which is highly expressed in mCRPC and treatment-emergent small cell neuroendocrine cancer (t-SCNC). CD46 is enriched in tumor cells upon treatment with androgen signaling inhibitors (ASI). Following dose escalation (Phase 1a), dose expansion was undertaken in 2 cohorts (Phase 1b): 1) Pts with *de novo* or t-SCNC and 2) pts with mCRPC without a t-SCNC component. Pts with adenocarcinoma enrolled in dose escalation and expansion are included in this analysis. **Methods:** Eligible pts had mCRPC, with progression on at least 1 ASI, with no prior chemotherapy for CRPC. Phase 1a pts received FOR46 0.1-3.0 mg/kg IV Q3 weeks (wks). The primary objectives in phase 1a were to assess adverse effects (AEs) and select the phase 1b dose; and in phase 1b to assess efficacy. For phase 1b, tumor biopsy in the CRPC setting for assignment to the 2 cohorts was required. CD46 expression was not required for inclusion in the expansion cohort, but was evaluated using a non-epitope specific CD46 polyclonal ab. Histology and CD46 expression were centrally reviewed. **Results:** Thirty-three pts were enrolled in phase 1a and 10 in phase 1b (including 6 treated in ph1a at the expansion dose or higher). Overall, 36 pts were treated at doses > 1.2 mg/kg. Following excess toxicity in pts with body mass indices > 30 (3 of 3 with Gr 4 neutropenia and 1 of 3 with Gr 3 fatigue at 2.4 mg/kg), further dosing was calculated using adjusted body weight (AJBW) rather than actual weight, allowing escalation to 3.0 mg/kg. The 2.7 mg/kg dose by AJBW was determined to be the MTD and phase 1b dose. The most common AEs at the 2.7 mg/kg dose were neutropenia (77% Gr 3 or 4), infusion reactions (37%, all < Gr 2), fatigue (31%, all < Gr 2) and peripheral neuropathy (24%, all < Gr 2)). Fourteen of 31 evaluable pts (45.2%) at > 1.2 mg/kg achieved a PSA_{50} response with 10 (32.3%) confirmed. Five pts were not evaluable for PSA response; 3 had no post-baseline PSA and 2 had baseline PSA < 1 ng/mL. The median duration of confirmed PSA_{50} response is >16 wks (range 6-48+ wks, with 4 ongoing at 12, 24, 25 and 48 wks). 18 pts had measurable lesions; 8 of 18 (44.4%) had tumor regression, with 4 (22.2%) confirmed partial responses (PR). The median duration of response is > 14 wks (range 9 -31+ weeks with 2 ongoing at 13 and 31 wks). Eight pts were evaluable for CD46 expression with a median H-score of 245 (range 0-300). Two pts with PRs had H-scores of 15 and 300; 4 with confirmed PSA_{50} had H-scores of 10, 15, 40 and 300. **Conclusions:** FOR46, a novel ADC targeting CD46, demonstrates clinical activity in mCRPC pts, with an acceptable safety profile, similar to other MMAE-containing ADCs. FOR46 merits further investigation in pts with mCRPC, alone and in combination with agents that enhance CD46 expression. Clinical trial information: NCT03575819. Research Sponsor: Fortis Therapeutics.

3002 **Oral Abstract Session**

Phase I, two-part, multicenter, first-in-human (FIH) study of DS-6000a in subjects with advanced renal cell carcinoma (RCC) and ovarian tumors (OVC).

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Background: Cadherin 6 (CDH6) is part of the cadherin family, which is involved with cell-cell adhesion, organ development, and epithelial-mesenchymal transition. CDH6 is found to be overexpressed in various cancers, particularly RCC and OVC. DS-6000a is an antibody-drug conjugate, comprised of an humanized anti-CDH6 IgG1 monoclonal antibody attached to a topoisomerase I (TOP1) inhibitor payload via a cleavable linker. DS-6000a specifically binds to CDH6 on the surface of tumor cells and is internalized upon binding. The payload is then released, resulting in target cell apoptosis. In preclinical studies, DS-6000a inhibited tumor growth and induced tumor regression in CDH6-expressing RCC and OVC. Here, we report initial results from a phase I trial of DS-6000a in patients (pts) with advanced RCC and OVC (NCT04707248). **Methods:** This dose-escalation (Part A) and expansion (Part B) study will recruit pts with advanced RCC and OVC. DS-6000a is administered IV as monotherapy on Day 1 of 21-day cycles. Part A assesses safety, tolerability, and maximum tolerated dose or recommended dose for expansion (RDE) using Bayesian optimal interval design; additional pts are enrolled to examine safety and efficacy. The starting dose of DS-6000a is 1.6 mg/kg followed by 3.2, 4.8, 6.4, 8, and 9.6 mg/kg. Part B will assess safety, tolerability and efficacy at the RDE. **Results:** Part A interim results are presented. At data cutoff (19 NOV 2021), 22 pts had enrolled (7 RCC, 15 OVC). All RCC pts had received an immune checkpoint inhibitor and the majority of OVC had platinum resistant (Pt-R) disease; median age was 63.5 years (range, 41-78); median of 4 (range, 1-12) prior lines of therapy were administered; and median treatment duration was 8.0 wks (range, 3-33.14). Fifteen pts (68.2%) were ongoing at the cutoff date. Treatment-emergent adverse events (TEAEs) occurred in 19 pts (86.4%). Related TEAEs occurred in 17 pts (77.3%). The most common related TEAEs (>20%) were fatigue and nausea (45.5% each), and vomiting (27.3%). Grade ≥3 related TEAEs occurred in 4 pts (18.2%); the most common was neutropenia (13.6%). One patient (4.5%) had a Grade 3 febrile neutropenia. One dose-limiting toxicity of Grade 4 thrombocytopenia (9.6 mg/kg) occurred. There was no study drug discontinuation due to a TEAE. Among 15 evaluable pts, 2 partial responses (PRs; 1 confirmed in RCC and 1 unconfirmed PR in Pt-R OVC) were observed; 9 pts had stable disease. Moreover, 5 out of 11 OVC evaluable pts showed CA-125 responses using GCIG criteria and all CA-125 responders had Pt-R disease. **Conclusions:** The interim data from dose-escalation of this FIH study showed acceptable tolerability with early signals of efficacy in heavily pretreated pts with advanced RCC and Pt-R OVC, which support further clinical evaluation of DS-6000a in the planned dose-expansion cohorts in advanced RCC and OVC. Clinical trial information: NCT04707248. Research Sponsor: Daiichi Sankyo.

3003 **Oral Abstract Session**

First-in-human study of PC14586, a small molecule structural corrector of Y220C mutant p53, in patients with advanced solid tumors harboring a *TP53* Y220C mutation.

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Background: The p53 tumor suppressor protein is a transcription factor that acts to maintain genome stability in response to cellular stress. Spontaneous mutation of the *TP53* gene leading to inactivation of the p53 protein is the most common mutational event across all human cancers. PC14586 is a novel, small molecule structural corrector that binds selectively to p53 Y220C mutant protein and restores the p53 wildtype conformation and transcriptional activity, resulting in potent preclinical antitumor activity. This Phase 1 multicenter dose escalation study assesses PC14586 safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy in patients (pts) with advanced solid tumors that harbor the *TP53* Y220C mutation. **Methods:** Eligible adult pts with locally advanced or metastastic TP53 Y220C mutant solid tumors received increasing doses of oral PC14586 using the modified Toxicity Probability Interval design to estimate toxicity and to determine maximum tolerated dose and recommended phase 2 dose. Plasma PK was characterized using standard methods. Preliminary efficacy was assessed by RECIST v1.1. Reporting of interim results was approved by the study's Safety Review Committee. **Results:** As of 08 Feb 2022, 29 pts (62% female, median age 62 years) with a variety of *TP53* Y220C mutant solid tumor types (median number of prior lines of therapy 3; range 1 to 8) were treated in 7 dose cohorts of PC14586: 150 mg QD (3 pts), 300 mg QD (3 pts), 600 mg QD (4 pts), 1150 mg QD (5 pts), 2000 mg QD (7 pts), 2500 mg QD (4 pts) and 1500 mg BID (3 pts). PC14586 was generally well-tolerated; treatment-related AEs were observed in 79% of pts that were all Grade 1/2 in severity except 2 Grade 3 AEs (alanine aminotransferase increased and neutrophil count decreased). The most common AEs (≥15% of pts) were nausea (34%), vomiting (24%), fatigue (21%), and aspartate aminotransferase increased (17%). There were no dose limiting toxicities and enrollment continues. PK analysis showed dose proportional increases in Cmax and AUC. Amongst 21 efficacy evaluable pts, PRs were observed in 5 pts: 1 small cell lung and 1 breast with confirmed PR (cPR), both ongoing; 1 colorectal with unconfirmed PR (uPR), and 2 prostate with uPR and ongoing. In the 3 highest dose cohorts (total daily dose 2000 to 3000 mg), there were 3 PRs (2 uPR, 1cPR) and 7 SD out of 10 efficacy evaluable pts (all ongoing). Observations of decreasing p53 Y220C circulating tumor DNA and decreasing numbers of circulating tumor cells in pts further support on-target anti-tumor activity of PC14586. **Conclusions:** Enrollment to a Phase 1 study is feasible in a *TP53* mutation selective population. PC14586 is safe and tolerated up to 3000 mg daily. Preliminary efficacy was achieved in heavily pretreated pts. Additional safety, PK, PD and efficacy data will be reported at the annual meeting. Clinical trial information: NCT04585750. Research Sponsor: PMV Pharmaceuticals, Inc.

3004 **Oral Abstract Session**

A phase Ia/Ib, dose-escalation/expansion study of the MDM2–p53 antagonist BI 907828 in patients with solid tumors, including advanced/metastatic liposarcoma (LPS).

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Background: The highly potent MDM2–p53 antagonist BI 907828 showed antitumor efficacy *in vivo*, particularly in *TP53* wild-type, *MDM2*-amplified de-differentiated LPS (DDLPS) patient-derived xenografts and syngeneic models. This phase I study (NCT03449381) is assessing BI 907828 monotherapy in patients with advanced solid tumors, including LPS. In Part A (dose escalation), patients received one of two BI 907828 dosing schedules: Arm A, day 1 of 21-day cycles (q3w); Arm B, days 1 and 8 of 28-day cycles. Based on previously reported results from Part A (LoRusso ASCO 2021), the MTD was 60 mg q3w and the recommended dose for expansion (RDE) was selected as 45 mg q3w. **Methods:** In Part B (dose expansion), patients received BI 907828 45 mg q3w. The primary endpoint was PFS. Secondary endpoints/objectives included objective response rate, overall survival, the number of patients with grade ≥3 treatment-related AEs, and PK parameters. Here, we report overall safety data and efficacy data in the subgroup of patients with advanced LPS. **Results:** As of January 10, 2022, 90 patients had been enrolled; 49 (54.4%) were male, 55 (61.1%)/34 (37.8%) were ECOG PS 0/1, the median number of prior systemic therapies was 2 (range, 0–11), 44 had advanced LPS (28 DDLPS, 16 well-differentiated LPS [WDLPS]). At data cut-off, 31/90 patients (34.4%) had received treatment for ≥6 months. In the 41 evaluable patients with advanced LPS, best response of PR or SD was observed in 24/27 patients with DDLPS (88.9%) and 13/14 patients with WDLPS (92.9%). Two DDLPS and 4 WDLPS patients achieved a PR; all had MDM2-amplified disease. In Part A, 5/11 DDLPS patients and 4/8 WDLPS patients have achieved PFS ≥10.5 months. In the 42 patients who received the RDE of 45 mg q3w, 18 patients (42.9%) had grade ≥3 AEs; the most common grade ≥3 AEs were neutropenia (23.8%), thrombocytopenia (21.4%), and anemia (11.9%). Seven patients (16.7%) had SAEs; the most common were thrombocytopenia (4.8%) and pyrexia (4.8%). PK analysis showed that mean plasma exposures (C_{max} and $AUC_{0\text{-}inf}$) increased with dose and showed no significant deviation from linearity in the dose range 10–60 mg. A correlation was observed between exposure and GDF-15 levels in plasma, as a target engagement marker. **Conclusions:** BI 907828 showed a manageable safety profile, high plasma exposure, target engagement and encouraging signs of antitumor activity in patients with advanced DDLPS and WDLPS. The Part B dose expansion is ongoing. Clinical trial information: NCT03449381. Research Sponsor: Boehringer Ingelheim.

3005 **Oral Abstract Session**

A phase 1 study of TPST-1120 as a single agent and in combination with nivolumab in subjects with advanced solid tumors.

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Background: TPST-1120 is a first-in-class oral therapy that inhibits PPARα, a transcription factor that regulates fatty acid oxidation (FAO). TPST-1120 has diverse mechanisms of anti-tumor activity in preclinical studies, including inhibiting tumor proliferation, increasing the anti-angiogenic factor thrombospondin 1, and reducing T cell exhaustion. **Methods:** Subjects with advanced solid tumor malignancies received escalating doses of TPST-1120 as a single agent or in combination with nivolumab 480 mg IV every 4 weeks (combination cohort limited to RCC, cholangiocarcinoma [CCA] and HCC). Study objectives included evaluation of safety, pharmacokinetics, MTD, RP2D and anti-tumor activity as monotherapy and in combination with nivolumab. AEs were assessed per CTCAE v5 and efficacy per RECIST v1.1. **Results:** As of 14-Jan-2022, 35 subjects have been dosed (20 with TPST-1120 monotherapy at doses from 100 mg to 600 mg PO BID and 15 in combination with nivolumab at doses from 200 mg to 600 mg PO BID). Median prior lines of systemic therapy were 3 (2-11) in monotherapy and 2 (2-6) in combination cohorts. An MTD was not reached in monotherapy or combination, and the TPST-1120 RP2D was 600 mg PO BID for both cohorts. For TPST-1120 monotherapy, the most common treatment related AEs (TRAEs) were nausea (20%), fatigue (15%), and diarrhea (10%), all Grade 1-2. One monotherapy subject (5%) experienced a Grade 3 TRAE (hypertension). In the combination cohort the most common TRAEs related to either drug were fatigue (40%), diarrhea (27%) and nausea (20%), all Grade 1-2. Three combination subjects (19%) experienced Grade 3 TRAEs (one each arthralgia, hepatic enzyme increased, muscle spasms). A best response of stable disease was observed in 53% (10/19) of subjects treated with monotherapy. In combination, the ORR was 23% (3/13, all PRs) across all dose levels and 38% (3/8) at TPST-1120 dose levels $\geq$400 mg BID. These responses included 2 subjects with late-line RCC (2/2 RCC subjects enrolled, both with progression on prior anti-PD1 therapy) and one subject with heavily pre-treated CCA. At data cut off, 2 of 3 responding patients (CCA and one RCC) remained in PR and on study at 8.4 and 14 mo, respectively. **Conclusions:** TPST-1120 is a novel therapy designed to inhibit tumor proliferation and angiogenesis and stimulate anticancer immunity through inhibition of PPARα, a key regulator of FAO. The drug is well tolerated as a single agent and in combination with nivolumab. Promising objective responses have been observed in combination with nivolumab in subjects previously refractory to anti-PD-1 therapy, including 2/2 responders in late-line RCC, and a subject with heavily pretreated CCA, a tumor type generally not responsive to anti-PD-1 alone. Notably, all responders were treated at the two highest doses of TPST-1120 (ORR 38%). Updated study results including exploratory biomarkers will be presented. Clinical trial information: NCT03829436. Research Sponsor: Tempest Therapeutics.

3006 **Oral Abstract Session**

CRESTONE: Initial efficacy and safety of seribantumab in solid tumors harboring *NRG1* fusions.

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Background: *NRG1* fusions are rare oncogenic drivers found in ~0.2% of all solid tumors. These fusions elicit ERBB3/HER3 overactivation to drive tumor growth and cancer cell survival. Currently there are no approved targeted therapies for *NRG1* fusion-positive tumors. Furthermore, patients (pts) with tumors harboring *NRG1* fusions have poor outcomes with standard therapies. Seribantumab is a fully human anti-HER3 IgG2 monoclonal antibody that suppressed tumor growth in *NRG1* fusion-driven preclinical models. Here, we present initial clinical data from the CRESTONE study (NCT04383210). **Methods:** CRESTONE is a Phase 2, global, multicenter, open-label study of seribantumab in adult pts with locally advanced or metastatic solid tumors harboring *NRG1* fusions. A dose ranging phase established the RP2D as a 3g once weekly (QW) intravenous dose administered until treatment discontinuation criteria are met. In the expansion phase, cohort 1 will enroll at least 55 pts who had received at least one prior therapy and are naïve to ERBB-targeted therapy. Exploratory cohorts 2 or 3 will enroll pts previously treated with ERBB-targeted therapies and/or tumors harboring additional molecular alterations. The primary endpoint is objective response rate (ORR) by independent central review per RECIST v1.1. Initial data from cohort 1 pts who received seribantumab 3g QW with investigator (INV)-assessed response per RECIST v1.1 are reported. **Results:** By JAN-13-2022, 12 pts have received seribantumab 3g QW in cohort 1. Median age was 65 years (range 44–76), 67% were female, and median number of prior therapies was 1 (range 1–5). 92% (11/12) of pts had non-small cell lung cancer (NSCLC); 5 different NRG1 fusion partners (*ATP1B1*, *CD74*, *ITGB1*, *SDC4*, *SLC3A2*) were reported by local next-generation sequencing tests. Among 10 pts evaluable for INV-assessed response, the confirmed ORR was 30%, and the disease control rate was 90% (1 complete response, 2 partial responses, 6 stable disease, 1 progressive disease). 58% (7/12) of pts remain on study treatment, including 2 pts with NSCLC who achieved objective responses with an ongoing duration of response of 6 and 8.5 months. Seribantumab 3g QW was well tolerated with no drug discontinuations or dose reductions. Across all cohorts (n = 29), the most frequently (≥20%) reported treatment-related adverse events (TRAEs) were diarrhea (38%), fatigue (34%), and rash (24%), all were grade 1 or 2. One grade 3 TRAE of vomiting occurred; there were no Grade 4 or 5 TRAEs. Efficacy analysis is ongoing and updated efficacy data from evaluable pts in cohort 1 will be presented. **Conclusions:** Initial data indicate seribantumab induced durable responses in advanced solid tumors harboring *NRG1* fusions and has a favorable safety profile. These data support the continued evaluation of seribantumab in *NRG1* fusion-positive solid tumors in the ongoing CRESTONE study. Clinical trial information: NCT04383210. Research Sponsor: Elevation Oncology, Inc.

3007 **Oral Abstract Session**

Tumor agnostic efficacy and safety of erdafitinib in patients (pts) with advanced solid tumors with prespecified fibroblast growth factor receptor alterations (*FGFRalt*) in RAGNAR: Interim analysis (IA) results.

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Background: Erdafitinib (erda) is an oral selective pan-FGFR tyrosine kinase inhibitor approved to treat locally advanced or metastatic urothelial carcinoma (UC) in adults with susceptible *FGFR3/2alt* who have progressed during or after ≥ 1 line of platinum containing chemotherapy. *FGFRalt* are observed across a wide range of malignancies and may function as oncogenic drivers independent of the underlying tumor type. RAGNAR (NCT04083976) is an ongoing phase 2 open label, single arm tumor agnostic trial investigating the efficacy and safety of erda in pretreated adult and pediatric pts with advanced solid tumors and *FGFRalt*. Here, we report results from a planned IA of RAGNAR. **Methods:** Pts aged ≥ 6 y with advanced or metastatic solid tumors of any histology (except UC) with predefined *FGFR1-4alt* (mutations/fusions based on local/central test) and documented disease progression on ≥ 1 prior line of systemic therapy (tx) and no alternative standard tx received oral erda until disease progression or intolerable toxicity. The primary end point is objective response rate (ORR) by independent review committee (IRC). Secondary end points include investigator assessed ORR, duration of response (DOR), disease control rate (DCR), clinical benefit rate (CBR), PFS, OS, and treatment emergent adverse events (TEAEs). **Results:** As of the IA data cutoff, 178 pts were treated (median age 56.5 y [range 12-79], median 2 prior systemic tx). Only 9.0% of pts responded to last line of tx prior to study entry. ORR by IRC was 29.2% (95% CI, 22.7-36.5). Investigator assessed ORR was 26.4% (95% CI, 20.1-33.5). Responses were observed in 14 distinct tumor types, including gliomas, thoracic, gastrointestinal, gynecological, and rare tumors (Table). ORR in pts with *FGFR* mutations vs fusions was comparable (26.8% vs 27.0%, respectively). Median DOR, PFS, and OS were 7.1 mo (95% CI, 5.5-9.3), 5.2 mo (95% CI, 4.0-5.6), and 10.9 mo (95% CI, 7.9-14.3), respectively; DCR was 75.3% and CBR was 48.9%. All pts experienced TEAEs, including 69.1% with grade ≥ 3. Treatment-related serious TEAEs occurred in 7.3% of pts. **Conclusions:** RAGNAR data show, for the first time, evidence of efficacy for erda in heavily pretreated pts with a variety of hard to treat advanced *FGFR+* malignancies, including glioblastoma, pancreatic, and salivary gland cancers. Safety was consistent with the known erda safety profile. Clinical trial information: NCT04083976. Research Sponsor: Janssen Research & Development, LLC.

Tumor type	N (treated)	ORR* n (%)	Tumor type	N (treated)	ORR* n (%)
Total	**178**	**47 (26.4)**	**Esophageal**	6	1 (16.7)
Cholangiocarcinoma	31	13 (41.9)	**Low-grade glioma**	6	1 (16.7)
High-grade glioma	29	6 (20.7)	**Ovarian**	4	1 (25.0)
Breast	14	6 (42.9)	**Cancer of unknown primary**	8	2 (25.0)
Pancreatic	13	4 (30.8)	**Salivary gland**	5	5 (100.0)
Squamous NSCLC	11	3 (27.3)	**Duodenal**	1	1 (100.0)
Non–squamous NSCLC	7	1 (14.3)	**Thyroid**	1	1 (100.0)
Endometrial	6	2 (33.3)			

*Investigator assessed.

3008 **Oral Abstract Session**

Cobimetinib plus vemurafenib (C+V) in patients (Pts) with solid tumors with BRAF V600E/d/k/R mutation: Results from the targeted agent and profiling utilization registry (TAPUR) study.

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Background: TAPUR is a phase II basket study evaluating anti-tumor activity of commercially available targeted agents in pts with advanced cancers with genomic alterations. Results in a cohort of pts with solid tumors with *BRAF* V600E/D/K/R mutation (mut) treated with C+V are reported. **Methods:** Eligible pts had advanced solid tumors, no standard treatment (tx) options, measurable disease, ECOG performance status (PS) 0-2, and adequate organ function. Genomic testing was performed in CLIA-certified, CAP-accredited site selected labs. Pts matched to C+V had various solid tumors with *BRAF* V600E/D/K/R mut, or other *BRAF* mut if approved by the Molecular Tumor Board, and no *MAP2K1/2*, *MEK1/2*, *NRAS* mut. Recommended dosing was C, 60 mg orally daily for 21 days, 7 days off and V, 960 mg orally every 12 hours. Primary endpoint was disease control (DC), defined as complete (CR) or partial (PR) response or stable disease at 16+ wks (SD 16+) (RECIST v1.1). Low accruing histology-specific cohorts with the same genomic target and tx were collapsed into a single histology-pooled cohort for this analysis. For histology-pooled cohorts with sample size of 28, the results are evaluated based on a one-sided exact binomial test with a null DC rate of 15% vs. 35% (power = 0.84; $\alpha = 0.10$) and one-sided 90% confidence interval (CI). Other efficacy endpoint estimates are presented with two-sided 95% CIs. Secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. **Results:** 31 pts with solid tumors (13 histologies; 6/31 ovarian cancer) with *BRAF* muts were enrolled from Dec 2016 to Jan 2021 and collapsed into one histology pooled cohort for analysis. 3 pts were not evaluable due to lack of post-baseline tumor evaluation and excluded from efficacy analyses. Demographics and outcomes are summarized in the Table. Pts had tumors with *BRAF* V600E mut (N = 26), G469V mut (N = 1), K601E mut (N = 2), N581I (N = 1) and T599_V600insT (N = 1). 2 CR (breast and ovarian cancer; V600E), 14 PR (13 V600E, 1 N581I), and 3 SD16+ (2 V600E, 1 T599_V600insT) were observed for a DC rate of 68% (90% CI: 54%, 100%) and an objective response (OR) rate of 57% (95% CI: 37%, 76%). CR durations were 5.1 (ovarian cancer) and 108.9 wks (breast cancer) and median duration of PR was 20.5 wks (range: 8.0, 176.0). 19 pts experienced ≥1 Grade 1-5 AE/SAE at least possibly related to tx including 1 death attributed to tx-related kidney injury. **Conclusions:** C+V demonstrated evidence of anti-tumor activity in pts with advanced solid tumors with *BRAF* V600E and other muts. Clinical trial information: NCT02693535. Research Sponsor: Genentech, Pharmaceutical/Biotech Company.

Demographics and baseline characteristics (N = 31) and efficacy outcomes (N = 28).		
Median age, yrs (range)		63 (31, 79)
ECOG PS, %	0	23
	1	64
	2	13
Prior systemic regimens, %	0-2	48
	≥3	52
DC rate, % (OR or SD16+) (90% CI)		68 (54, 100)
OR rate, % (95% CI)		57 (37, 76)
Median PFS, wks (95% CI)		23.3 (13.3, 27.7)
Median OS, wks (95% CI)		60.9 (26.7, 116.3)

3009 **Poster Discussion Session**

Ulixertinib in patients with tumors with MAPK pathway alterations: Results from NCI-COG Pediatric MATCH trial Arm J (APEC1621J).

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Background: The NCI-Children's Oncology Group (COG) Pediatric Molecular Analysis for Therapy Choice (MATCH) trial assigns patients age 1 to 21 years with relapsed or refractory solid tumors, lymphomas, and histiocytic disorders to phase 2 treatment arms of molecularly-targeted therapies based on genetic alterations detected in their tumor. Arm J evaluated the ERK1/2 inhibitor ulixertinib (BVD-523FB) in patients whose tumors harbored activating alterations in the MAPK pathway (*ARAF*, *BRAF*, *HRAS*, *KRAS*, *NRAS*, *MAPK1*, *MAP2K1*, *GNA11*, *GNAQ* hotspot mutations; *NF1*inactivating mutations; *BRAF* fusions). **Methods:** As there were no prior pediatric data, ulixertinib was initially tested in a dose escalation cohort using a rolling 6 design to establish the recommended phase 2 dose (RP2D) before proceeding with enrollment to the phase 2 cohort. Ulixertinib was administered at 260 mg/m^2/dose PO BID (dose level 1, DL1, n = 15) or 350 mg/m^2/dose PO BID (dose level 2, DL2, n = 5). Patients were treated on continuous 28-day cycles for up to 2 years, until disease progression or intolerable toxicity; response assessment occurred every 2-3 cycles. The primary endpoint was objective response rate; secondary endpoints included safety/tolerability and progression-free survival (PFS). **Results:** Twenty patients (median age 12 years; range 5-20) were enrolled between November 2018 and March 2021. All patients were evaluable for response. High-grade glioma (HGG, n = 7) was most common, with CNS tumors comprising 55% (11/20) of diagnoses; all CNS tumors except one (HGG with *KRAS* and *NF1* mutations) harbored *BRAF* fusions or V600 mutations. Rhabdomyosarcoma (n = 5) was the most frequent non-CNS diagnosis, with *NRAS* mutations detected in 4 tumors. DL1 was declared the RP2D after first-cycle dose limiting toxicities (DLTs) occurred in 1/6 DLT-evaluable patients at DL1 and 2/5 patients at DL2 in the dose escalation cohort. Any-cycle DLTs in 8 patients in the dose escalation and primary cohorts included fatigue, anorexia, rash, nausea, vomiting, diarrhea, dehydration, increased creatinine, hypoalbuminemia, hypernatremia, and hip fracture. No objective responses were observed. Six-month PFS was 37% (95% CI: 17%, 58%). Three patients with CNS tumors achieved stable disease > 6 months (HGG with *BRAF* fusion, 15 cycles; glioneuronal tumor with *BRAF* V600E, 9 cycles; low-grade glioma with *BRAF* fusion, 7 cycles). Analyses of correlative studies, including pharmacokinetics and circulating tumor DNA, are ongoing. **Conclusions:** The pediatric RP2D of ulixertinib was established as 260 mg/m^2/dose PO BID. There were no objective responses in this cohort of children and young adults with treatment-refractory tumors with activating MAPK alterations. Clinical benefit of prolonged disease control was observed in 3 patients with *BRAF*-altered gliomas and glioneuronal tumors. Clinical trial information: NCT03698994. Research Sponsor: U.S. National Institutes of Health.

3010 **Poster Discussion Session**

Phase II study of vismodegib in patients with *SMO* or *PTCH1* mutated tumors: Results from NCI-MATCH ECOG-ACRIN Trial (EAY131) Subprotocol T.

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Background: NCI-MATCH (EAY131) is a platform trial enrolling patients (pts) with solid tumors, lymphomas, or multiple myeloma to targeted therapies based on matching genomic alterations (NCT02465060). Subprotocol Arm T evaluated vismodegib (GDC0449), a hedgehog signaling pathway inhibitor with anti-tumor activity in pts with tumors harboring *PTCH1* and *SMO* mutations. **Methods:** Pts whose tumors had *SMO* or *PTCH1* mutations were eligible; results were confirmed by NCI-MATCH central labs if possible. Pts received oral vismodegib (150 mg daily) for 4-week cycles until progression/toxicity. Tumor response was assessed every 2 cycles. Primary endpoint was ORR; secondary endpoints included PFS, 6-month PFS, OS, and predictive biomarkers. Cutaneous basal cell carcinomas were excluded. **Results:** Of 34 pts enrolled (6/20/16 – 9/22/20); 2 were ineligible and 1 did not start therapy. The 31 analyzable pts' demographics were primary tumor sites/histology [gastrointestinal (n = 9), skin/soft tissue (n = 7), gynecologic (n = 5), lung (n = 4), unknown primary (n = 4), ductal breast (n = 1), meningioma (n = 1)]; median age 64 (range 19-81); 48.4% women; 61.3% (19/31) > 3 lines of prior therapy; 74% (23/31) > 1 co-occurring mutation [median 2 co-alterations (range 1-20)]. 8/31 > 4 co-occurring alterations. 9 pts had *SMO* mutant tumors (all SNVs); 5/9 had > 1 co-occurring gene alterations. 22 pts had *PTCH1* alterations (7 SNVs and 15 indels); 18/22 pts had > 1 additional gene alteration. Of 31 analyzable pts, 22 were MATCH-confirmed (i.e. had central confirmation of tumor *PTCH1/SMO* mutations). MATCH-confirmed pts had ORR 9.1% (2/22) while all analyzable pts had ORR 6.5% (2/31). 2 PRs were seen in pts with a skin/soft tissue sarcoma (*PTCH*) and a meningioma (*SMO*) with a median duration of response 14 months. The 6-month PFS rate was similar in MATCH-confirmed and analyzable pts (22.4% and 23.2% respectively) and median PFS was identical at 1.8 months. Median OS was 9.1 months in MATCH-confirmed and 7.3 months in analyzable pts. Within analyzable *SMO* variants: 1 PR, 3 SD, 4 PD, and 1 unevaluable responses were documented. Within analyzable *PTCH1* variants: 1 PR, 7 SD, 10 PD, and 4 unevaluable responses were seen. 4 pts (12.9%) discontinued therapy due to AE. Among 33 pts starting therapy, 18 (54.5%) had grade 1-2 toxicity, while 2 (6.1%) had grade 3 treatment-related toxicity. Most common toxicities: grade 1-2 fatigue (n = 11), anorexia (n = 8), weight loss (n = 7), alopecia (n = 7), and dysgeusia (n = 6). There were 4 on-study deaths, but none were treatment related. **Conclusions:** Although the primary endpoint was not reached, vismodegib was well-tolerated with mostly grade 1-2 toxicities and substantial responses were seen in patients with SMOPro641Ala and PTCHGlu947Ter alterations. Further study of the impact of concomitant molecular alterations may yield additional insights into vismodegib mechanisms of response. Clinical trial information: NCT02465060. Research Sponsor: U.S. National Institutes of Health, This study was coordinated by the ECOG-ACRIN Cancer Research Group (Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported by the National Cancer Institute of the National Institutes of Health under award numbers: U10CA180820, U10CA180794, UG1CA233302, UG1CA233180, UG1CA233290, UG1CA233341, UG1CA233193, and UG1CA233329.

3011 **Poster Discussion Session**

A multicenter, open-label, single-arm, phase 1 dose-escalation study to evaluate the safety, tolerability, and anti-tumor activity of FCN-159 in adults with neurofibromatosis type 1.

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Background: Neurofibromatosis type 1 (NF1) is an autosomal-dominant genetic disease that increases susceptibility to malignant tumors. Up to 50% of patients with NF1 present with plexiform neurofibroma (PN). Surgery, a common treatment strategy for patients with PN, has limited efficacy. NF1 is caused by mutations in the gene that encodes neurofibromin; the NF1 mutation then leads to tumorigenesis via dysregulation of the Ras/Raf/MEK/ERK pathway. FCN-159 is anti-tumorigenic via highly potent, selective inhibition of MEK1/2. This study aims to assess the safety of FCN-159 in patients with NF1-related PN. **Methods:** This is a multicenter, open-label, single-arm, phase 1 dose-escalation and phase 2 dose-expansion study (NCT04954001). Patients with NF1-related PN that was not completely resectable or not suitable for surgery were enrolled in the study; they received FCN-159 monotherapy continuously in 28-day cycles. Here, we report safety and clinical efficacy data from adults enrolled in phase 1. **Results:** As of the data cutoff of December 1, 2021, 19 adults from 3 hospitals in China have been enrolled in the phase 1 dose-escalation study, 3 in 4 mg, 4 in 6 mg, 8 in 8 mg, and 4 in 12 mg. The most common neurofibroma-related complications were disfigurement and pain, occurring in 10 patients (52.6%) and 4 patients (21.1%) at baseline, respectively. Four patients experienced dose-limiting toxicity; G3 folliculitis was reported in 1 patient (16.7%) receiving the 8-mg dose and 3 (100%) patients receiving the 12-mg dose. The maximum tolerated dose was determined to be 8 mg. Study-drug-related treatment-emergent adverse events (TEAEs) were observed in all 19 patients (100%); the majority were grade 1 or 2 in severity. Nine (47.4%) patients reported grade 3 study drug-related TEAEs; 4 patients experienced paronychia and 5 experienced folliculitis, which were the most common causes of dose reduction (42.1%) and drug interruption (21.2%). One patient experienced a serious adverse event of rhegmatogenous retinal detachment, but this was considered unrelated to the study drug as it was preexisting at baseline. Of the 16 patients with at least 1 post-baseline tumor assessment, all (100%) had reduced tumor size and 6 (37.5%) had a reduction in tumor size of > 20%. Three out of 6 patients with a second tumor assessment result had further tumor shrinkage; tumor volumes in the remaining 3 patients were similar to those at first assessment. The largest reduction in tumor size was 84.2%. **Conclusions:** Overall, FCN-159 at 8 mg is well tolerated, with easy to manage adverse events, and showed promising anti-neurofibroma activity in phase 1; this warrants further investigation in a phase 2 study on efficacy and safety in this indication. Clinical trial information: NCT04954001. Research Sponsor: Fosun Pharmaceutical Development Co., Ltd.

3012 **Poster Discussion Session**

NCI 9938: Phase I clinical trial of ATR inhibitor berzosertib (M6620, VX-970) in combination with irinotecan in patients with advanced solid tumors.

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Background: Ataxia telangiectasia and Rad3 related (ATR) is activated in response to replication stress from topoisomerase 1 inhibitors. Selective ATR inhibition with berzosertib potentiates the efficacy of irinotecan in colorectal mouse xenograft models. We hypothesized that berzosertib in combination with irinotecan is well tolerated, modulates the DNA damage repair response to irinotecan, and the combination is associated with clinical activity. **Methods:** This phase I study utilized a modified Storer's up and down dose escalation design. Dose Levels (DLs) combined berzosertib 60 to 270 mg/m^2 with irinotecan 180 mg/m^2, every 2 weeks in a 4-week cycle. The primary endpoint was identification of the maximum tolerated dose (MTD) and recommended phase II dose (RP2D). Activity, pharmacokinetics (PK), and pharmacodynamics (PD) were secondary endpoints. The identification of molecular subpopulations sensitized to the combination was exploratory. **Results:** Between July 2016 and July 2021, 51 patients (pts) enrolled, of whom 50 received treatment. Pts most commonly had colorectal cancer (CRC, 39%), pancreatic cancer (24%), small cell lung cancer (SCLC, 6%) and non-small cell lung cancer (6%). The median number of prior lines of therapy was 4 (range, 2 to 11). In Stage I, 1 of 3 evaluable pts experienced dose-limiting toxicity (DLT) of grade 3 lung infection at DL3 (berzosertib 180 mg/m^2 - irinotecan 180 mg/m^2), and Stage II was initiated enrolling cohorts of 5 pts. In Stage II, 4 of the first 11 pts treated at DL4 (berzosertib 270 mg/m^2 - irinotecan 180 mg/m^2) were unable to complete the DLT evaluation period due to clinically significant toxicity not meeting DLT criteria: grade 2 diarrhea (1 pt), grade 3 diarrhea (1 pt), and grade 3 neutrophil decrease (2 pts). The protocol was amended to limit dose escalation beyond DL4. At DL4, 1 of 21 evaluable pts experienced DLT (grade 4 febrile neutropenia). Most common treatment-related grade $\geq$ 3 toxicities were neutrophil decrease (34%), lymphocyte decrease (30%), WBC decrease (28%), anemia (20%), diarrhea (16%), fatigue (8%) and hypokalemia (8%). 2 partial responses were observed, occurring in pts with pancreatic cancer and *ATM* alterations: 32% decrease in an ATM E11828/ATM K1109* tumor lasting 15.3 months and 68% decrease in an ATM R3008H/germline ATM R1882* tumor ongoing at 11 months. An additional pt with ATM S214fs*40 mutant colorectal cancer (CRC) experienced a 26% decrease lasting 7.5 months. **Conclusions:** Berzosertib 270 mg/m^2 - irinotecan 180 mg/m^2 was declared the RP2D. The combination is associated with manageable side effects and promising disease activity in ATM mutant solid tumors. PK and PD studies are in process. Tumor biopsy studies are planned in a 15 pt dose expansion cohort at DL4, enrolling pts with CRC, pancreatic cancer, SCLC and DNA damage repair deficient tumors. Clinical trial information: NCT02595931. Research Sponsor: U.S. National Institutes of Health.

3013 **Poster Discussion Session**

First-in-human, phase I study of TT-00420, a multiple kinase inhibitor, as a single agent in advanced solid tumors.

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Background: TT-00420 is a spectrum-selective multi-kinase inhibitor that targets cell proliferation, angiogenesis, and immune-oncology pathways by inhibiting Aurora kinases A/B and Janus kinases (JAK) involved in cytokine signaling and receptor tyrosine kinases (FGFRs and VEGFRs) involved in the tumor microenvironment. TT-00420 has demonstrated anti-tumor activity in both *in vitro* and *in vivo* preclinical models of solid tumors, including triple-negative breast cancer (TNBC) and cholangiocarcinoma (CCA). **Methods:** This phase I, first-in-human, dose escalation and expansion study of TT-00420 (NCT03654547) enrolled adult patients with advanced or metastatic solid tumors. Capsules in 1 mg or 5 mg formulation were administered orally once daily in 28-day cycles. Dose escalation was guided by Bayesian modeling with overdose control. The primary safety endpoints were to determine dose limiting toxicities (DLTs) and a dose recommended for dose expansion (DRDE). Secondary endpoints included pharmacokinetics (PK) and preliminary efficacy evaluated per RECIST v1.1 criterion. **Results:** As of February 7, 2022, 48 advanced solid tumor patients were enrolled in the study, and received at least one dose of TT-00420 in 7 dose levels: 1 mg *q.d.* (N = 1), 3 mg *q.d.* (N = 1), 5 mg *q.d.* (N = 4), 8 mg *q.d.* (N = 10), 10 mg *q.d.* (N = 6), 12 mg *q.d.* (N = 20), and 15 mg *q.d.* (N = 6). DLTs were observed in 3 out of 40 DLT-evaluable patients, including 1 patient at 8 mg *q.d.* who had Grade (Gr) 3 palmar-plantar erythrodysaesthesia syndrome and 2 patients at 15 mg *q.d.* who both had Gr 3 hypertension. Among the twenty (20) safety evaluable patients treated at 12 mg, the DRDE, drug-related TEAEs included hypertension (n = 11, 55.0%; Gr 3: n = 6, 30%); diarrhea (n = 7, 35%, Gr 3: n = 1, 5%); mucosal inflammation (n = 7, 35%; Gr 3: n = 1, 5%); palmar-plantar erythrodysaesthesia syndrome (n = 6, 30%; Gr 3: n = 0, 0%); and vomiting (n = 4, 20%; Gr 3: n = 0, 0%). No grade 4 suspected adverse events were reported. Out of 42 patients who had at least one post-baseline scan, 7 (16.7%) had a best response of partial response (PR) and 22 (52.4%) had stable disease (SD). Among 7 PRs, 3 were CCA patients (one for each treated at 8 mg, 10 mg, or 12 mg), 2 were TNBC patients (one for each at 10 mg, or 12 mg), 1 was HER2-negative BC patient at 12 mg, and 1 was CRPC patient at 12 mg. Sustainable stable disease for six months or longer was observed in patients with colon cancer (n = 1), head and neck cancer (n = 1), and peritoneal mesothelioma (n = 1). **Conclusions:** TT-00420 monotherapy was well tolerated and had favorable PK characteristics. The TEAEs observed in dose escalation and dose expansion cohorts were manageable with concomitant treatment and/or dose interruptions of TT-00420 and reversible upon the discontinuation of TT-00420 treatment. Taking safety, efficacy and clinical PK into consideration, 10 mg *p.o. q.d.* was recommended for phase II study of TT-00420 in patients with advanced CCA. Clinical trial information: NCT03654547. Research Sponsor: TransThera Sciences (Nanjing), Inc.

3014 **Poster Discussion Session**

Efficacy proof-of-concept from a phase 1 study of a novel therapeutic peptide, ST101, targeting the oncogenic transcription factor C/EBPβ in patients with refractory solid tumors.

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Background: The oncogenic transcription factor CCAAT/enhancer-binding protein β (C/EBPβ) promotes tumor survival and proliferation and inhibits differentiation. ST101 is a peptide antagonist of C/EBPβ, with anti-tumor activity in prostate cancer (PC), glioblastoma (GBM), breast cancer (BC), melanoma, and other pre-clinical models. **Methods:** This phase 1 study enrolled patients (pts) with refractory solid tumors with varying histologies. The primary objective was to evaluate safety/tolerability of ST101 and to determine the recommended phase 2 dose (RP2D). Secondary and exploratory objectives included pharmacokinetics (PK), preliminary efficacy (RECIST 1.1), and pharmacodynamic (PD) evaluation. The study used a 3+3 dose-escalation design, with once-weekly IV infusion dosing of ST101 at 0.5, 1, 2, 4, 6, 9 mg/kg or a flat dose of 500 mg. **Results:** Enrollment in phase 1 was completed in November 2021 with a total of 25 pts with multi-metastatic disease that were refractory to standard therapy. As of February 15, 2022, five pts remain on study with a median treatment duration of 27 weeks' (16-77). There were no DLTs, dose modifications, or serious adverse events (SAEs) related to ST101. The only AEs of note were G1-2 histaminergic infusion-related reactions (IRRs), largely pruritis and urticaria, managed with antihistamines, montelukast, and interruption/slowing of infusion. IRRs affected 93% of pts on the first dose at $\geq$4mg/kg and led to prolongation of infusion time. Intensity and frequency of IRRs decrease with repeat dosing. No other AEs were consistently reported. There was no evidence of accumulation upon continued exposure of ST101 and no anti-drug antibodies. Tumor immunohistochemistry showed dose-proportionate staining for ST101 and decreased tumor proliferation in several pts represented by decreased Ki67 expression. Population PK analysis supported flat dosing in phase 2. Five pts continue on treatment with one confirmed partial response in a patient with cutaneous melanoma lasting >42 weeks and four pts with ongoing stable disease. **Conclusions:** ST101 demonstrated safety at all doses explored and evidence of efficacy across dose levels, particularly higher doses and in pts with melanoma. PK and PD support a dose relationship for efficacy and selection of 500 mg as the RP2D. Pts are now enrolling in phase 2 cohorts to assess response in cutaneous melanoma, GBM, castrate-resistant PC, and HR^+ BC. Clinical trial information: NCT04478279. Research Sponsor: Sapience Therapeutics.

Phase 1 pts demonstrating clinical benefit (SD, PR, CR).

Dose (mg/kg)	Tumor type	Response	Duration (weeks)
0.5	Signet ring adenocarcinoma	SD	77+
2	Small bowel adenocarcinoma	SD	18
2	Abdominal sarcoma	SD	9
4	Cutaneous melanoma	PR	42+
6	Hepatocellular carcinoma	SD	18
6	Esophageal adenocarcinoma	SD	9
9	Cutaneous melanoma	SD	27+
Flat dose (mg)			
500	Uveal melanoma	SD	16+
500	Mucosal melanoma	SD	16+

+indicates ongoing treatment.

3015 **Poster Discussion Session**

Expanding clinical actionability in individual patient profiles with the Molecular Oncology Almanac.

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Background: The clinical care of oncology patients is routinely informed by tumor and inherited genetic profiles. This is accomplished by molecular pathologists synthesizing the growing body of clinical guidelines and scientific evidence that associates cancer genome alterations and therapeutic response, and applying that knowledge during case reviews. Many academic medical centers formalize this process in the form of molecular tumor boards. As the number of cases for review and literature continue to increase, there is opportunity to leverage clinical interpretation algorithms to computationally prioritize molecular features and both enhance and automate the sample contextualization process. Here, we present the Molecular Oncology Almanac (MOAlmanac) to enable the rapid assessment of tumor actionability. **Methods:** Molecular Oncology Almanac is an open source clinical interpretation algorithm and paired knowledge base for precision cancer medicine. It is used to rapidly characterize and identify genomic features related to therapeutic sensitivity and resistance and of prognostic relevance. This is performed by assessing not only individual genomic features (e.g. somatic variants, copy number alterations, germline variants, and fusions) but also interactions between these events as well as secondary features such as mutational burden, mutational signatures, MSI status, and aneuploidy. MOAlmanac summarizes all clinically relevant findings into a web-based actionability report. The underlying knowledge base can be accessed through our API endpoints and web browser, and entries may be recommended through either Github or our browser extension. In addition, we developed a cloud-based web portal on top of the Terra framework to increase accessibility. **Results:** A total of 32,108 samples from 30,607 patients across 66 cancer types received targeted sequencing to characterize somatic variants, copy number alterations, and fusions from PROFILE's Oncopanel and were evaluated with MOAlmanac. Based on Oncopanel's tier 1 and tier 2 criteria for clinical actionability, we observed that 8,285 samples (26%, 0 - 69% by cancer type) of patients harbored at least one alteration suggesting therapeutic sensitivity based on FDA approvals or clinical guidelines. Actionability increases to 18,117 samples (56%, 0 - 85% by cancer type) when considering an expanded set of evidence to include relationships captured from clinical trials, clinical, preclinical, and inferential evidence; consequently providing at least one therapeutic hypothesis to otherwise variant-negative patients. **Conclusions:** Clinical actionability of molecular tumor data was increased in individual patients by expanding the set of evidence considered. Source code and a web portal for this project are available at moalmanac.org. Research Sponsor: U.S. National Institutes of Health.

3016 **Poster Discussion Session**

Genomic landscape of acquired resistance to targeted therapies in patients with solid tumors: A study from the National Center for Precision Medicine (PRISM).

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Background: Despite the effectiveness of the various targeted therapies currently approved in solid tumors, acquired resistance remains a persistent problem that limits the ultimate effectiveness of these treatments. Polyclonal resistance to targeted therapy has been described in multiple solid tumors through high throughput analysis of multiple tumor tissue samples from a single patient. However, biopsies at the time of acquired resistance to targeted agents may not always be feasible and may not capture the genetic heterogeneity that could exist within a patient. We used here sequencing of circulating tumor DNA (ctDNA) to characterize the landscape of secondary resistance mechanisms in a large cohort of patients with solid tumors. **Methods:** This study enrolled patients with advanced cancer from two institutional molecular profiling program STING (NCT04932525, sponsor: Gustave Roussy) or BIP (NCT02534649sponsor: Institut Bergonié). Genomic analysis was performed for each patient by using the Foundation One Liquid CDx Assay (324 genes, tumor mutational burden [TMB], microsatellite instability status). **Results:** 3435 patients with metastatic disease entered the study. Among them 992 patients (29%) received a targeted therapy matched to a specific molecular alteration before ctDNA. The main tumor types were: prostate cancer (349, 35%), luminal breast cancer (236, 24%), oncogene-addicted non-small cell lung cancer (129, 13%), *KRAS*-wild type colorectal cancer (126, 13 %). The most frequent class of targeted agents were androgen receptor pathway inhibitor (n = 350, 35%), aromatase inhibitor (236, 24%), anti-*EGFR* monoclonal antibodies (166, 17%), anti-*EGFR* tyrosine kinase inhibitors (83, 8%). ctDNA sequencing revealed DNA aberrations involved in secondary resistance in 308 patients (31%). The most frequent aberrations were *AR* mutations/amplifications, *ESR1* point mutations, *KRAS* point mutations, *EGFR* point mutations. Among patients with resistance mutation, polyclonal aberrations were identified in 123 patients (40%). The median number of polyclonal aberrations per patient was 2 (range: 2-16). Polyclonal aberrations involved at least 2 different genes in 32 patients (10%). Preliminary results suggest that patients with polyclonal aberrations had worse outcome in comparison with patients with one or no detected aberration and final data will be presented at the time of the congress. **Conclusions:** We report here the first comprehensive landscape of genomic aberrations in ctDNA involved in resistance to targeted therapies in cancer patients. Polyclonal secondary genomic aberrations represent a frequent clinical resistance mechanism that may explain the poor rate of sustained complete remission observed with targeted therapies and must guide the development of future combinatorial strategies. Research Sponsor: None.

3017 **Poster Discussion Session**

Dual tissue and plasma testing to improve detection of actionable variants in patients with solid cancers.

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Background: Next generation sequencing (NGS) of tumor tissue and plasma (circulating tumor DNA [ctDNA]) are used clinically to identify actionable genomic alterations, with implications for treatment selection and disease surveillance. Early studies have observed that solid tumor tissue and ctDNA testing may capture both overlapping and complementary alterations. Using the Tempus database, we examined whether dual tissue and ctDNA testing, "dual testing", improved identification of actionable variants compared with either modality alone. **Methods:** We used Tempus Lens to retrospectively analyze 3153 de-identified stage 4 patients (breast [N = 644], colorectal [N = 841], non-small cell lung cancer (NSCLC) [N = 1232], and prostate [N = 436]). Each patient had dual testing—Tempus xF (ctDNA, 105 panel genes) and Tempus xT (tumor tissue, 595-648 panel genes), representing 6306 total samples. Samples were defined as concurrent if biopsied ≤30 days apart and longitudinal if plasma was collected between 31–365 days after tissue biopsy. All analyses were limited to single nucleotide variants and insertions/deletions that met the limit of detection criteria for both assays (104 genes). Indication matched actionable variants were defined by OncoKB Level 1 and 2 evidence, or R1 within both xF and xT (13 genes). **Results:** Of the 3153 patients with dual testing, 37% (1168) had actionable variants identified by at least one test. 94% (1100/1168) of these patients had variants identified via solid tumor profiling alone, 73% (856) had variants identified via ctDNA profiling alone, and 64% (745) had perfectly concordant variants. Thus, dual testing identified additional variants in 36% (423/1168) of these patients compared to any singular test. Of the 423 patients who had additional actionable alterations discovered through dual testing, ctDNA revealed unique alterations—which were not found in solid tissue testing—in 22% (95/423) of patients. Of these patients, 72% (68/95) had all actionable variants identified solely from ctDNA. Of the 251 patients with additional alterations identified by concurrent dual testing, 24% (61/251) had unique alterations identified in plasma. Similarly, of the 172 patients with additional alterations identified by longitudinal dual testing, 20% (34/172) had unique alterations identified in ctDNA alone. **Conclusions:** In the largest study of its kind, we show that dual tumor tissue and ctDNA testing—with samples collected either concurrently or longitudinally—identified more patients with actionable alterations than single modality testing alone and therefore should be considered as part of routine NGS testing. Additional studies to explore the genetic and intra-patient tumor heterogeneity of these variants as well as the impact of time between tissue and plasma sampling assessments and implications for timing of therapeutic recommendations are underway. Research Sponsor: None.

3018 **Poster Discussion Session**

Differential diagnosis of hematologic and solid tumors using targeted transcriptome and artificial intelligence.

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Background: Diagnosis and classification of tumors is becoming increasingly dependent on biological and molecular biomarkers. RNA expression profiling using next generation sequencing (NGS) provides information on various biological and molecular changes in the cancer and in the microenvironment. We explored the potential of using targeted transcriptome and artificial intelligence (AI) in the differential diagnosis and classification of various hematologic and solid tumors. **Methods:** RNA from hematologic neoplasms (N = 2606) and solid tumors (N = 2038) as well as normal bone marrow and lymph node control (N = 806) were sequenced by NGS using a targeted 1408-gene panel. The hematologic neoplasms included 20 different subtypes. Solid tumors included 24 different subtypes. Machine learning is used for comparing two classes at a time. Geometric Mean Naïve Bayesian (GMNB) classifier is used to provide differential diagnosis across 45 diagnostic entities with assigned ranking. **Results:** Machine learning showed high accuracy in distinguishing between two diagnoses with AUC varied between 1 (Sarcoma vs GIST) and 0.841 (MDS vs normal control) (examples in Table). For differential diagnosis between all 45 different diagnoses, we used 3045 samples for training the GMNB algorithm and 1415 samples for testing. Correct first choice diagnosis was obtained in 100% of ALL, 88% of AML, 85% of DLBCL, 82% of colorectal cancer, 88% of lung cancer, 72% of CLL, and 72% of follicular lymphoma. The algorithm had difficulty in typically overlapping diagnoses and diagnosed as first choice 19% of MDS, 46% of normal, and 12% of MPN. Diagnosis improved significantly when second choice was considered. **Conclusions:** Targeted RNA profiling with proper AI can provide highly useful tools for the pathologic diagnosis and classification of various cancers. Additional information such as mutation profile and clinical information can improve these algorithms, reduce subjectivity, and minimize errors in pathologic diagnoses. Research Sponsor: None.

Two classes	AUC	% Sensitivity	% Specificity	Leave one out AUC
Normal (N) vs AML	0.971	95.2	91	0.967
N vs ALL	0.98	95.5	98.7	0.984
N vs CLL	0.988	97	97.3	0.998
N vs MPN	0.925	90.9	83	0.894
N vs MDS	0.841	82	70.1	0.818
Marginal vs CLL	0.987	98.7	91.6	0.983
CLL vs Mantle	0.993	96.6	95.8	0.99
AML vs MDS	0.883	86.1	69.8	0.871
Breast vs Colorectal	0.979	95.6	96.1	0.984
Lung vs Colorectal	0.972	98	92.9	0.979
Lung vs Breast	0.971	97.6	89.8	0.98
Breast vs Ovarian	0.966	100	91.2	0.987
Ovarian vs Endometrial	0.962	92	93.7	0.906
Pancreas vs Colorectal	0.978	98	91.9	0.979
Pancreas vs Esophageal	0.979	95.9	97.1	0.984
Hodgkin vs Normal LN	0.977	95.8	87.7	0.936
Hodgkin vs T-lymphoma	0.964	91.7	90.8	0.938
Hodgkin vs DLBCL	0.969	92.8	98.5	0.959
DLBCL vs Follicular	0.975	95.6	91	0.974
DLBCL vs T-lymphoma	0.963	91.1	89.7	0.944
Sarcoma vs Ovarian	0.983	94.9	98.4	0.984
Sarcoma vs Lung	0.99	98.6	96.3	0.99
Sarcoma vs GIST	1	99.3	100	1

3019 **Poster Discussion Session**

AI-enabled identification prediction of homologous recombination deficiency (HRD) from histopathology images.

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Background: Homologous recombination deficient (HRD) tumors are highly responsive to platinum-based chemotherapy and poly (ADP-ribose) polymerase inhibitor (PARPi) therapy. Pathogenic BRCA-1 and BRCA-2 (BRCA1/2) alterations are key members of the HR DNA repair pathway but genomic instability status, including loss of heterozygosity, telomeric allelic imbalance and large scale state transitions across the genome are also predictive of HRD. HRD testing is currently performed by next generation sequencing which can take 2-4 weeks for results, has a high failure rate, requires significant tissue and is costly. We developed and tested the ability of an AI enabled platform to predict HRD status from the analysis of whole slide imaging of the diagnostic H&E slide. This platform, iPREDICT-HRD is rapid, precise, and cost effective. **Methods:** The AI engine was trained on 120 H&E slides that were used to identify tumor prior to manual microdisseection for HRD assessment by NGS. Histopathological features were extracted, followed by feature mapping to predict HRD status based on the results of NGS testing. ResNet AI algorithm was trained to segment, annotate and predict HRD status. 10 lac tiles of 256x256 size at 40x magnification were generated per pathological class. 70% of the data set was used for training and 30% for validation of the AI model. **Results:** Using single blinded clinical samples, iPREDICT-HRD tool detected HRD + ve samples with 99.3% accuracy with 100% sensitivity and 99% specificity in the test set. Patch-level predictions of HRD status demonstrated intra-tumor heterogeneity within the H&E slides. Visual inspection of the heatmap suggested the presence of patches with high predictive ability of HRD status and this outperformed an average HRD score for slides with heterogeneity. **Conclusions:** AI-enabled prediction of HRD status can be accurately performed on diagnostic H&E slides potentially yielding results quickly and afforadably, even when limited tissue is available for testing. Research Sponsor: None.

3020 **Poster Discussion Session**

A clinical AI-driven multiplex immunofluorescence imaging pipeline to characterize tumor microenvironment heterogeneity.

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Background: Understanding the underlying heterogeneity of the tumor microenvironment (TME) on a single-cell level is becoming increasingly important to predict a patient's response to immunotherapy. Conventional imaging methods can help reveal tissue heterogeneity, but are not optimal for identifying multiple cellular subpopulations or cellular interactions from a single slide image, limiting their use in clinical settings. Here, we present a clinical artificial intelligence (AI)-driven multiplex immunofluorescence (MxIF) imaging pipeline based on novel cell segmentation and cell typing methods to evaluate tumor cellular heterogeneity, immune cell composition, and cell-to-cell interactions. **Methods:** A machine learning (ML)-based cell segmentation algorithm was trained on a manually annotated dataset created from 219 different regions of interest (ROIs) that contained 85,991 cells from various tissues (colon, kidney, lung, lymph node, tonsil, and ureter). A dataset containing 58,676 cells from 146 ROIs was used for validation and accuracy was determined between automated and manually annotated images; accuracy was further evaluated by calculating the f1-score using available methods (DeepCell and Stardist). Marker stains with a low signal-to-noise ratio were automatically enhanced, allowing for adequate cell-to-cell interaction analysis. **Results:** An automated MxIF image processing workflow was developed. Validation of the trained cell segmentation model showed high accuracy (0.80 f1-score), demonstrating superior performance compared to other methods (DeepCell and Stardist - 0.55 and 0.78 f1-score, respectively). The pathologist-determined accuracy (0.84 mean f1-score) indicated a near-human performance of the developed method. Normalized expression values obtained from the cell typing model allowed automated cell recognition. We analyzed cellular heterogeneity across 3 regions of colorectal cancer (CRC), gastric cancer (GC), and non-small cell lung cancer (NSCLC) samples. While proportions of immune cells varied, proportions of malignant epithelial cells were stable across all regions of each sample, as concordant percentages of Ki67+ cells were identified (CRC-19%; GC-21%; NSCLC-5%). Analysis of cell-to-cell interactions and immune communities identified tumor-, immune-, and stromal-enriched communities in all tumor samples that were stable across regions. **Conclusions:** By analyzing complex tumor tissue at single-cell resolution with high accuracy, this AI-driven MxIF imaging technology is able to characterize tumor and microenvironment heterogeneity across cancer types. This novel AI-based tool is currently being integrated into several ongoing prospective clinical studies to aid in the development of predictive and prognostic biomarkers. Research Sponsor: None.

3021 **Poster Session**

First-in-human, phase I study of AK109, an anti-VEGFR2 antibody, in patients (pts) with advanced or metastatic solid tumors.

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Background: AK109 is a fully-human monoclonal antibody that specifically binds to vascular endothelial growth factor receptor 2 (VEGFR2), thereby block vascular endothelial growth factor (VEGF)/VEGFR2 signaling pathway to inhibit angiogenesis, endothelial cell migration and proliferation of tumor cells. This phase I study is the first-in-human trial of AK109, which was designed to evaluate safety, tolerability of AK109, to determine the maximum tolerated dose (MTD), recommend phase II dose (RP2D) and to gain preliminary data on pharmacokinetics (PK), pharmacodynamics, immunogenicity and clinical activity for AK109 in pts with advanced or metastatic solid tumors resistant to standard therapies (NCT04547205). **Methods:** This open-label, multi-center, phase I study included a dose escalation phase (part 1) using a 3+3 design to determine MTD and potential RP2D (n = 36 max), with planned dosing of 2, 4, 8, 12 and 18 mg/kg q2w and 15mg q3w, followed by a dose expansion phase (part 2), at 2 potential RP2Ds in q2w or q3w respectively (n = 24-30). The PK characteristics, dose limiting toxicity (DLT), adverse events per CTCAE 5.0 and efficacy (ORR, DCR, DoR, PFS per RECIST v1.1, OS, etc.) of AK109 were evaluated. **Results:** As of December 30th, 2021 (median follow-up: 6.0 months), 40 pts (median age: 59.5 years) were enrolled, 16 pts in part 1 and 24 pts in part 2. No DLT was observed AK109 in part 1. Tumor types included gastric cancer (n = 9), non-small cell lung cancer (n = 8), hepatocellular carcinoma (n = 8), colorectal cancer (n = 5), pancreatic carcinoma (n = 2) and oesophagus cancer (n = 2), etc. Preliminary PK analyses showed systemic exposure in C_{max} and AUC_{last} increased dose proportionally at doses of 8 mg/kg and above, with a mean half-life of 8.5 to 10 days. 12mg/kg q2w and 15mg/kg q3w were selected as RP2Ds. Average exposure of AK109 was 6.9 cycles. Eight pts received over 10 cycles of AK109. Treatment related adverse events(TRAE) occurred in 38 (95%) of all pts. Grade 3 and 4 TRAE occurred in 16 (40%) of all pts. The most common TRAEs were proteinuria (22/40, 55%), hypertension (13/40, 32.5%) and AST increased (11/40, 27.5%). Serious adverse event (SAE) occurred in 11 (27.5%) pts, 2 (5%) of which were AK109 related. ORR and DCR were 10.0% and 62.5%, respectively. The median PFS of non-small cell lung cancer (n = 8) and gastric cancer (n = 9) were 5.6 months (95% CI, 1.3, NE) and 5.5 months (95% CI, 1.4, NE), respectively. **Conclusions:** AK109 showed manageable safety and promising anti-tumor activity. Two phase II studies of AK109 combined with AK104 (anti PD-1/CTLA-4 bi-specific antibody) are ongoing to evaluate the efficacy of AK109 combined with AK104 in patients with multiple solid tumors (NCT05142423, NCT04982276). Clinical trial information: NCT04547205. Research Sponsor: Akeso Biopharma, Inc.

3022 **Poster Session**

Safety of the cyclin dependent kinase 9 (CDK9) inhibitor FIT039 for cervical intraepithelial neoplasia (CIN) 1 or 2 in a phase I/II trial.

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Background: Human papillomaviruses (HPVs) infect uterine cervical epithelial cells, leading to cervical intraepithelial neoplasia (CIN) and cervical cancer. However, there is no treatment for HPV infection in the uterine cervix prior to vaccination. We recently reported that cyclin dependent kinase 9 (CDK9) plays a critical role in viral RNA transcription of DNA viruses such as HPVs in host cells, and that FIT-039, a specific inhibitor of CDK9, suppresses the proliferation of several DNA viruses. Here, we evaluated the safety and antiviral effect of a FIT039-releasing vaginal tablet (FIT039CT) for CIN1 or 2 (CIN1/2). **Methods:** A multi-institutional, single-blind, placebo-controlled randomized phase I/II clinical trial involving 2 cohorts was designed to evaluate the safety of transvaginal FIT039CT for CIN1/2 as follows:. In the first cohort, 8 healthy women were randomized into FIT039CT (50mg/day or 100mg/day) or control group. In the second cohort, 14 women with a primary diagnosis of CIN1/2 were randomized into either FIT039CT (100mg/day) or control group. The primary endpoints were adverse events and plasma concentrations of FIT039. **Results:** 22 patients (8 volunteers, 11 CIN1 and 3 CIN2) were enrolled. There were no serious adverse events. Adverse events considered related to treatment were mild (vaginal discharge Grade 1: FIT039CT 16/17 women [94%] vs placebo 2/6 [33%]) and self-limiting in both cohorts. No patient discontinued this study due to adverse events. Maximum concentration (C max) and terminal elimination half-life (t 1/2) of serum FIT039 concentrations after single transvaginal treatment of FIT039CT were similar between the two doses as follows; C max (mean ± standard deviation) was 4.5 ± 0.5 ng/mL (50mg/day) and 4.4 ±1.4 ng/mL (100mg/day) at 6-7 hours; mean t1/2 was 14.8 ± 2.1 hours (50mg/day) and 12.1 ± 2.6 hours (100mg/day) hours. **Conclusions:** This study demonstrated the safety and validity of transvaginal FIT039CT once a day and may contribute to the development of an antiviral agent that can cure CIN1/2, and supports the design of the ongoing phase 2 clinical study. Clinical trial information: jRCT2051180201. Research Sponsor: Japan Agency for Medical Research and Development (AMED, 20lk0201081h0003), Pharmaceutical/Biotech Company.

3023 **Poster Session**

A phase I study to evaluate the safety, tolerability, and pharmacokinetics of MSB0254 in Chinese patients with solid tumors.

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Background: MSB0254 is a humanized vascular endothelial growth factor receptor 2 (VEGFR-2) monoclonal antibody. MSB0254 inhibits angiogenesis induced by either VEGF-A or –C. This trial is a phase I study to evaluate MSB0254's safety, tolerability and PK profiles, as well as early anti-cancer activities in Chinese patients with advanced solid tumors. **Methods:** In this phase I study (NCT04381325), locally advanced or metastatic solid tumor patients failed previous standard treatments were enrolled. In the dose escalation phase, following 3+3 rules, MSB0254 was given intravenously Q2W (every 2 weeks) at 4mg/kg, 8mg/kg, 12mg/kg, 16mg/kg, and Q3W at 20mg/kg. In the dose expansion phase, patients with selected tumor types will be treated with MSB0254 at 16mg/kg Q2W or 20mg/kg Q3W. Primary objectives were to evaluate the safety and tolerability and to identify maximum tolerable dose (MTD) and/or Recommended Phase 2 Dose (RP2D). Secondary objectives included the assessment of pharmacokinetics, immunogenicity, and preliminary efficacy per RECIST1.1. **Results:** As of 10th Jan, 2022, a total of 22 Chinese patients have been enrolled into the dose escalation phase and treated with MSB0254 at different dose levels from 4-16mg/kg Q2W or 20mg/kg Q3W. MTD was not reached. One DLT was reported in 12mg/kg Q2W dose cohort. A subject with intra-cholangial carcinoma developed G3 (grade 3) upper gastrointestinal hemorrhage on the C1D13. The adverse event was resolved after symptomatic treatment. The most common treatment-emergent adverse events (TEAEs) (>10%) included: hypertension (27.3%), AST increased (27.3%), γ-GGT increased (22.7%), neutrophil count decreased (18.2%), proteinuria (18.2%), WBC count decreased (13.6%), platelet count decreased (13.6%) and anemia (13.6%). Three subjects (13.6%) experienced G3 TEAEs: 1 upper gastrointestinal hemorrhage, 1 anemia and 1 Hypertriglyceridemia. No G4/5 TEAE was observed. And three subjects (13.6%) experienced 3 SAEs: 1 upper gastrointestinal hemorrhage, 1 G2 intestinal obstruction caused hospitalization and 1 G2 fatigue caused hospitalization. MSB0254 displayed a dose proportional pharmacokinetic profile between 4-16 mg/kg Q2W with calculated $T_{1/2}$ of 6-9 days. Eighteen subjects had at least one tumor assessment per RECIST 1.1 after MSB0254 treatment. Eleven subjects (61.1%) had best response of stable disease (SD). Four of them had stable disease for more than 6 months, including a neuroendocrine tumor (NET), a gastric cancer, an epithelioid hemangioendothelioma (EHE) and a submaxillary gland carcinoma patient. **Conclusions:** MSB0254 demonstrated a manageable safety profile and preliminary antitumor activity in patients with advanced solid tumors. 16mk/kg Q2W is recommended as RP2D. 20mg/kg Q3W is still under investigation. The study of MSB0254 on the expansion phase in selected tumor patients is ongoing. Clinical trial information: NCT04381325. Research Sponsor: Suzhou Transcenta Therapeutics Co., Ltd.

3024 **Poster Session**

VEGF inhibitors (VEGFi) activity in liver metastases (mets) regardless of primary cancer type: Meta-analysis and systematic review.

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Background: Liver metastasis is a poor prognostic factor in several cancers and is associated with poor response to immunotherapy (IO) in melanoma and lung cancer. VEGFi have activity in hepatocarcinoma (HCC) and is hypothesized to be due the hypoxic microenvironment. Whether this is also true for liver mets is unknown. We sought to assess the efficacy of VEGFi in liver mets utilizing randomized-controlled clinical trials (RCTs) testing the efficacy of VEGFi, regardless of primary cancer site. **Methods:** Systematic searches of PubMed, Cochrane CENTRAL, and Embase were conducted from January 1, 2000, to January 1, 2022. All RCTs that compared a backbone of systemic therapy (chemotherapy [chemo] and/or IO and/or targeted therapy [TT]) or best supportive care (BSC) with vs without VEGFi in patients (pts) with liver mets from any cancer were selected. HCC trials were excluded. Study design, cancer type, number of pts, lines of treatment, study drugs and hazard ratios (HRs) with 95% CIs for overall survival (OS) and progression-free survival (PFS) were extracted. Pooled effects of VEGFi in pts with liver mets across different cancer types were estimated using random effect model with inverse variance. Heterogeneity between studies was assessed by I^2 statistics. Sensitivity analyses were performed considering prespecified subgroups of trials. **Results:** 3170 pts with liver mets from 19 RCTs were included in this meta-analysis: 8 colorectal cancer, 4 non-small cell lung cancer, 4 renal cell cancer & urothelial cancer, 1 pancreatic cancer, 1 GIST and 1 gastric cancer. Backbone systemic therapy in these trials included: chemo (11), TT (2), IO (2), chemo+IO (1), chemo+TT (1); and 2 BSC trials. Moderate heterogeneity between studies for both PFS (I^2= 55%) and OS (I^2= 46%) was seen. The addition of VEGFi to standard systemic therapy or BSC was associated with superior PFS (HR = 0.61; 95% CI, 0.50-0.74; $p < 0.0001$) and OS (HR = 0.86; 95%CI, 0.76-0.99; $p = 0.0334$) in pts with liver mets, regardless of whether pts had only liver mets or concurrent other sites of mets. In the subset of RCTs with data on pts without liver mets, the benefit with VEGFi was more pronounced in patients with liver mets (HR = 0.56) vs those without liver mets (HR = 0.64) for PFS, but not for OS. **Conclusions:** The addition of VEGFi to standard management improved survival outcomes in pts with liver mets across different cancer types and warrants further investigation. VEGFi added to IO may be effective in pts with resistant liver mets. Research Sponsor: None.

3025 **Poster Session**

Dose-finding and -expansion studies of trastuzumab deruxtecan in combination with other anti-cancer agents in patients (pts) with advanced/metastatic HER2+ (DESTINY-Breast07 [DB-07]) and HER2-low (DESTINY-Breast08 [DB-08]) breast cancer (BC).

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Background: Trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate composed of a humanized anti-HER2 monoclonal antibody and a topoisomerase I inhibitor payload, is approved for pts with unresectable or metastatic HER2+ BC with ≥2 prior anti-HER2–based therapies. T-DXd showed improved progression-free survival vs trastuzumab emtansine (T-DM1) as an earlier-line treatment (tx) for pts with HER2+ metastatic BC in the phase 3 DESTINY-Breast03 trial (Cortes J, et al. *Ann Oncol*. 2021;32:S1283-S1346. Abstract LBA1). Preliminary antitumor activity of T-DXd was shown in heavily pretreated pts with HER2-low advanced/metastatic BC in the phase 1 DS8201-A-J101 trial (Modi S, et al. *J Clin Oncol*. 2020;38:1887-1896). We report preliminary results from the dose-finding phase of 2 trials investigating T-DXd combination tx in HER2+ or HER2-low metastatic BC. **Methods:** DB-07 (phase 1b/2; NCT04538742) and DB-08 (phase 1b; NCT04556773) are 2-part, modular, open-label, multicenter trials of T-DXd combined with other anticancer tx in pts with advanced/metastatic BC that is HER2+ (DB-07) or HER2 low (DB-08). Part 1 of each study is an ongoing dose-finding phase; pts must have ≥1 prior tx for metastatic BC. Part 2 of each study is a dose-expansion phase; pts must have no (DB-07) or ≤1 (DB-08) prior tx for metastatic BC. We report preliminary results from the T-DXd + pertuzumab module of DB-07 part 1 (data cutoff: Oct 15, 2021) and T-DXd + anastrozole and T-DXd + fulvestrant modules of DB-08 part 1 (data cutoff: Sep 27, 2021); pts in the DB-08 modules must be hormone receptor positive. The part 1 primary objective was to assess safety and tolerability and determine the recommended phase 2 dose (RP2D) according to the modified toxicity probability interval-2 algorithm. Pts were followed up beyond the 21-day dose-limiting toxicity (DLT) period (28 days for T-DXd + fulvestrant) for safety events. **Results:** In DB-07, 7 pts were enrolled and received T-DXd 5.4 mg/kg + pertuzumab 420 mg (loading dose: 840 mg) every 3 wk (q3w; not evaluable for DLTs, n = 1). In DB-08, 6 pts were enrolled and received T-DXd 5.4 mg/kg q3w + anastrozole 1 mg daily (not evaluable for DLTs, n = 1); another 6 pts were enrolled and received T-DXd 5.4 mg/kg q3w + fulvestrant 500 mg every 4 wk (loading dose: 500 mg cycle 1 days 1 and 15). For all 3 modules, no DLTs were reported in any DLT-evaluable pts; the dose levels used in part 1 were approved to be the RP2Ds for use in the dose-expansion part of each corresponding module. No deaths on study or cases of interstitial lung disease/pneumonitis were reported to date. **Conclusions:** The RP2Ds for the T-DXd combinations were the standard doses for BC of each individual drug. These studies are ongoing, with additional T-DXd combinations being evaluated and further follow-up underway. Clinical trial information: NCT04538742; NCT04556773. Research Sponsor: This study is funded by AstraZeneca Pharmaceuticals. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

3026 **Poster Session**

Safety, pharmacodynamic, and clinical response evaluation of nilotinib and paclitaxel in adults with refractory solid tumors.

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Background: The combination of the BCR-Abl kinase inhibitor nilotinib and the anti-tubulin agent paclitaxel was identified in the NCI-ALMANAC study to have greater-than-additive activity in the NCI-60 cell line panel and greater-than-single-agent antitumor activity in xenograft models, in which this combination induces tumor epithelial-mesenchymal transition (EMT). A phase 1 study was initiated to establish the safety, tolerability, and recommended phase 2 dose (RP2D) of this combination in patients (pts) with advanced solid tumors and to examine the pharmacokinetic (PK) and pharmacodynamic (PD) effects of the combination to understand the mechanism of action (NCT02379416). The dose escalation phase established the RP2D as 300 mg oral nilotinib twice daily and 80 mg/m^2 intravenous paclitaxel on days (D) 1, 8, and 15 of each 28-day cycle. Here, we report the safety, preliminary PD, and efficacy data for this combination. **Methods:** Nilotinib and paclitaxel were administered as noted above, with a 1-day (escalation cohort) or 2-day (expansion cohort) paclitaxel-only run-in during the first cycle to enable comparison of the PK and PD effects of the combination vs. single-agent paclitaxel. Paired biopsies to assess tumor molecular response were collected from expansion cohort pts at baseline, cycle (C) 1 D2, and C1D28, with an optional biopsy at progression; accrual continued until ≥ 12 sufficient-quality paired biopsies were obtained. Blood specimens to assess molecular responses in circulating tumor cells (CTCs) were obtained at several timepoints during C1 and longitudinally every cycle thereafter. EMT biomarkers were measured in tumor and CTC specimens using quantitative immunofluorescence microscopy assays. **Results:** A total of 44 pts were enrolled. Three pts had partial responses (PR), and 1 had an unconfirmed PR (9%); 23 pts (52%) had a best response of stable disease (SD), including 7 pts on study for ≥ 10 cycles. The most common grade (Gr) 3-4 treatment-related adverse events were hematologic and hypophosphatemia. No pts experienced Gr ≥ 3 peripheral neuropathy. The median time on treatment was 67 days. Two pts with granulosa cell ovarian carcinoma had durable responses, completing 74+ and 64 cycles. Multiple patient biopsies and corresponding CTC specimens exhibited treatment-induced EMT. Longitudinal analysis of CTC EMT phenotypes in the 2 pts with extended PR revealed a substantial increase in mesenchymal-like CTCs prior to progression for the pt on study for 64 cycles; such increases were not observed in the pt still on study after 74+ cycles. Further PD analyses are ongoing. **Conclusions:** The combination of nilotinib and paclitaxel demonstrates promising disease control with durable response in select patients. Tumor PD analyses to discover the underlying pharmacology of this active regimen are ongoing. Funded by NCI Contract No. HHSN261201500003I. Clinical trial information: NCT02379416. Research Sponsor: U.S. National Institutes of Health.

3027 **Poster Session**

TLD-1, a novel liposomal doxorubicin, in patients (pts) with advanced solid tumors: Dose escalation and expansion part of a multicenter open-label phase I trial (SAKK 65/16).

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Background: TLD-1 is a novel liposomal doxorubicin that compared favorably to conventional liposomal formulations of doxorubicin in preclinical in vivo mouse breast cancer models. This phase I first-in-human trial is aiming to determine the recommended phase II dose (RP2D), toxicity profile, pharmacokinetics and preliminary activity. **Methods:** Patients with a maximum of 3 prior lines of systemic chemotherapy and preferably anthracycline-sensitive disease were eligible. TLD-1 was administered on day 1 iv over 60-90 minutes (depending on individual dose) q 21 days, for up to 6 or 9 cycles (according to prior anthracycline-exposure) with premedication of 8mg dexamethasone. Dose escalation with dose levels (DL) 1-7 of 10, 16, 23, 30, 35, 40 and 45mg/m^2 started with an accelerated titration design, treating one pt at each DL up to DL6 (40mg/m^2) followed by a modified continual reassessment method at DL7 due to observed toxicity. **Results:** 30 pts (F:M = 24:6) have been treated, one each at DLs 1-6, 15 pts at DL7 and an additional 9 pts at DL6. Most frequent tumor types included breast (n = 13), ovarian (n = 6), cervical cancer (n = 2) and cholangiocarcinoma (n = 2). Median age was 67.5 years (range:38-83), 13 pts were exposed to prior anthracyclines. The median number of cycles was 4 (range:1-9). No dose-limiting toxicities (DLT) occurred during cycle 1. At DLs 1 to 5, no treatment-related G3 AEs (TRAE) were observed. At DL6, there was one case of mucositis G3, one of palmar-plantar-erythrodysesthesia (PPE) G3 and one of anemia and neutropenia G3 each. One patient with pre-existing valvular cardiopathy developed symptoms of heart-failure G3 after 8 cycles. Echocardiography showed severe mitral regurgitation with normal LV-EF. In addition one case of urinary-tract infection G3 was seen. Dose-modifications or -delays due to AEs occurred in 7/50 cycles. At DL7, one case of mucositis G3, 3 events of PPE G3 and one case of fatigue G3 were reported. In addition, one case of infection with shingles occurred. Dose-modifications or -delays due to AEs occurred in 12/61 cycles. Shingles and heart failure were reported as SAEs. All toxicities listed above were categorized as TRAE. 29/30 pts were evaluable for response. Three breast cancer pts had a partial response, 2 at DL7 and 1 at DL6, 14 pts had stable disease. **Conclusions:** No DLT was observed up to DL7. RP2D was defined at 40mg/m^2 due to cumulative PPE G3 at DL7. The trial is ongoing with a comparative PK-part evaluating the two iv liposomal formulations of doxorubicin TLD-1 and Caelyx. Clinical trial information: NCT03387917. Research Sponsor: InnoMedica Holding AG.

3028 **Poster Session**

Phase 1 study of OBT076, a first-in-class anti-DEC205 ADC, in patients with advanced/metastatic solid tumors: Safety, efficacy, and PK/PD results.

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Background: OBT076, an Antibody Drug Conjugate (ADC) consisting of a fully human IgG1 antibody conjugated via a cleavable linker to the derivative microtubule inhibitor DM4. It has specificity for the CD205/Ly75 target antigen which is an endocytic receptor overexpressed on the cell surface and immunosuppressive dendritic cells. This phase 1 study evaluates safety, tolerability, PK/PD and preliminary efficacy of OBT076 in solid tumor patients with high expression of target protein CD205 (CAP-CLIA validated centralized IHC test). **Methods:** Open label, two parts trial in patients with metastatic CD205+ve solid tumors who progressed on standard therapy. Part 1 of the study consisted in dose escalation from 1.6 mg/kg to 3.5 mg/kg. An mTPI design is used to guide to determine the maximum tolerated dose (MTD) Treatment was given on day 1 every 3 weeks followed by GCSF on day 8. Blood samples and flow cytometry were used to assess PK/PD. Tumor response was assessed every three cycles. Part 2 of trial is an expansion basket trial enriched in indications where preliminary efficacy has been shown. **Results:** The study completed Part 1 dose escalation. Part 2 expansion phase is ongoing. Between Dec 2019 and January 2022, 20 patients were enrolled (18 patients in the dose escalation and 2 in the ongoing expansion). The median age 61, 9 patients were males and 9 had ECOG PS 0. All patients had at least one metastatic site and 90% received at least 2 lines of chemotherapy in the metastatic setting. Recommended dose for the expansion phase is 3.0 mg/kg. No other significant side effects have been observed. PK data showed that Cmax of 40.000-90.000 ng/ml was achieved between 2.5 and 3.5mg/kg dose and is comparable to the therapeutic dose in mouse models. In part 1 of the study, 7 patients derived clinical benefit despite being in disease progression at trial entry. One patient with gastric cancer with linitis plastica experienced major improvement with complete disappearance of ascites and metastatic adenopathy after cycle 3. The six other patients had lasting stable disease and received between 5-14+ cycles with median of 5 cycles. Two patients with low PD-L-1 expression received checkpoint inhibitor treatment with pembrolizumab after 2 and 5 cycles of OBT076, both patients experienced near complete response after only one to two cycles. **Conclusions:** OBT076 at 3.0mg/kg has shown favorable safety profile with manageable neutropenia. The preliminary efficacy has shown preliminary antitumoral single agent activity in gastric, ovarian and lung cancer. The two patients who received a sequential administration of pembrolizumab after OBT076 showed major tumor activity. Sequential administration of OBT076 followed by a PD-1 inhibitor was also supported by PD markers and warrants further evaluation. Clinical trial information: NCT04064359. Research Sponsor: Oxford Biotherapeutics.

dose cohort (mg/kg)	1.6	2.5	3.5	3.0
N (patients)	3	9	3	3
DLTs	0	1*	1*	0

Neutropenia was the DLT*.

3029 **Poster Session**

First-in-human study of OBI-999: A globo H-targeting antibody-drug conjugate in patients with advanced solid tumors.

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Background: OBI-999 is a novel antibody-drug conjugate, composed of a humanized monoclonal IgG1 antibody which targets the tumor-associated carbohydrate antigen Globo H, conjugated with monomethyl auristatin E (MMAE, vedotin). Upon binding to Globo H, OBI-999 is internalized into the tumor cell, and the linker (Thiobridge) connecting MMAE (an ultrapotent antimitotic agent) to the monoclonal antibody is cleaved by cathepsin B to release MMAE, thereby causing cell cycle arrest by inhibiting tubulin polymerization. We conducted a first-in-human, phase 1, dose-escalation study of OBI-999 monotherapy in patients with advanced cancer (NTC04084366). **Methods:** OBI-999 was administered intravenously at doses of 0.4, 0.8, 1.2, and 1.6 mg/kg on Day 1 of a 21-day cycle. Patients received study treatment until disease progression, unacceptable toxicity, or up to 2 years of treatment. **Results:** Overall, 15 adult patients were treated. OBI-999 administered on Day 1 of each 21-day cycle was well tolerated up to 1.2 mg/kg, the maximum tolerated dose (MTD). Treatment-related AEs (TRAEs) were noted in 40% (6/15) of patients. TRAEs ≥Grade 3 were noted in 27% (4/15) of patients; of whom 3 had neutropenia and 2 had anemia. OBI-999 exhibited non-linear pharmacokinetics from 0.4 mg/kg to 1.6 mg/kg, with lower clearance at higher doses. A retrospective validated automated immunohistochemistry assessment indicated 50% of patients with advanced solid tumors had high Globo H staining (H-score cutoff ≥100). Of 3 patients treated at the 1.6 mg/kg dose level; 2 developed Grade 4 neutropenia during Cycle 1 and the third developed Grade 4 neutropenia on Cycle 2 Day 15. One patient (1.6 mg/kg) with Grade 4 neutropenia also developed Grade 4 renal insufficiency and died from progressive disease (direct bilirubin, 3.5 mg/dL). Five (33.3%) patients had stable disease (SD), including 1 patient with adenoid cystic carcinoma of the oropharynx (SD for 13 cycles); 1 patient with gastroesophageal junction adenocarcinoma (SD for 8 cycles), and 3 patients with other tumor types (SD for 4, 2, and 2 cycles). **Conclusions:** We completed the dose-escalation portion of the study. OBI-999 was well tolerated. The recommended phase 2 dose was determined to be 1.2 mg/kg once every 3 weeks. Dose-dependent, non-cumulative neutropenia was dose limiting. We are currently enrolling patients with high Globo H expressing solid tumors (H-score ≥100) in the expansion phase of the study, which includes pancreatic, colorectal, and cancers of other histologic subtypes. Clinical trial information: NTC04084366. Research Sponsor: OBI Pharma Inc.

3030 **Poster Session**

Safety, pharmacokinetics, and clinical activity of OBI-3424, an AKR1C3-activated prodrug, in patients with advanced or metastatic solid tumors: A phase 1 dose-escalation study.

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Background: OBI-3424 is a novel nitrogen mustard prodrug that can be selectively converted in the presence of the AKR1C3 enzyme into the bis-alkylating agent OBI-2660, which forms intra- and inter-strand DNA crosslinks resulting in cell death. This selective mode of activation distinguishes OBI-3424 from traditional alkylating agents, and potentially improves the safety profile and antitumor activity against chemo- and radio-resistant tumors. We conducted a first-in-human, phase 1, dose-escalation study of OBI-3424 monotherapy in patients with advanced solid tumors (NCT03592264). **Methods:** OBI-3424 was administered intravenously at doses of 1, 2, 4, 6, 8, or 12 mg/m^2 (Days 1 and 8 every 21 days, Schedule A) or 8, 10, 12, or 14 mg/m^2 (Day 1 every 21 days, Schedule B). A "3+3" design was used for dose escalation. Patients received study treatment until disease progression, unacceptable toxicity, or up to 2 years of treatment. **Results:** Overall, 39 adult patients were treated. In patients receiving Schedule A, the maximum tolerated dose (MTD) of OBI-3424 was determined to be 8 mg/m^2. Dose limiting toxicities (DLTs) were reported at the 12 mg/m^2 dose level, including thrombocytopenia (Grade 3-4, 5 of 6 patients) and anemia (Grade 3-4, 5 of 6 patients). Platelet count nadirs were noted on Day 15 or Day 22. These cytopenias led to dose modification and resulted in protocol amendment (Schedule B). In Schedule B, the MTD was not reached at the maximum dose tested (14 mg/m^2). Grade 3 or higher anemia was noted in 3 of 6 patients treated at 14 mg/m^2; the recommended phase 2 dose (RP2D) is 12 mg/m^2 (Day 1 every 21 days). Treatment-related AEs (TRAEs) were noted in 82% (32/39) of patients. The most common TRAEs were anemia (64%), thrombocytopenia (51%), nausea (26%), and fatigue (21%). No patient had a fatal TRAE, 49% had ≥Grade 3 TRAEs, including 3 patients who had serious TRAEs. OBI-3424 showed linear pharmacokinetics from 1 to 14 mg/m^2, with minimal accumulation after repeated dosing. A retrospective validated automated immunohistochemistry assessment indicated that 27% of patients had high AKR1C3 staining (H-score ≥135). Best confirmed response was stable disease in 21 patients (54%). **Conclusions:** We completed the dose-escalation portion of the study. The RP2D was determined to be 12 mg/m^2 once every 3 weeks. OBI-3424 was well tolerated. Dose-dependent, non-cumulative thrombocytopenia and anemia were dose limiting. We are currently enrolling patients with pancreatic cancer and other tumor types with overexpression of AKR1C3 (H-score ≥135) in the expansion phase of the study. Clinical trial information: NCT03592264. Research Sponsor: OBI Pharma Inc.

3031 **Poster Session**

BOLD-100-001 (TRIO039): A phase 1b dose-escalation study of BOLD-100 in combination with FOLFOX chemotherapy in patients with advanced gastrointestinal solid cancers: Interim safety, tolerability, and efficacy.

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Background: BOLD-100 is a first-in-class ruthenium-based anticancer agent in Phase 1b / 2 clinical development for the treatment of advanced gastrointestinal (GI) cancers in combination with FOLFOX. Being developed primarily as a combinational agent, BOLD-100 induces cellular stress through modulation of the unfolded protein response, production of reactive oxygen species and induction of DNA damage. BOLD-100 demonstrates synergy in established preclinical models in combination with various anticancer therapies, particularly in resistant cell lines. **Methods:** This is a prospective, Phase 1b dose-escalation (Part A) and Phase 2 dose-expansion (Part B) study of BOLD-100 in combination with FOLFOX for colorectal (CRC), pancreatic (PDAC), gastric (GC) and biliary tract (BTC) cancers. Patients (pts) receive BOLD-100 with FOLFOX on day 1 of each 14-day cycle. In Part A, pts are enrolled in a 3+3 design to determine the combination recommended Phase 2 dose (RP2D), with BOLD-100 dose-escalation (420, 500 and 625 mg/m2) up to dose level 3. Part B comprises 5 cohorts treated at the RP2D until progressive disease or unacceptable toxicity. In Part A, reported here, the primary endpoints are safety, tolerability and maximum tolerated dose; the Part B endpoints are efficacy (primary), pharmacokinetic (PK) and pharmacodynamic parameters (secondary), and duration of response (exploratory) (NCT04421820). **Results:** As of 07 Feb 2022 (contains Part A preliminary data), 19 pts (mean age 65 years) were treated: 9 (47%) CRC, 5 (26%) BTC, 4 (21%) PDAC, 1 (5%) GC. Patients had a median of 3 prior systemic therapies, and 18 (95%) were enrolled with stage IV disease. Median number of cycles completed was 5 (range 1-15). 18 pts reported ≥1 treatment-emergent adverse events (AEs), most commonly fatigue (n = 12, 63%), nausea (n = 9, 47%) and stomatitis (n = 8, 42%). The majority of AEs were grade (G) 1-2. 7 G4 AEs (all neutropenia), and 1 unrelated G5 AE of pulmonary embolism occurred. There were 8 serious AEs in 6 different pts, with 1 SAE of dyspnea reported as related to BOLD-100. 2 pts experienced infusion-related reactions, related to chemotherapy. 2 dose-limiting toxicities have been observed: G3-4 neutropenia complicated by fever > 38.5°C or infection (n = 1, cohort #2) and inability to receive planned doses due to AEs (n = 1, cohort #3). To date for evaluable pts (n = 16), disease control rate of 75%, 1 partial response (48% target lesion reduction) and 11 stable disease have been observed. **Conclusions:** BOLD-100 plus FOLFOX is well-tolerated with no clinically significant safety findings. Dose-escalation data supports a BOLD-100 RP2D of 625 mg/m2 for the expansion phase. Progression-free survival, overall survival, and PK data are forthcoming. Clinical trial information: NCT04421820. Research Sponsor: Bold therapeutics.

3032 **Poster Session**

Increased systemic toxicities from antibody-drug conjugates (ADCs) with cleavable versus non-cleavable linkers: A meta-analysis of commercially available ADCs.

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Background: Though in theory ADCs should deliver high-dose chemotherapy directly to target cells with few systemic effects, in clinical practice numerous side effects have been observed. We hypothesized that ADCs with cleavable linkers would have more systemic toxicities than those with non-cleavable linkers due to the increased free payload released systemically. To compare their side effect profiles, we conducted a meta-analysis of adverse events (AEs) of commercially available ADCs. **Methods:** Systematic review yielded 12 phase II/III clinical trials that led to the FDA approval of commercially available ADCs. Polatuzumab vedotin was not included because it was only studied in combination with other agents. Any grade AEs and grade ≥3 AEs occurring in at least 5% of patients in each study were recorded. The estimated inverse variance weighted absolute average risk and 95% confidence interval (CI) were estimated for each AE. Absolute risk differences and 95% CIs were estimated by linker type. **Results:** Data from 2,417 patients treated with 9 ADCs were pooled. 7 ADCs had cleavable linkers (N = 1,082), and 2 had non-cleavable linkers (N = 1,335). At least half of studies reported thrombocytopenia, neutropenia, anemia, increased AST and ALT, nausea, vomiting, diarrhea, hypokalemia, headache, and fatigue, as well as rates of all grade and grade ≥3 AEs. AEs ≥ grade 3 occurred in 43% of patients overall, 47% in the cleavable linker arms and 34% in the non-cleavable arms. This was significantly different (weighted risk difference -12.9%; 95% CI -17.1% to -8.8%). There was also a significant difference favoring non-cleavable linkers for ≥ grade 3 neutropenia (-9.1%; 95% CI -12% to -6.2%) and ≥ grade 3 anemia (-1.7%; 95% CI -3.3% to -0.1%). Cleavable linkers were significantly associated with increased AST all grade (3.9%; 95% CI 0.3% to 7.5%) and increased ALT all grade (3.7%; 95% CI 0.2% to 7.3%), though notably the CI approached 0 on the low end of difference for each. There was no significant difference in rates of all grade AEs or in rates of discontinuation due to AEs. There was no significant difference in rates of all grade nausea, vomiting, diarrhea, hypokalemia, or headache. Finally, there was no significant difference in rates of grade ≥3 thrombocytopenia, increased AST/ALT, or fatigue. **Conclusions:** Cleavable linkers appear to have significantly higher rates of ≥ grade 3 AEs and neutropenia within the limitations of this non-randomized comparison and treatment of heterogeneous malignancies. The increased payload in the circulation likely accounts for this; however, it may also make them more efficacious, as suggested by the results of the DESTINY-Breast03 trial. In the final analysis, we will compare the efficacy of cleavable vs non-cleavable ADCs indirectly using the standard of care for each tumor and line of therapy, with the exception of breast cancer. Research Sponsor: None.

3033 **Poster Session**

Enabling circulating cell-free mRNA theranostics from PD-L1, ALK, ROS1, NTRK to transcriptomic profiling.

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Background: Circulating cell-free mRNA (cfmRNA) expression can be considered as a compendium of transcripts collected from all organs. It has the capability of integrating functional and genetic information of tissues, highlighting this analyte's unique potential as a non-invasive biomarker in early detection, therapy selection and patient follow-up of cancer management. Plasma cfmRNA is usually made up of degraded small fragments of smaller than 200 nucleotides, very low concentration, and with different terminal modification, these properties make it difficult to detect. We have developed, validated and automated a cfmRNA clinical testing workflow for simultaneous measurement of PD-L1 expression, ALK, ROS1 and NTRK fusions. This proprietary real-time qPCR-based process is exosome-free, highly sensitive and requires only half milliliter of plasma with 72-hour turnaround. A plasma cfmRNA profiling database covering 750 genes in 9 major cancer pathways was also established with novel cancer type-specific characteristics. **Methods:** Circulating cfRNA was extracted from 400 uL of plasma and reverse transcribed to cDNA. The cDNA pool then served as the universal source for multi-biomarker tests. All target primer and probe sets were selected based on RNA secondary structures. Plasma PD-L1 expression, ALK, ROS1, NTRK fusions and transcriptomic profiling were performed by Circulogene CLIA/CAP-complied testing platform. **Results:** Limit of detection (LOD) for PD-L1, ALK/ROS1 and NTRK were 1.0 copy/uL, 17.5 copies/uL and 28 copies/uL, respectively. For scoring of PD-L1 expression, based on Keynote trials, we used the 30th percentile Ct value as cutoff in qPCR which corresponded to IHC $\geq$ 50% TPS; while the 66th percentile Ct value corresponded to IHC $\geq$ 1% TPS. PD-L1 cfmRNA was demonstrated to be an excellent surrogate marker of tissue PD-L1 protein for clinical outcomes with immunotherapy. In a global cfmRNA landscape, a functional transcriptomic databank was also established, including differential gene expression, classification, functional clustering and cancer type-specific signatures. **Conclusions:** Liquid biopsy qPCR tests targeting PD-L1 expression, ALK, ROS1 and NTRK fusions are commercially available and filling the gap of tissue-based assays and NGS. Our groundbreaking cfmRNA work has research, clinical, and diagnostic value, and provides greater dimensionality to the current knowledge of cfmRNA research and makes a significant jump into understanding and devising strategies to tailor cancer Dx and Rx. Research Sponsor: None.

3034 **Poster Session**

Multicancer early detection with a spectroscopic liquid biopsy platform.

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Background: A rapid, low-cost, sensitive, multi-cancer early detection (MCED) test would be transformational in the diagnostics field. Earlier cancer detection and instigation of treatment can increase survival rates. An effective test must accurately identify the small proportion of patients with typically non-specific symptoms who actually have cancer. Such symptoms don't easily segregate by organ system, necessitating a multi-cancer approach. **Methods:** In this large-scale study (n = 2094 patients) we applied the Dxcover Cancer Liquid Biopsy to differentiate cancer against non-cancer, as well as organ specific tests to identify cancers of the brain, breast, colorectal, kidney, lung, ovary, pancreas, and prostate. The test uses Fourier transform infrared spectroscopy to analyze all macromolecules in a minute volume of patient serum, and machine learning to build a classifier of the resultant spectral profiles for calling the likelihood of cancer. **Results:** For the overall cancer classification, our model achieved 90% sensitivity with 61% specificity when tuned for sensitivity, with detection rates of 93% for stage I, 84% for stage II, 92% for stage III and 95% for stage IV. We also tuned for maximum sensitivity or specificity, whilst the other statistic was fixed above a minimum value of 45%. This resulted in 94% sensitivity with 47% specificity, and 94% specificity with 48% sensitivity, respectively. For organ specific cancer classifiers area under the curve values were calculated for all cancers: brain (0.90), breast (0.74), colorectal (0.91), kidney (0.91), lung (0.90), ovarian (0.85), pancreatic (0.81) and prostate (0.85). **Conclusions:** Cancer treatment is often more effective when given earlier and this low-cost strategy can facilitate the requisite earlier diagnosis. With further development, the Dxcover MCED test could have a significant impact on early detection of cancer, which is vital in the quest for improved survival and quality of life. Research Sponsor: Dxcover Ltd.

3035 **Poster Session**

Blood-based detection of actionable alterations from NCI-MATCH patients with no tissue results.

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Background: The National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) multi-arm phase II clinical trial tested tumor tissue from 5,954 patients with advanced refractory cancer to assign treatment based on the molecular profile. Molecular profiling was successful for 93% of patients. For 267 of the patients who were not enrolled because molecular profiling was not successful, plasma cfDNA was evaluated to provide insight into the potential utility of blood-based testing in a broad spectrum of histologies when tissue is not evaluable. **Methods:** Cell-free DNA was extracted from plasma collected from Streck blood tubes and quantitated. Libraries were constructed using ^{3} 15 ng cfDNA into the Illumina TruSight Oncology 500 ctDNA RUO Assay, including unique molecular identifiers and duplex barcodes for error correction. Libraries were sequenced on the NovaSeq 6000 with S4 XP flow cells. **Results:** Of the 267 samples, 250 samples (94%) were evaluable, representing 72 histologies, including colorectal cancer (N = 36), lung adenocarcinoma (N = 15), pancreatic adenocarcinoma (N = 14), and invasive breast carcinoma (N = 12). Of these, 231 (92%) had ^{3} 1 OncoKB annotated mutation, with 208 patients (83%) having putative somatic mutations detected in genes not commonly associated with clonal hematopoiesis. The most common somatic mutations were in *TP53*, *KRAS*, *APC*, and *PIK3CA*, reported in 51%, 20%, 12%, and 12% of patients respectively. A total of 109 patients (44%) had ^{3} 1 actionable mutation of interest (aMOI) reported that could have been used for treatment assignment in the NCI-MATCH clinical trial. After applying histology and molecular exclusions, 75 patients (30%) had ^{3} 1 aMOI. The most common assignable treatment arms were *Z1B/Z1BX1* (palbociclib with *CCND1/2/3*, N = 13), Z1F (copanlisib with *PIK3CA* Mutations, N = 13), S1/S1X1 (trametinib with *NF1* mutation, N = 12), and Z1C/Z1CX1 (palbociclib with *CDK4/CDK6* Amplification and Rb Expression by IHC, N = 10). Mutations in genes commonly associated with clonal hematopoiesis (CH) were prevalent in this population. Along with the expected high frequency of *DNMT3A* (21% of patients) and *TET2* (11%) mutations, *PPM1D* mutations were the highest amongst CH genes, with 61 patients (24%) having ^{3} 1 *PPM1D* mutation, likely due to the heavily pre-treated nature of these patients. **Conclusions:** Variants observed in the blood are consistent with what is reported in the tissue. Using liquid biopsy when tissue is not evaluable can expand the ability of patients to obtain mutation information that can inform treatment compared to using tumor tissue only. Cell-free DNA provided valuable mutation information for these patients and could have resulted in up to an additional 75 patients being eligible for treatment selection based on their mutation profile. These results indicate that blood-based screening could be a tool for future NCI-sponsored clinical studies. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

3036 **Poster Session**

Test performance and clinical validity of circulating tumor DNA (ctDNA) in predicting relapse in solid tumors treated with curative intent therapy.

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Background: Studies have explored the prognostic value of ctDNA in predicting relapse in solid tumors treated with curative intent. These studies have evaluated ctDNA at specific 'landmark' timepoint or over numerous 'surveillance' time points. However, variable results have led to uncertainty about the clinical validity of this tool. Here, we quantify the predictive and discriminatory accuracy of ctDNA and explore sources of heterogeneity at both landmark and surveillance time points across different tumor sites. **Methods:** A search of MEDLINE (host: PubMed) identified studies evaluating ctDNA after curative intent therapy in solid tumors. Odds ratios (OR) for disease recurrence at both landmark and surveillance time points for each study were calculated and pooled in a meta-analysis using the Peto method. Pooled sensitivity and specificity weighted by individual study inverse variance were estimated and meta-regression utilizing linear regression weighted by inverse variance was performed to explore associations between patient and tumor characteristics and the OR for disease recurrence. **Results:** Of 23 studies identified; 16 (750 patients) and 14 studies (853 patients) reported on landmark and surveillance time points respectively. The median time from completion of definitive therapy to landmark testing was 51.5 days (range 3-120). The pooled OR for recurrence at landmark was 22.22 (95% CI 14.82-33.30) and at surveillance was 27.51 (95% CI 19.1-39.63). The pooled sensitivity for ctDNA at landmark and surveillance time points were 59.9% and 73.2%. The corresponding specificities were 90.9% and 86.6%. Subgroup results are shown in the table. There was lower predictive accuracy with the use of tumor site specific panels, in patients receiving adjuvant chemotherapy and in lung cancer. Meta-regression showed that longer time to landmark and higher number of surveillance blood draws were associated with higher prognostic accuracy, as was a history of smoking. **Conclusions:** Although ctDNA at both landmark and surveillance time points shows high prognostic accuracy, it has low sensitivity, suboptimal specificity and therefore weak discriminatory accuracy to predict relapse in patients with solid tumors treated with curative intent. Testing methodology, time points and patient populations need to be optimized before it can be incorporated routinely in clinical practice. Research Sponsor: None.

Surveillance Studies by Subgroup (studies/patients)	OR (95% CI)	Subgroup difference p
Disease site		
1. Lung (5/176)	11.37 (6.13-21.06)	0.001
2. Breast (3/187)	27.76 (13.53-56.95)	
3. Colorectal (5/426)	53.36 (28-101.70)	
4. Bladder (1/64)	104.64 (26.64-410.95)	
Panel		
1. Patient specific (8/605)	51.70 (31.4-85.14)	< 0.001
2. Tumor sitespecific (6/248)	13.28 (7.77-22.70)	
Adjuvant chemotherapy		
1. No (5/287)	58.74 (27.46-125.66)	
2. Yes (9/566)	21.92 (14.46-33.24)	0.03

3037 **Poster Session**

An ultra-sensitive assay using cell-free DNA fragmentomics for multi-cancer early detection.

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Background: Although most cancer can benefit from early detection by more effective treatments and better prognosis, current screening programs are only limited to tumor-specific tests for a subset of common cancers. To benefit a broader population and outweigh the risks of single-cancer tests, an effective and affordable multi-cancer test should be developed for sensitive early detection of multiple cancers and accurate prediction of cancer tissue of origin simultaneously. **Methods:** In this study, we enrolled 971 cancer patients of the most prevalent and lethal cancer types, including primary liver cancer (PLC, *N*= 381), colorectal adenocarcinoma (CRC, *N*= 298), and lung adenocarcinoma (LUAD, *N*= 292), as well as 243 healthy controls. The participants were randomly divided into a training cohort and a test cohort in a 1:1 ratio. Five fragmentomic features representing cfDNA fragmentation size, motif sequence, and copy number variation were extracted from processed whole-genome sequencing (WGS) data of the participants to build the base models. Each base model implemented five machine learning algorithms for model training, and the optimal base models were used to create the final multi-dimensional model through ensemble stacked machine learning. The integrated multi-cancer model is composed of the first-level binary cancer detection model and the second-level multi-classification cancer origin model. The training cohort was used to train the models with 10-fold cross-validation. The test cohort remained untouched during model construction and was solely used for performance evaluation. **Results:** Our cancer samples are highlighted by mostly early-stage diseases (early-stage PLC: 88.5%; CRC: 100.0%; LUAD: 100.0%). The cancer detection model reached an area under the curve (AUC) of 0.983 for differentiating cancer patients from healthy individuals in the test cohort. At 95.0% specificity, the sensitivity of detecting all cancer is 95.5%, and 100.0%, 94.6%, and 90.4% for PLC, CRC, and LUAD, respectively. Its sensitivity is consistently high for early-stage, small-size tumors. The cancer origin model demonstrated an overall 93.1% accuracy for predicting tissue of origin in the test cohort (97.4%, 94.3%, and 85.6% for PLC, CRC, and LUAD, respectively). Furthermore, the model's cancer detection and origin classification performance remained robust when reducing sequencing depth to $1\times$ (cancer detection: $\geq$ 91.5% sensitivity at 95.0% specificity; cancer origin: $\geq$ 91.6% accuracy). **Conclusions:** We utilized multiple plasma cfDNA fragmentomic features to build an ensemble stacked machine learning model. The assay reached ultrasensitivity and accuracy for multi-cancer early detection, shedding light on leveraging cfDNA fragmentomics for early screening in clinical practice. Research Sponsor: None.

3038 **Poster Session**

Utilization of cell-free DNA fragmentomics in minimal residual disease detection for non-small cell lung cancer.

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Background: Non-small-cell lung cancer (NSCLC) is the leading cause of worldwide cancer-related deaths. Currently, ~30-55% of the NSCLC patients develop recurrence due to minimal residual disease (MRD) after receiving surgical resection of the tumor. Therefore, there is an urgent clinical need to accurately predict the MRD risk in post-surgical NSCLC patients. However, the current targeted ctDNA mutation profiling method is limited by the cost of design and synthesis of patient-specific panels and relatively low sensitivity. Cell-free DNA (cfDNA) fragmentomics have recently shown great accuracy and affordability in early cancer detection. This retrospective study aims to develop an ultrasensitive and affordable fragmentomic assay for MRD detection in NSCLC patients. **Methods:** A total of 116 NSCLC patients (54 stage I, 21 stage II, 40 stage III and 1 stage IV), who received curative surgical resections (32 patients relapsed during follow-up, median relapse time: 315.5 days), enrolled in the Lung Cancer Tempo-spatial Heterogeneity (LuCaTH) cohort. A total of 231 plasma samples, collected at 7 days post-surgery and 3 months thereafter, were used for whole-genome sequencings (~5X). The cfDNA fragment size profile was used to fit a Regularized Cox Regression model. A leave-one-out cross-validation (LOOCV) was used to evaluate the model's predictive performance, and the optimal cutoff for predicting relapse was determined by identifying the Youden index to the predicted relative risk for all samples. **Results:** Our machine learning model showed an excellent performance in detecting patients with a high risk of recurrence. At 7 days post-surgery, the high-risk patients detected by our model showed an increased risk of 3 times compared to the low-risk patients (hazard ratio [HR] = 3.2, $p < 0.001$). Multivariate analysis confirmed that the association between model-determined high-risk status and patient relapses was not affected by the baseline clinical variables (age, sex, smoking, stage, etc.). Furthermore, the longitudinal analysis showed that our model was capable of detecting high-risk patients who were 11 times more likely to develop recurrence, independent from other clinical factors (multivariate HR = 11.8, $p < 0.001$). Overall, our model was able to identify high-risk status in 26 of 32 relapsed patients (81.2% sensitivity), preceding radiographic relapse by a median of 216 days. Furthermore, the sensitivity for MRD detection reached 91% while combining the model prediction with mutation-based ctDNA results. **Conclusions:** We have developed a predictive model for patient recurrence by detecting the fragmentomic profiling of plasma cfDNA contributed by the MRD. Despite being limited by the relatively small cohort size, our model has shown great sensitivity in predicting patient recurrence, therefore exhibiting a great potential to guide adjuvant therapy decisions. Research Sponsor: National Science Foundation of China.

3039 **Poster Session**

Plasma first: Accelerating lung cancer diagnosis through liquid biopsy.

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Background: Molecular profiling of tumor tissue is the gold standard for treatment decision making in advanced non-small cell lung cancer. Results may be delayed or unavailable due to insufficient tissue samples or prolonged wait times for biopsy, pathology assessment and testing. We piloted the use of plasma molecular testing as part of the initial diagnostic work-up for patients with suspected advanced lung cancer (NCT04863924). **Methods:** Patients with radiologic evidence of advanced lung cancer referred to the lung rapid diagnostic program underwent plasma circulating tumor DNA (ctDNA) testing using InVisionFirst-Lung, a next-generation sequencing (NGS) assay targeting 37 genes. Standard tissue testing was performed with comprehensive NGS (Oncomine). The primary endpoint was time to treatment in stage IV NSCLC patients compared to an historical pre-COVID-19 cohort (2018-9). Secondary endpoints included actionable targets identified in plasma, % of patients starting targeted therapy based on liquid biopsy and result turnaround time (TAT). **Results:** Between July 1 to December 31, 2021, 60 patients were enrolled. Median age was 70 years (range 33-91), 52% were female, 57% Caucasian, 48% never smokers. Of these, 73% had NSCLC, 12% small cell, 10% non-lung pathology and 5% declined tissue biopsy. Of 44 NSCLC patients, 5 (11%) had early-stage disease and underwent curative therapy. Most stage IV patients (79%) had systemic treatment. Median time to treatment initiation in the study cohort was 34 days (n = 31, range 10-90) versus 62 days (n = 101, range 13-159) in the historical cohort ($p<0.0001$). Two thirds (N = 23) of stage IV NSCLC patients had actionable alterations identified, (30% in current/ex-smokers); 18 started targeted therapy including 10 based on plasma results before tissue results were available. Median TAT was 7 days for plasma from blood draw to reporting (range 4-14) and 26 days for tissue molecular testing (range 11-42), $p<0.0001$. Concordance was high between plasma and tissue testing (70%). Liquid biopsy identified actionable alterations for 3 patients not identified by tissue NGS. In 4 cases, plasma testing failed to identify actionable alterations detected in tissue, due to undetectable plasma ctDNA. **Conclusions:** Liquid biopsy in the initial diagnostic workup of patients with suspected advanced NSCLC leads to faster molecular results and shortens time to treatment compared to tissue testing alone. Supplementing the current standard of tissue molecular testing with a plasma-first approach during the diagnostic work up of patients with suspected advanced lung cancer may increase access to precision medicine and improve patient outcomes. Clinical trial information: NCT04863924. Research Sponsor: Lung Health Foundation, Pharmaceutical/Biotech Company, Princess Margaret Cancer Foundation (Invest in Research Grant), the Division of Medical Oncology/Hematology Fellowship Award, and Merck LCIC.

Actionable alterations detected in stage IV NSCLC (n = 39).

Molecular alteration	N (%)
EGFR L858R	7 (18)
EGFR exon 19 deletion	5 (13)
KRAS G12C	4 (10)
EGFR exon 20 insertion	2 (5)
ERBB2 exon 20 insertion	2 (5)
EGFR L861Q	1 (2.5)
MET exon 14 skipping mutation	1 (2.5)
ALK fusion	1 (2.5)

3040 **Poster Session**

A cell-free RNA-based next-generation sequencing (NGS) assay for the detection of actionable gene fusions in patients with non–small cell lung cancer (NSCLC).

Yukti Choudhury, Chae Yin Cher, Jia Min Ho, Claire Chan, Mun Wei Teh, Kao Chin Ngeow, Michelle Pek; Lucence Diagnostics, Singapore, Singapore; Lucence Health, Palo Alto, CA

Background: Gene fusions and alternate RNA splice forms represent clinically actionable driver and resistance-conferring alterations in NSCLC and other cancers. Where tissue samples are inadequate for molecular testing, liquid biopsies could address the gap in detection of clinically relevant gene fusions. Targeted cell-free (cf) DNA-based NGS methods are typically used for non-invasive blood-based testing of gene fusions, but have limited sensitivity if fusion breakpoints involve long intronic regions or repetitive sequences (e.g. *NTRKs* and *NRG1*). RNA-based approaches are not affected by introns, can identify expressed fusion genes and can discriminate splicing. We developed an NGS assay optimized for cfRNA analyte for the detection of actionable gene fusions and exon deletion/skipping events in liquid biopsies. **Methods:** A highly multiplexed molecular-barcoded primer panel was designed for cfRNA-based detection of actionable fusion genes in NSCLC (*ALK*, *BRAF*, *FGFR2*, *FGFR3*, *MET* (including exon 14 skipping), *NRG1*, *NTRK1/2/3*, *RET* and *ROS1*) covering > 90% of reported driver and partner gene exons in COSMIC database. The panel also targets housekeeping genes as endogenous sample controls. We developed a custom bioinformatics pipeline to call fusions and exon skipping based on split and spanning reads. **Results:** In initial analytical validation using fragmented RNA from pre-characterized reference material (representing 32 unique fusions at known copy numbers), the assay could detect as low as 10 fusion copies with a sensitivity of 97.6% and a specificity of 100%. For clinical testing, cfRNA co-eluted with cfDNA in nucleic acid extracts from plasma was used. In plasma samples (n = 103) from advanced NSCLC, 76% (15/21) of fusions (5 *ALK*, 3 *RET*, 2 *ROS1*, 5 *MET* ex14 skipping, 1 *FGFR3-TACC3*) detected in a clinically validated cfDNA assay (LiquidHALLMARK) were also detected in corresponding cfRNA. In a subset of samples that were driver-negative untreated or tyrosine kinase-inhibitor treated, the cfRNA assay yielded 9 gene fusions or breakpoints (1 *CD74-NRG1*, 4 *BRAF*, 2 *MET*, 2 *FGFR3-TACC3* fusions) that could not be detected by the cfDNA assay. This represents an increase of 8.7% (9/103) of actionable alterations (driver or resistance) identified using cfRNA. Together cfRNA and cfDNA resulted in 30 fusion events to be detected compared to 21 by the cfDNA assay alone, representing a 42.8% (9/21) increase in fusion-specific detection of the combined assay. **Conclusions:** This novel cfRNA assay can detect actionable gene fusions and exon skipping events in liquid biopsies with high sensitivity. Combining cfRNA with more routine cfDNA testing can increase the total actionable diagnostic information from non-invasive testing in NSCLC patients where tissue samples are lacking, especially for gene fusions not amenable to detection in cfDNA. Research Sponsor: Lucence Diagnostics.

3041 **Poster Session**

Early detection of cancer using cell-free DNA (cfDNA) size analysis on a multiplexed amplicon-based next-generation sequencing (NGS) platform.

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Background: Tumor-derived cfDNA fragments are observed to be shorter in length than normal cfDNA. This size (length) difference can be analyzed as a tumor-specific signal. Whole genome or probe hybridization-based NGS methods can capture cfDNA fragments of native sizes. However, amplicon-based NGS assays are not directly amenable to cfDNA size analysis due to predetermination of amplicon sizes by design. Here we present a method to extract relative distribution of cfDNA fragment lengths from a targeted amplicon-based assay and show its utility in cancer detection. **Methods:** The LiquidHALLMARK cfDNA assay is an amplicon-based NGS test for the sensitive detection of genomic alterations in 80 genes. Although panel design is optimized for cfDNA with average amplicon length of ~150 bp, the consecutive tiling design of amplicons for genes with contiguously targeted regions, e.g. *BRCA* permits the formation of longer amplicons (> 150 bp) from physically subsequent primer pairs, provided longer template cfDNA molecules are present. Cancer samples (n = 281), clinically tested by LiquidHALLMARK during Sep 2020-Sep 2021, and healthy samples (n = 28) were included for analysis. For each sample, fragment lengths were inferred from sequencing alignment files, and binned into "short" (0-150 bp) and "long" (151-500 bp) groups. A relative "size ratio" of the total number of short vs. long fragments per sample was calculated, and examined with clinical features, plasma cfDNA concentration (cfDNA/ml) and highest mutation allele frequency (AF%), in a model to predict cancer. **Results:** Calculated size ratios (relative abundance of short fragments) were higher in cancer than normal samples (median 47.6 vs. 31.2, $p < 0.001$). Cholangiocarcinoma and colorectal cancer samples had the highest size ratios (medians: 62.9 and 60.9, respectively) in agreement with a genome-wide NGS study that profiled cfDNA sizes. Size ratios were higher in metastatic (n = 143) compared to early stage (n = 30) lung cancers ($p = 0.0039$), indicating a stage-dependent accumulation of shorter cfDNA fragments. Size ratio was correlated with cfDNA/ml ($r = 0.63$, $p < 0.01$) and AF% ($r = 0.42$, $p < 0.01$). In 20-fold cross-validation of a logistic regression model trained to predict cancer, average area under curve (AUC) was 0.82 using size ratio, 0.86 using cfDNA/ml, and increased to 0.95 with the two features combined. **Conclusions:** Our analysis shows that it is feasible to derive meaningful cfDNA fragment size information from amplicon-based NGS data. Importantly, relative fragment size distributions observed in cancer and healthy plasma samples by this method are concordant with alternate target capture methods. Fragment size ratios derived from relatively small, targeted amplicon panels are a novel feature that, combined with other molecular and clinical features, can enhance non-invasive methods of cancer detection. Research Sponsor: Lucence Diagnostics.

3042 **Poster Session**

Detection of homologous recombination deficiency (HRD) in cell-free DNA (cfDNA) using an amplicon-based next-generation sequencing (NGS) assay.

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Background: Homologous recombination (HR) deficiency is characterized by tumor genomic instability, often due to alterations in *BRCA1/2* and other HR-related genes. HRD predicts sensitivity to PARP inhibitors (PARPi) in prostate, ovarian and breast cancers. For the subset of cancers that have genomic instability without detectable alterations in HR genes, profiling biomarkers of HRD such as loss of heterozygosity (LOH) could identify additional HRD positive (HRD+) patients that may benefit from PARPi. Here, we present a novel cfDNA NGS assay that can detect tumor LOH non-invasively to improve assessment of HRD+ status. **Methods:** An amplicon-based HRD NGS assay covering > 1000 SNPs was developed to detect LOH both globally and on the gene level in cfDNA. Analytical validation was done using LOH+ *BRCA*-mutant cell lines in limiting dilution admixtures. Clinical performance was assessed by benchmarking findings from 46 tumor tissue DNA samples against results from an orthogonal NGS-based genomic scarring assay. Clinical utility of the HRD assay was evaluated in 75 cfDNA samples, including 72% (54/75) from *BRCA*-associated cancers (36 breast, 12 prostate, 4 ovarian, 2 pancreatic) and 28% from other cancer types. All cfDNA samples were previously clinically tested by an NGS assay that included *BRCA1/2* (LiquidHALLMARK). A subset of cfDNA samples identified as HRD+ were further assessed for alterations in 26 key HR genes (*ARID1A, ATM, ATR, ATRX, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCC, FANCG, FANCL, MRE11, NBN, PALB2, PTEN, RAD51, RAD51B, RAD51C, RAD51D, RAD54L,* and *XRCC2*). **Results:** In analytical validation, the assay could detect HRD in admixtures with as low as 18% tumor fraction. In tissue samples, overall concordance of HRD status with the orthogonal test was 91.3% (42/46), with a positive percent agreement of 94.4% (34/36) and negative percent agreement of 80.0% (8/10). In cfDNA, 26.7% (20/75) of samples were HRD+, including 29.6% of *BRCA*-associated cancers (16/54; 12 breast, 2 prostate, 1 ovarian, and 1 pancreatic) and 19.1% (4/21) of other cancer types. In the three HRD+ breast cancers with pathogenic *BRCA* mutations, the assay also identified *BRCA*-specific LOH. Nine HRD+ breast cancers (two *BRCA*+ and seven *BRCA*-) were further analyzed for alterations in 26 HR genes. Of the two *BRCA*+ HRD+ breast cancers, one harbored an additional *PTEN* loss-of-function (LOF) mutation. Of the seven *BRCA*- HRD+ breast cancers, one harbored biallelic *PALB2* and *CDK12* LOF mutations, while another harbored a *CDK12* LOF mutation. **Conclusions:** LOH detection in cfDNA provides additional diagnostic yield of HRD+ status in multiple cancer types, even in the absence of pathogenic HR gene alterations. Further clinical studies to evaluate the utility of HRD detection in cfDNA using LOH and to determine concordance with tumor tissue are ongoing. Research Sponsor: Lucence Diagnostics.

3043 **Poster Session**

Systemic levels of the soluble co-inhibitory immune checkpoints, CTLA-4, LAG-3, PD-1/PD-L1, and TIM-3 are markedly increased in basal cell carcinoma.

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Background: Although co-inhibitory immune checkpoint proteins are primarily involved in promoting inhibitory cell-cell interactions in adaptive immunity, especially tumor immunity, the soluble cell-free variants of these molecules are also detectable in the circulation of cancer patients where they retain immunosuppressive activity. Nevertheless, little is known about the systemic levels of these soluble co-inhibitory immune checkpoints in patients with various subtypes of basal cell carcinoma (BCC), which is the most invasive and treatment-resistant type of this most commonly occurring malignancy. **Methods:** In the current study, we have measured the systemic concentrations of five prominent co-inhibitory immune checkpoints, namely CTLA-4, LAG-3, PD-1/PD-L1 and TIM-3, as well as those of C-reactive protein (CRP) and vitamin D (VD), in a cohort of patients (n = 40) with BCC, relative to those of a group of control participants (n = 20), using the combination of multiplex bead array, laser nephelometry and ELISA technologies, respectively. **Results:** The median systemic concentrations of CRP and VD were comparable between the two groups; however, those of all five immune checkpoints were significantly elevated (P= 0.0184 - P£0.00001), with those of CTLA-4 and PD-1 being highly correlated (r = 0.87; P< 0.00001). **Conclusions:** This seemingly novel finding not only identifies the existence of significant systemic immunosuppression in BCC, but also underscores the therapeutic promise of immune checkpoint targeted therapy, as well as the potential of these proteins to serve as prognostic/predictive biomarkers in BCC. Research Sponsor: University of Pretoria, South Africa.

3044 **Poster Session**

Dysregulation of immune checkpoint proteins in patients with newly diagnosed early breast cancer.

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Background: Checkpoint proteins regulate the immune system. Breast cancer (BC) cells can up-regulate or down-regulate these proteins to evade anti-tumor immune responses. Soluble forms of immune checkpoint molecules (ICMs) can be measured in human plasma. The study aimed to measure the systemic levels of a series of co-stimulatory and co-inhibitory ICMs at diagnosis, post-neo-adjuvant chemotherapy (NAC) and post-surgery in newly- diagnosed BC patients (pts) relative to those of a healthy control group. **Methods:** Soluble ICMs were measured using multiplex bead array technology in plasma from 72 BC pts and 45 healthy controls. Data was prospectively obtained and levels compared between pre-treatment, post-NAC, and post-surgery using non-parametric tests (Mann-Whitney & Kruskal-Wallis). **Results:** Pre-treatment levels of the soluble stimulatory molecules *viz.* GITR ($p<0.0001$), GITRL ($p< 0.020$), CD27 ($p< 0.024$), CD40 ($p< 0.021$), ICOS ($p< 0.009$), as well as the inhibitory molecules PD-L1 ($p< 0.0001$), CTLA-4 ($p< 0.005$), TIM-3 ($p< 0.0004$), HVEM ($p< 0.0004$) were significantly lower in early BC pts compared to controls. Post-treatment, there were significant increases in most ICM levels (Table), with the exception of CTLA-4, which decreased significantly following treatment. On the other hand, pre-treatment plasma concentrations of CCL5 (RANTES) (84.22 vs. 48.72 pg/mL, $p<0.0001$), M-CSF (84.41 vs 13.34 pg/mL, $p<0.0001$), FGF-21 (24.36 vs. 8.64 pg/mL, $p<0.001$) and GDF-15 (806.82 vs. 430.03 pg/mL, $p<0.0001$) were significantly increased in the breast cancer pts compared to healthy controls. A pathological complete response (pCR) was documented in 65% of pts (mostly TNBC). There were no correlations between pre-treatment ICM levels, CCL5, M-CSF, FGF-21 and GDF-15 and pCR. **Conclusions:** We identified low levels of stimulatory and inhibitory ICMs in newly-diagnosed, non-metastatic BC pts compared to healthy controls. Following treatment, with the exception of CTLA-4, most of these pre-treatment abnormalities of systemic ICM levels corrected. NAC is associated with upregulation of sPD-L1 and most other ICMs. These results indicate that early BC is associated with down-regulation of soluble stimulatory and inhibitory ICMs. Newly-diagnosed early BC pts appear to have generalized immune-suppression independent of subtype and stage. To our knowledge, this is the first study to describe the effect of treatment on systemic ICMs in early BC pts. Research Sponsor: CANSA, Pharmaceutical/Biotech Company.

ICM	Control Median (pg/mL)	Diagnosis (Group A) Median (pg/mL)	Post-NAC (Group B) Median (pg/mL)	Post-surgery (Group C) Median (pg/mL)	Group A vs Group B
CD80	2329	1678	3048	3611	P < 0,0001
CTLA-4	2618	1566	598	687	P < 0,0001
LAG-3	150416	131275	464880	500133	P < 0,0001
PD-L1	3342	1647	4794	5215	P < 0,0001
TIM-3	5047	3897	9975	9615	P < 0,0001
CD27	4577	3342	5351	5427	P < 0,0001
CD28	46135	32914	44277	50058	P < 0,0415
GITR	3797	1497	4035	4434	P < 0,0001
ICOS	26506	15123	26586	29746	P < 0,0001

3045 **Poster Session**

Characterization of genomic landscape using comprehensive circulating cell-free tumor DNA next generation sequencing in advanced thyroid carcinoma.

Valentina Tarasova, Jill Tsai, Bryan McIver, Julie E. Hallanger-Johnson, Colleen Veloski, Sarimar Agosto Salgado, Jude Masannat, Leylah Drusbosky, Christine H. Chung; Department of Head and Neck-Endocrine Oncology, Moffitt Cancer Center, Tampa, FL; Guardant Health, Inc., Redwood City, CA; Moffitt Cancer Center, Tampa, FL

Background: Availability of targeted therapies in thyroid carcinoma (TC) has challenged the conventional treatment algorithms and established urgency for timely identification of targetable genetic abnormalities. Tissue-based next generation sequencing (NGS) is often limited by tumor insufficiency and slow turn-around time. Plasma-based circulating tumor DNA (ctDNA) NGS overcomes these barriers and has been widely adopted across advanced-stage solid tumors. To date, plasma-based NGS characterization of genomic alterations in TC has not been determined. Herein, we profile potential actionable mutations detected via ctDNA in patients with advanced TC subtypes. **Methods:** A retrospective analysis of Guardant Health, Inc database was performed using the commercially available Guardant360 plasma-NGS test on advanced metastatic TC samples collected between 2016 and 2021. Patients with papillary TC (PTC), follicular TC (FTC), poorly differentiated TC (PDTC), medullary TC (MTC), and anaplastic TC (ATC) were clustered into four groups (G1: ATC, G2: PTC, FTC, and PDTC, G3: MTC, and G4: unspecified TC). The landscape of genetic alterations, frequencies of alterations in clinically relevant genes, and tumor mutation burden (TMB) were analyzed. **Results:** Of the 1,108 patients included, 47.1% were male. The median age was 65 years old (range 13-98), and 0.18% (n = 5) patients were under 18 years old. Alteration frequencies of selected, clinically relevant genes are demonstrated in the table below. TMB analysis was performed on 315 samples, and the mean TMB was higher in G1 compared to G2, G3, and G4 (p= 0.0029, 0.0826, and 0.0112, respectively). **Conclusions:** Plasma-based comprehensive NGS by Guardant360 may be utilized in patients with advanced metastatic TC for detecting clinically relevant genetic alterations for the selection of available targeted therapies, immunotherapy, or determination of the clinical trial eligibility. Future validation of the clinical utility by analysis of paired tumor and plasma samples is warranted. Research Sponsor: None.

	Group 1 ATC n = 93	Group 2 PTC, FTC, PDTC n = 99	Group 3 MTC n = 34	Group 4 Unspecified TC n = 882	Total n = 1108
BRAF	28.0%	17.2%	5.9%	15.3%	16.2%
RAS (HRAS/KRAS/NRAS)	16.1%	15.2%	2.9%	15.6%	15.3%
RET mutations	2.2%	0	38.2%	4.3%	4.8%
RET fusions	1.1%	0	0	0.9%	0.8%
ALK fusions	0	0	2.9%	0.3%	0.4%
NTRK fusions	0	0	0	0.2%	0.2%
PTEN	7.5%	2.0%	0	4.3%	4.2%
TERT	18.3%	14.1%	0	11.0%	11.5%
TP53	58.1%	29.3%	8.8%	34.9%	35.3%

3046 **Poster Session**

Identification of markers for tumor- and immune-derived extracellular vesicles (EVs) in preclinical models.

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Background: Extracellular Vesicles (EV) are of broad interest as carriers of molecular signatures of tumor progression and cancer treatment response. EVs, which contain nucleic acids, lipids, and proteins, are released from cells for waste excretion and communication. Numerous proteins and markers are expressed within and on the surface of EVs, but classification markers for murine EV subsets are lacking. To identify tumor and dendritic cell- derived EV markers for preclinical models of breast cancer, we investigated surface marker repertoires of EVs produced by the murine breast cancer and dendritic cell lines, 4T1 and DC2.4. **Methods:** Cells were cultured in serum free media for 2 days. EVs were harvested and isolated by ultrafiltration followed by size exclusion chromatography. EV particle size and concentration were estimated by nanoparticle tracking analysis and microBCA. To identify highly expressed EV markers, a mouse EV multiplex flow cytometry assay was performed using detection antibodies, CD9, CD63, and CD81, with sets of >35 barcoded capture beads, representing more than 100 specific capture: detection combinations. EV marker expression was analyzed using the FCM_{PASS}/MPA_{PASS} software (nano.ccr.cancer.gov). > 250 beads were assessed for each capture- and detection- antibody combination for each EV type and dilution tested; mean fluorescent intensity was determined; and pairwise comparisons between test and control sample sets were evaluated by t-tests. **Results:** Breast cancer (4T1)-derived EVs but not dendritic cell (DC2.4)-derived EVs were strongly detected with CD326 (EpCAM) and CD49b (integrin alpha5, VLA-2) capture beads, using each of the three tetraspanin antibodies. Both types of EVs were detected with anti-CD9 and anti-CD81 when captured by anti-CD44 and anti-CD49e (integrin beta1, VLA-5) beads. DC2.4 EVs were distinctively identified by CD11b capture. CD63 capture and detection antibodies robustly recognized EVs from 4T1 but provided minimal recognition of DC2.4 EVs. Mouse serum EVs from non-tumor bearing mice, showed minimal or no detectable CD326 or CD11b. **Conclusions:** Multiparametric MPA_{PASS}-processed EV repertoire analysis of EVs from murine breast cancer and dendritic cell lines identified CD9, CD81, CD44, and CD49e as common epitopes among both types of evaluated EVs. CD326, CD49b, and CD63 distinguished 4T1 from DC2.4 EVs, and CD11b distinctively identified the DC2.4 EVs. The absence of detected CD326+ and CD11b+ in the serum of non-tumor bearing mice indicates the potential of these two markers for detection of specific tumor and antigen presenting cell EV subsets in serum from mice bearing CD326+ tumors such as 4T1. These results establish a foundation for further tests of detection and tracking of tumor-specific CD326+ EVs as "liquid biopsies" in blood samples as correlates to tumor progression and/or response to treatment. Research Sponsor: U.S. National Institutes of Health.

3047 **Poster Session**

Cell-free RNA in liquid biopsy and biomarkers profiling of hematologic and solid tumors.

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Background: Expressed RNA can capture mutations, changes in expression levels due to methylation, and provide information on cell of origin, growth, and proliferation status. We developed an approach to isolate fragmented RNA from peripheral blood plasma and explored its potential to be used in liquid biopsy. **Methods:** Peripheral blood cfRNA was extracted from patients with neoplasms in B-cell (#105), T-cell (#16), Myeloid (#73), and from solid tumors (#44), Normal individuals (#51), and reactive post-transplant (#137). RNA was sequenced using a 1459-gene panel. Expression profile was generated using Cufflinks. **Results:** cfRNA levels of various solid tumor biomarkers (CA-125, CA-15-3, CEA 8, Keratin19, Keratin6A...) were significantly higher ($P < 0.0001$) in samples from solid tumors as compared with normal control. Similarly, cfRNA lymphoid markers (CD19, CD22, CD79A, and CD79B...) and cfRNA myeloid markers (CD33, CD14, CD117, CD56...) were all higher in B-cell lymphoid neoplasms and myeloid neoplasms, respectively ($P < 0.0001$), as compared with control. In evaluating the host immune system, cfRNA CD4:CD8B and CD3D:CD19 ratios in normal controls were as expected (median: 5.92 and 6.87, respectively) and were significantly lower in solid tumors (median 3.40 and 2.23, respectively, $P < 0.0002$). Solid tumor cfRNA showed CTLA4:CD8B ratio significantly higher in tumors than in normal (median 0.74 vs 0.19, $P = 0.0001$), while there was no difference in cfRNA PD-L1:CD8B ratio (median 1.45 vs 1.77, $P = 0.96$). Similar distinct patterns are noted for various cytokine and chemokines. cfRNA was highly predictive of diagnosis (AUC > 0.98) of solid tumors, B-cell lymphoid neoplasms, T-cell lymphoid neoplasms, and myeloid neoplasms as compared with normal control. When a specific neoplastic disease was considered against all cases including control and other neoplasms, the AUC varied between 0.77 and 0.949. **Conclusions:** This data shows that liquid biopsy using targeted sequencing of cfRNA in patients with various types of cancer provides comprehensive and reliable information on the neoplastic disease as well as the host. Research Sponsor: None.

Groups	AUC	Sensitivity (%)	Specificity (%)	No. of genes	Leave one out AUC
Normal (N) vs B-cell Lymphoid	0.984	96.3	98	60	0.995
N vs Myeloid	0.996	96.6	98	30	0.994
N vs Solid tumors	0.997	97.8	98	30	0.98
N vs T-lymphoid	0.999	100	98	30	0.98
N vs Reactive	0.77	82.9	53.7	200	0.624
B-Lymphoid vs all others	0.783	86.8	59	200	0.725
Myeloid vs all others	0.754	78.1	60.7	8	0.743
Solid tumors vs all others	0.817	88.9	62.7	450	0.729
T-Lymphoid vs all others	0.949	93.8	86.9	10	0.881
Reactive vs all others	0.77	82.9	53.4	200	0.641

3048 **Poster Session**

Combining cell-free RNA (cfRNA) with cell-free total nucleic acid (cfTNA) as a new paradigm for liquid biopsy.

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Background: Expressed RNA can capture mutations, gene fusions, and biomarker profiles. In principle, each abnormal cell has one copy of mutated gene, but numerous copies of mutated RNA. Cell-free RNA (cfRNA) is not used due to the assumption that it is degraded. Next Generation Sequencing (NGS) by design is particularly adaptable for fragmented DNA and RNA. We developed an approach to isolate cell-free total nucleic acid (cfTNA) and cell-free RNA (cfRNA) from peripheral blood. Using targeted sequencing, we explored the potential of this approach to detect mutations, fusion mRNA, and copy number variation (CNV) in solid tumors and hematologic neoplasms. **Methods:** Peripheral blood cfTNA and cfRNA were extracted from B-cell lymphoid neoplasms (#105), T-cell neoplasms (#16), Myeloid neoplasms (#73), solid tumors (#44), and Normal individuals (#51), and sequenced using a targeted panel of 1459 genes. **Results:** Numbers of mutations detected in solid tumors and hematologic neoplasms were significantly ($P > 0.0001$) higher in cfRNA (No. = 1229) than in cfTNA (No. = 1004). Overall variant allele frequency (VAF) was significantly higher in cfRNA than in cfTNA ($P < 0.0001$). However, numerous mutations detected by RNA were not detected by cfTNA and vice versa. In general, nonsense mutations were more likely to be detected by cfTNA than by cfRNA and at higher VAF. Low-level mutations (VAF < 10%) were more likely to be detected by cfRNA than by cfTNA. For example, 136 mutations in TP53 gene were detected using cfRNA and only 70 mutations were detected in cfTNA. KRAS mutations were also higher in cfRNA (#33) as compared with cfTNA (#21). In contrast, when most of the mutations were nonsense, as in ASXL1 gene, more mutations were detected by cfTNA (24 vs 23). When mutations were detected in both cfRNA and cfTNA, mutation load (level of mutant copies) was overall slightly higher in cfTNA ($P = 0.06$), likely due to higher degradation of RNA, but varied significantly dependent on the type of mutated gene and type of mutation. cfRNA was reliable in detecting fusion transcripts in solid tumors and in hematologic neoplasms (SLC34A2-ROS1, DDX5-BCL6, ETV6-RUNX1, RUNX1T1-RUNX1, PML-RARA, RUNX1-ZFPM2, DEK-NUP214, EP300-ZNF384) irrespective of the breakpoint or partner gene. The cfTNA detected various CNVs expected by cytogenetic analysis when tumor fraction was adequate (VAF > 10%). **Conclusions:** This data demonstrates that using cfRNA and cfTNA provides complementary comprehensive information for evaluating mutations, fusion genes, and CNV. This approach increased sensitivity and reliability of liquid biopsy. Furthermore, the cfRNA provides critical information on relative expression of various genes that can be used as biomarkers in characterizing the neoplastic process (see ASCO abstract, Liquid Biopsy Based on Cell-Free RNA and Biomarkers profiling of hematologic and solid tumors). Research Sponsor: None.

3049 **Poster Session**

Serum concentrations of oncometabolite, 2-hydroxyglutarate (2HG), as biomarkers for isocitrate dehydrogenase (*IDH1/2*) mutations in cholangiocarcinoma (ICCA).

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Background: Mutations in IDH1/2 genes are common in low-grade glioma (GM) and occur in approximately 20% of intrahepatic cholangiocarcinoma (ICCA). Mutant IDHs leads to preferential accumulation of the R-relative (R2HG) to the S-enantiomer (S2HG) of 2HG. We investigated the utility of circulating R2HG, total R2HG+S2HG (tRS) and ratio of R2HG/S2HG (rRS) as biomarkers in GM and ICCA patients (pts). **Methods:** Blood and tumor tissues samples were obtained from pts with IDH1/2-mutant GM and ICCA. IDH mutation was confirmed by either immunohistochemistry (GM pts) or next generation sequencing (ICCA pts). Samples were analyzed for S2HG and R2HG using a validated HPLC tandem mass spectrometry method. Tissue and serum R2HG, tRS and rRS were compared with paired t-tests for GM pts. Serum S2HG, R2HG, tRS and rRS were compared with unpaired t-tests between GM and ICCA pts. A $p<0.05$ was considered statistically significant. **Results:** Blood and tumor samples were collected from 21 pts (GM = 11, ICCA=10). Tumor tissues were insufficient for analysis in 1 GM and 8 ICCA pts. Tissue S2HG, R2HG, tRS, and rRS were 0.72±0.68 ng/g, 48.92±58.92 ng/g, 66.87±80.35 ng/g and 55.77±36.23 for GM pts. There were no differences in R2HG and tRS between tissue and serum samples, while S2HG was significantly higher in serum samples ($p = 0.001$) and rRS was significantly higher in tissue samples for GM pts ($p = 0.001$). rRS were 144.8 and 244.9 respectively in 2 ICCA pts with sufficient tissues. There was no difference in serum S2HG between GM and ICCA pts. However, serum R2HG, tRS and rRS were significantly higher in ICCA pts. **Conclusions:** In *IDH*1/2 mutant GM and ICCA pts, R2HG was increased relative to S2HG in tumor tissues. In GM pts, the accumulation of R2HG in tumor tissues was not reflected in blood, likely due to the inability of 2HG to diffuse across the blood-brain barrier. Serum R2HG, tRS and rRS were significantly elevated in ICCA pts. These biomarkers have no clinical utilities in GM pts. However, they can potentially be used to identify IDH mutations in ICCA pts, especially given the inability to obtain tumor tissue in some ICCA pts. Clinical trial information: NCT03991832. Research Sponsor: University Health Network, Toronto.

Comparison of S2HG, R2HG, tRS, and rRS in the serum of IDH1/2-mutant ICCA vs. GM pts. SD = standard deviation.

Biomarkers	IDH-mutant ICCA (n = 10)	IDH-mutant GM (n = 11)	p-value
Serum S2HG (SD) (ng/mL)	81.5 ± 48.9	60.8 ± 39.1	0.29
Serum R2HG (SD) (ng/mL)	461.9 ± 397.4	55.0 ± 20.0	0.003
Serum tRS (SD) (ng/mL	543.4 ± 392.7	115.9 ± 54.7	0.002
Serum rRS	7.70 ± 8.58	1.08 ± 0.48	0.02

3050 **Poster Session**

A circulating miRNA-based AI prediction system to identify multiple types of cancer.

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Background: Cancer is a major problem for human health. Development of an early diagnostic tool can increase the survival of cancer patients. Liquid biopsies have many advantages over traditional tumor tissue biopsies. Circulating microRNAs (miRNAs) are one type of liquid biopsies in part because they regulate the expression and thus functions of their target genes. Circulating miRNAs are stable, non-invasive and changes in their expression are detectable in the early stage of cancer progression, often before clear evidence of tissue biopsy/image tests. To date, there are few liquid biopsy-based tools for multiple-cancer diagnosis and their performance is unsatisfactory. The development of a non-invasive, effective early detection system for cancers is urgently needed. **Methods:** We integrated and investigated circulating miRNA expression data of 5046 non-cancer samples along with 3856 cancer samples of 6 major cancer types downloaded from publicly available databases. We used these expression data along with gender to establish a multiple cancer type AI prediction system. Furthermore, we built comprehensive interaction networks (miRNA-drug, miRNA-target gene) and performed functional enrichment analysis. **Results:** We constructed high-performance AI prediction model that can detect and differentiate 6 cancer groups from one non-cancer group. A median of sensitivity of 93.84% in test data was achieved for the multiple cancer classification task. A panel of gender and 15 most important circulating miRNAs was further shown to achieve excellent performance (sensitivity = 90.44%), with just a bit of decrease in the sensitivity of using the full set (gender and 2565 miRNAs). The 15 key circulating miRNAs worked well for the early stage (stage 1: sensitivity = 88%), much better than other liquid-biopsy results reported in the literature. This is important because these miRNAs and the AI system can be used to significantly decrease clinical cost and increase efficiency of early diagnosis, not to mention it is non-invasive. Finally, we constructed comprehensive interaction networks (drug/ target gene) for these key miRNAs to explore potential therapeutic strategies and understand the underlying biological mechanisms. **Conclusions:** In the study, we constructed the multiple-cancer prediction AI system to classify groups of normal individuals and cancer patients of multiple types, while finding key circulating miRNAs. As several key circulating miRNAs were shown to be potential drug targets or serve as diagnosis biomarkers to fulfill the aim of cancer precision medicine, this work represents a significant step toward achieving the goal of developing a non-invasive tool for early diagnosis of cancers. Research Sponsor: Taipei, Taichung, Kaohsiung Veterans General Hospital, Tri-Service General Hospital, Academia Sinica Joint Research Program.

3051 **Poster Session**

Circulating tumor DNA (ctDNA) in HER2 exon 20 insertion mutations and responses in NSCLC HER2 exon 20 insertion treated with poziotinib.

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Background: ctDNA levels in plasma samples permits temporal assessment of tumor mutational status and tumor burden during therapy. Poziotinib is an oral HER2 TKI in development for NSCLC patients harboring HER2 exon 20 insertion mutations. We assessed serial plasma samples for changes in HER2 exon 20 insertion mutations and other driver mutations in first- and second-line patients comparing to clinical response per RECIST1.1. **Methods:** NSCLC patients harboring HER2 exon 20 insertion mutations were enrolled into the poziotinib ZENITH20 using tumor tissue based NGS. Serial plasma samples were collected at baseline, at C3D1, at Day 1 of every other cycle until disease progression. The Guardant360[a] 74-gene liquid biopsy assay was used to assess changes in tumor-associated somatic variants including the target variant HER2 exon20 insertion as well as other emergent driver mutations in ctDNA as expressed as percent variant allele frequency (%VAF). **Results:** 23 first- and second-line NSCLC patients were evaluable with tumor tissue confirmation of HER2 exon 20 insertion mutations. 22 of 23 (96%) had baseline plasma samples with detectable ctDNA. 21 of 22 samples had detectable HER2 exon 20 insertion mutations (mean % VAF 20±5) resulting in a concordance of 95% versus tissue based NGS. 7 patients had serial testing through C7D1 permitting assessment of ctDNA dynamics and comparison to clinical responses. 5 of 7 (71%) serially tested patients treated with poziotinib at 16mg QD had undetectable HER2 exon 20 insertion at C3D1 which was associated with a tumor response PR. Tumor escape (PD) was observed in 2 of the 5 patients which correlated with increases in target HER2 exon 20 insertion VAF in the plasma with the remaining 3 patients ≥PR. Notably, the rise in HER2 exon 20 in ctDNA occurred prior to tumor escape. In one patient treated with poziotinib at 16 mg QD we observed undetectable levels of the HER2 exon 20 insertion in ctDNA at C3D1 which continued through C16. This patient's responses correlated with patient tumor response of SD at C2 which then became PR through C9 and CR through C17. **Conclusions:** Poziotinib treatment resulted in reductions in HER2 exon 20 insertion mutations in ctDNA preceded and correlated with the clinical tumor response. Increases in ctDNA HER2 exon 20 insertion mutations were observed prior to confirmation of tumor escape. Serial monitoring of ctDNA is a potential predictive biomarker for treatment response and disease progression. Future evaluation in a larger population is required to confirm the impact of these findings. Research Sponsor: Spectrum Pharmaceuticals Inc.

3052 **Poster Session**

PD-L1 is overexpressed on tumorspheres cultured from circulating cancer stem cells in patients with breast cancer.

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Background: Circulating cancer cells, and in particular their very rare subpopulation, circulating cancer stem cells (cCSCs), are responsible for recurrence and metastasis. The exact role of cCSCs in escape of cancer from immunosurveillance is still unknown, but recent studies revealed that enhanced PDL-1 expression in cancer stem cells is linked to immune evasion and could crucially contribute to the maintenance of CSC self-renewal. Understanding the mechanisms behind this PDL-1 overexpression in cancer stem cells is critical for developing more effective anti-PD-1/PD-L1 therapy. Therefore the aim of the study was to determine the number of tumorspheres and expression of PD-L1 on tumorspheres cultured from cCSC in breast cancer patients. **Methods:** 110 patients with breast cancer in different stages of disease were included in this study. The determination of circulating cancer stem cells was performed using the sphere-forming assay. Additionally anti-PDL-1 antibody staining was applied to examine PDL-1 expression on breast tumorspheres. **Results:** We have developed an innovative *in vitro* platform for detection of cCSCs from peripheral blood of cancer patients. The number of tumorspheres increased significantly with tumor progression and aggressiveness of primary tumor. Patients with metastatic disease had statistically more tumorspheres as compared to patients without metastasis (30 vs 10/100μl blood, $p < 0.05$). Patients with multiple metastasis had more tumorspheres compared to patients with single metastases (60 vs 30/100μl blood, $p < 0.05$). The number of tumorspheres was positively correlated with Ki-67, Her2 status and grade score in primary breast tumors. We observed high PDL-1 expression and their considerable heterogeneity in enriched tumorspheres. **Conclusions:** The number of tumorspheres cultured from peripheral blood directly reflects aggressiveness and proliferation capacity of primary tumor. The presence of tumorspheres with expression of PDL-1 might suggest their immunregulatory potential. Better understanding of the interaction between cCSCs and tumor immunology may help to identify strategies to eradicate the minor subpopulation that escapes conventional therapy attack, thus providing a solution to the problem of drug resistance and metastasis. Research Sponsor: None.

3053 **Poster Session**

Prospective characterization of circulating tumor cell kinetics in patients treated with radiation therapy per definitive intent oligometastatic paradigm.

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Background: Definitive intent oligometastatic paradigm describes a state with limited metastatic sites amenable to comprehensive radiation therapy (RT). We characterized circulating tumor cell (CTC) kinetics in response to definitive RT among patients with oligometastatic cancer and identify a CTC kinetic profile associated with progression free survival (PFS). **Methods:** In this single-institution prospective correlative biomarker study, we enrolled patients with any solid malignancy, ≤ 5 metastatic sites in ≤3 anatomic organ systems undergoing definitive intent RT to all disease sites. Blood specimens were collected prior to RT (baseline), during RT and at follow up visits up to 24 months post RT. Additional lines of therapy were administered per standard of care. CTCs were captured and enumerated using a previously reported nanotechnology-based assay functionalized with aEpCAM, aHER-2, and aEGFR to facilitate biomimetic cell rolling and dendrimer-mediated multivalent binding. Disease status was assessed per RECIST 1.1 criteria. On exploratory analysis disease status was correlated with CTCs as a continuous and ordinal variable (cut-point upper bound of the 3rd quartile). A favorable CTC clearance profile was defined as a decrease in CTC count between pre-treatment and end of treatment - an unfavorable CTC clearance profile was defined as the opposite. **Results:** We enrolled 43 patients with median follow up of 14.3 months corresponding to 255 CTC measurements. Median baseline CTC count was 28 CTCs/ml (range 0.17-1085). Thirty four patients (79%) received stereotactic body radiation therapy. On Wilcoxon signed-rank test there was no association between pre-treatment CTC count and number of disease sites (median 1 metastatic site/patient, range 1-5) nor metastases site (bone, brain, visceral), $p > 0.05$. Thirty one patients (72%) experienced local or systemic progression at subsequent time points. For 90% of patients, a CTC count <15/ml < 100 days post-RT corresponded to durable local control of irradiated lesions. Patients with a favorable versus unfavorable clearance profile had significantly longer PFS (median 13 vs 4 months, log rank test, $p = 0.0011$). During the post-RT period 24 patients (56%) went on to receive systemic therapy (cytotoxic chemotherapy, hormone therapy, immunotherapy, kinase inhibitors). On logistic regression, CTC > 15/ml at a given time point was associated with clinical disease progression within the subsequent 6 months (odds ratio 3.31, $p = 0.007$). An increase in CTCs to > 15/ml preceded radiographic or biochemical progression in 8 of 31 (26%) of patients experiencing disease progression. **Conclusions:** Our data suggests CTCs may serve as a biomarker for disease control in oligometastatic disease and may predict disease progression prior to standard assessments for patients receiving diverse therapies. Clinical trial information: NCT03161821. Research Sponsor: None.

3054 **Poster Session**

Monitoring engorgement of phagocytic circulating stromal cells during chemo-radiotherapy induction predicts survival in unresectable stage 2/3 NSCLC.

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Background: Circulating stromal cells, ie Cancer Associated Macrophage-Like cells (CAMLs), are prevalent in the circulation of non-small cell lung carcinoma (NSCLC) patients (pts), appearing as giant phagocytic macrophages that represent an inflammatory pro-tumorigenic microenvironment. Previously it was shown that pts with engorged CAMLs of ≥50μm after treatment are prognostic for poor clinical outcomes. However, analyzing the dynamic changes in CAMLs over time or in response to treatment, ie chemoradiation (CRT) and immunotherapy (IMT) has not been evaluated. We monitored n = 182 unresectable NSCLC stage II/III pts treated with CRT alone (n = 91) or with concurrent IMT (n = 91) to evaluate changes in CAMLs before and after CRT induction at it relates to progression free survival (PFS) or overall survival (OS). **Methods:** We prospectively procured pts from 3 different regimes, treated with CRT alone (n = 91), treated concurrently with CRT & Atezolizumab (n = 40, clinical trial NCT02525757), or treated concurrently with Durvalumab (n = 51). We recruited 182 pts with pathologically confirmed stage II/III unresectable NSCLC. A total of 15 mL blood samples were drawn prior to start of therapy at baseline (BL) and ~5 weeks (T1) after CRT induction. Blood filtration was done using CellSieve filters, then CAMLs were identified and measured to evaluate PFS & OS hazard ratios (HRs) by censored univariate and multivariate analyses at 2 years. **Results:** CAMLs were found in 89% of all samples tested. Increases in CAML size between BL & T1 were significantly correlated with worse clinical outcomes, with higher CAML increases correlated with increasingly worse outcomes, including CAML increases >10μm resulting in PFS HR=1.7 p = 0.027 & OS HR=1.9 p = 0.045, through increases >40μm resulting in PFS HR=2.1 p = 0.013 & OS HR=2.5 p = 0.020. Increases of CAMLs >35μm was optimal at stratifying pts PFS HR=2.2 p = 0.005 & OS HR=2.8 p = 0.005. Specifically, pts treated with only CRT and increasing CAMLs >35μmhad significantly worse PFS HR=2.7 p = 0.029 & OS HR=4.1 p = 0.013. In parallel, pts treated with CRT+IMT and increasing CAMLs >35μm had near significance for worse PFS (HR=2.1 p = 0.073) & OS (HR=2.3, p = 0.147), though follow up clinical data is ongoing. **Conclusions:** Our data suggest that in unresectable stage II/III NSCLC, tracking the increase of pro inflammatory immune cells (CAMLs) in circulation during therapy induction can identify pts less responsive to CRT or PD-L1/PD-1 IMTs. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

3055 **Poster Session**

Defining resistance mechanisms to CDK4/6 inhibition in hormone receptor-positive HER2-negative metastatic breast cancer (MBC) through a machine learning approach applied to circulating tumor DNA (ctDNA).

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Background: Although cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) are a primary treatment for hormone receptor-positive/HER2 negative MBC, data regarding resistance mechanisms are still an unmet need. The aim of the study was to highlight new resistance pathways using machine learning (ML) to detect multiparametric patterns in complex datasets. **Methods:** The study retrospectively analyzed a cohort of 610 hormone receptor positive HER2 negative MBC patients (pts) at Northwestern University, Massachusetts General Hospital and Washington University in St. Louis between 2015-2020 with baseline ctDNA testing by Guardant360. Pathways were defined based on previous work (Sanchez-Vega F et al, Cell. 2018) (i.e., RTK, RAS, RAF, MEK, NRF2, ER, WNT, MYC, P53, cell cycle, notch, PI3K). Only pathogenic variants according to OncoKB were included in the models. Associations among single nucleotide (SNVs) and copy number (CNVs) variations, pathway classification and previous exposure to CDK4/6i were explored through logistic regression and Gradient boosted machines (GBMs) ML algorithm. **Results:** at baseline, 322 pts (52.8%) were previously treated with CDK4/6i. The most detected pathway alterations were SNVs in PI3K (37.1%), P53 (31.8%), ER (29.2%) and RTK (22.3%). After stepwise logistic regression, RB1, NF1 and ESR1 SNVs were associated with previous exposure to CDK4/6i (respectively OR: 3.55 P = 0.017; OR: 3.06 P = 0.026 and OR: 1.82 P < 0.001), while SNVs in the ER pathway were associated with CDK4/6i (1.56 P < 0.001). Two GBMs models were designed based on gene variants (training AUC: 0.695, cross validation AUC: 0.631) and oncogenic pathways (training AUC: 0.713, cross validation AUC: 0.619). The highest relative importance (RI) was observed for ESR1 SNVs (RI: 35.35), TP53 SNVs (RI: 11.33), NF1 SNVs (RI: 3.45), SMAD4 SNVs (RI: 3.39) and RB1 SNVs (RI: 3.33). Alterations at a pathway level with the highest RI were ER SNVs (RI: 33.50), P53 SNVs (RI: 14.98), PI3K SNVs (RI: 14.40), RTK SNVs (RI: 10.55), RTK CNVs (RI: 10.26), cell cycle CNVs (RI: 6.99), cell cycle SNVs (RI: 6.77) and RAS SNVs (RI: 6.54). Of the previously highlighted pathway alterations, a significant impact on PFS after ctDNA collection was observed among *de novo* pts treated with CDK4/6i (165 pts) for ER SNVs (P < 0.0001), RTK SNVs (P = 0.0011), RTK CNVs (P = 0.0006), Cell cycle CNVs (P = 0.0010) and Cell cycle SNVs (P = 0.0143). No impact was observed on PFS for pts who had not received a CDK4/6i-based regimen. **Conclusions:** The combination of ctDNA-based datasets and machine learning algorithms defined novel resistance pathways for patients treated with CDK4/6i. Although preliminary, these results suggest that alterations of the ER, RTK and Cell cycle pathways might be crucial to optimize treatment strategy and drug development. Research Sponsor: Lynn Sage Breast Cancer Foundation.

3056 **Poster Session**

Tracking changes in circulating stromal cells and circulating tumor cells predicts responsiveness of new line induction in metastatic breast cancer after 1 cycle of therapy.

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Background: In metastatic Breast Cancer (mBC), Circulating Tumor Cells (CTCs) are established prognostic indicators of patients (pts) not responding to new lines of therapy and who have poor clinical outcomes. However, CTCs are typically found in < 20% of mBC pts and many pts without CTCs will also progress. Recently an inflammatory pro-tumorigenic macrophage emanating from tumor stroma (i.e. Cancer associated macrophage-like cell [CAML]) was found in > 90% of mBC pts and were also indicative of poor clinical outcomes. As CTCs & CAMLs are isolated in conjunction from a single blood sample, and both are prognostic for therapy response, we evaluated CTCs & CAMLs before and after initiation of new therapies in mBC to determine their combined prognostic/predictive values. **Methods:** An observational prospective 2-year multi-institutional study was undertaken to evaluate CTCs & CAMLs before, and after, induction of any new line of therapy in pts with diagnosed mBC (n = 101). Anonymized and blinded blood samples were taken at baseline (BL), prior to starting a new systemic therapy, and a 2nd sample (T1) taken after therapy initiation (~30 days). Blood was filtered by CellSieve filtration. The quantities and subtypes of CTCs & CAMLs were analyzed based on RECIST v1.1 for progression-free survival (PFS) and overall survival (OS) hazard ratios (HRs) by censored univariate & multivariate analysis at 2 years. **Results:** CTCs were identified in 35% (n = 35/101) of pts at BL & 24% (n = 24/101) at T1, with a single CTC at T1 being highly prognostic for worse PFS HR = 6.2 95%CI 3.0-13.2, p < 0.001 & OS (HR = 5.1 95%CI 2.0-13.4, p = 0.002. In parallel, CAMLs were found in 93% of BL and 86% of T1 samples, and whose decreases were significantly prognostic for improved PFS (HR = 2.7, 95%CI 1.4-5.1, p = 0.006) and OS (HR = 4.4 95%CI 1.5-13.2, p = 0.018) when CTCs were absent. Overall ≥1 CTC at T1 (n = 24) had median PFS = 2.4 & mOS = 4.8 months (mos), however, in pts without CTCs plus an increase in CAMLs (n = 36) had mPFS = 5.9 & mOS = 14.1 mos, while in pts without CTCs plus a decrease in CAMLs (n = 41) had mPFS = 14.8 & mOS = 18.8 mos. **Conclusions:** Our data confirms that pts with persistent CTCs have the worst clinical outcomes. Further, simultaneous CAML quantification provided a new dynamic predictive blood based biomarker in pts without detectable CTCs which may be useful to better individualize therapy and improve outcomes, though future studies are need to validate these findings. Research Sponsor: DARPA DOD, Pharmaceutical/Biotech Company.

3057 **Poster Session**

Resolution ctDx FIRST plasma assay as a companion diagnostic for adagrasib and its application to longitudinal monitoring.

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Background: KRAS is one of the most commonly mutated oncogenes in cancer. There is a significant need for new treatment options for patients with non–small cell lung cancer (NSCLC) harboring the *KRAS* G12C mutation. Adagrasib is an investigational, highly selective, oral small molecule inhibitor of KRAS G12C that has demonstrated clinical benefit in patients with *KRAS G12C*–mutant NSCLC and CRC. Detection of KRAS G12C in cfDNA is minimally invasive and is of benefit to NSCLC patients, many without lesions accessible by tissue biopsy testing. **Methods:** Resolution ctDx FIRST is a 113 gene comprehensive genomic profiling assay that identifies oncogenic alterations including substitutions, insertions, deletions, gene fusions, and homozygous deletions using targeted NGS sequencing of cfDNA. The Resolution ctDx FIRST assay is being developed as a companion diagnostic for adagrasib in NSCLC patients of the Mirati Study 849-001. **Results:** The LOD95 for SNVs and indels in KRAS and EGFR at a cfDNA input level of 15ng ranged from 0.34% to 0.82%. No false positives were detected in any samples from healthy donors (N = 60). A total of 230 NSCLC plasma samples were orthogonally tested using a ddPCR assay for *KRAS* G12C, using 76 plasma samples from Study 849-001 where KRAS G12C positive results had previously been obtained by a tissue assay, and 154 commercially procured NSCLC samples representative of the trial population. The PPA and NPA for Resolution ctDx FIRST plasma testing relative to ddPCR assay (95% CI) were 87.0% (75.1–94.6%) and 97.6% (94.1–99.4%) respectively. Of 112 Study 849-001 patients, 71 (63.4%) were tested for KRAS G12C mutations with Resolution ctDx FIRST in pretreatment plasma samples. Seventy-four commercially procured matched tissue and plasma samples were tested by Resolution ctDx FIRST and tissue assay. The PPA and NPA for Resolution ctDx FIRST plasma testing relative to tissue assay (95% CI) were 66.2% (54.0-77.0%) and 100% (94.7-100%) respectively. The detection of *EGFR* variants in the Resolution ctDx FIRST assay was compared to results from a ddPCR assay for each variant. A total of 165 NSCLC plasma samples generated a total of 317 comparative valid results. PPA was 100% for EGFR L858R, 88.9% for EGFR T790M, and 91.3% for EGFR Exon 19 Deletions. NPA was 97.8% for EGFR L858R, 100% for EGFR T790M, and 100% for EGFR Exon 19 Deletions. Application of the assay in longitudinally collected NSCLC and CRC patient samples will be presented highlighting changes of VAF over time including identification of oncogenes involved in emerging resistance. **Conclusions:** The Resolution ctDx FIRST assay offers highly sensitive, specific, and robust test results, and meets analytical requirements for clinical applications. Research Sponsor: Mirati Therapeutics, Inc.

Variant	LoD95 (%MAF)	95% CI (%MAF)
KRAS G12C	0.50%	0.379%, 0.667%
EGFR exon 19 deletions	0.34%	0.241%, 0.476%
EGFR L858R	0.38%	0.289%, 0.493%
EGFR T790M	0.82%	0.680%, 0.989%

3058 **Poster Session**

T-cell receptor repertoire analysis based on RNA sequencing data from tumor cells and tumor-infiltrating lymphocytes.

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Background: T-cell receptor (TCR) repertoire has been thought to be indicative in cancer progression and treatment response. Previous methods mainly focused on peripheral blood or fresh tumor tissue, which were sometimes logistically limited in clinical settings. Tumor-infiltrating lymphocytes (TILs), which harbored TCR characteristics, were also mingled with tumor cells (TCs), which brought hurdles in extracting TCR signals from bulk RNA sequencing data. Here we employed a set of RNA sequencing data from paired FFPE tumor samples and their micro-dissected TILs, to analyze and compare the TCR features in tumor cells and TILs. **Methods:** RNA sequencing data of 14 tumor cell samples and matched TILs were downloaded from NCBI-SRA (accession: PRJEB36554). Raw data were cleaned up by Trim Galore (v0.6.2). TCR clonotypes were assembled and quantified from clean fastq files by MiXCR (v3.0.4). Diversity and clonality metrics were analyzed using VDJtools (v1.2.1) and in-house Pearl scripts. **Results:** The median mapping rates of sequencing reads to TCR regions were 0.29% and 1.80% for TCs and TILs respectively ($p = 0.00051$). TCR diversity of TCs and TILs was characterized by Shannon and Simpson index respectively. The median Shannon index was 1.889 and 2.694 in TCs and TILs ($p = 0.00034$, unpaired Wilcoxon rank-sum test); the median Simpson index was 0.8724 and 0.9420 in TCs and TILs ($p = 0.0058$). **Conclusions:** RNA isolated from clinical FFPE samples could be used for TCR analysis. Micro-dissection of TILs could enhance TCR signals of unprocessed tumor tissues. Research Sponsor: None.

3059 **Poster Session**

Imaging of solid tumors using 68Ga-FAP-2286.

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Background: Fibroblast Activation Protein (FAP) is a transmembrane protein overexpressed on cancer associated fibroblasts (CAFs), and is abundantly present in many epithelial cancers, suggesting FAP is an attractive imaging and therapeutic target. FAP-2286 is a cyclic peptide that binds to FAP and is currently being evaluated as a radioligand therapy to treat patients (pts) with FAP-positive solid tumors. The role of 68Ga-FAP-2286 as a diagnostic agent is unknown. We present an interim analysis of the ability of 68Ga-FAP-2286 to detect metastatic disease across multiple cancer types. **Methods:** This is a first in human Phase I/II study of 68Ga-FAP-2286 (NCT04621435) with a planned total enrollment of 65 pts across 3 cohorts: dosimetry cohort (n = 5), cohort with RECIST measurable disease (n = 30) and a cohort at risk for metastases without measurable disease (n = 30). By the cutoff date of February 12, 2022, 27 pts were enrolled (3 in cohort 1, 15 in cohort 2 and 9 in cohort 3). For each pt, the five largest lesions were included for analysis, and for each lesion, the maximum standardized uptake value (SUVmax) of the 68Ga-FAP-2286 and the size (short axis for lymph nodes) were documented. In pts who had an available FDG PET performed within 8 weeks of 68Ga-FAP-2286 PET, uptake on the two scans was compared. **Results:** Of the 27 enrolled pts, 9 had bladder cancer, 5 sarcoma, 4 head and neck squamous cell cancer (HNSCCA), 3 breast cancer (BC), and 3 castration resistant prostate cancer (CRPC). Most pts (89%, 24/27) had tumors positive for uptake on 68Ga-FAP-2286 PET, including 30 lesions < 1.5 cm, and 17 less than 1.0 cm. 16 pts had a paired FDG PET. In these pts, the average SUVmax on 68Ga-FAP-2286 PET was 244% higher than on FDG PET. Only two pts had higher uptake on FDG PET than on 68Ga-FAP-2286 PET (HNSCCA and DSRCT). The highest relative uptake was seen in 2 pts with BC (both 3.4 times higher on 68Ga-FAP-2286 PET); the average SUVmax in BC was 16.6. The lowest uptake on 68Ga-FAP-2286 PET was CRPC with an average SUVmax of 7.0. Sarcoma had variable uptake with one pt having an SUVmax of 4.5 (Ewing's), while two pts had an SUVmax over 30 (both undifferentiated pleomorphic). Although sarcoma had high uptake on 68Ga-FAP-2286 PET, it was similar to FDG PET uptake across the 5 pts (ratio to FDG PET = 1.0). **Conclusions:** 68Ga-FAP-2286 is a promising imaging agent across cancers, although its benefit is not seen equally. BC had the highest absolute uptake and highest relative uptake compared to FDG PET; prostate cancer had the lowest uptake. Further work should be undertaken to define the settings where 68Ga-FAP-2286 PET may inform clinical decision making, and which pts may benefit from FAP-targeted radioligand therapy. Clinical trial information: NCT04621435. Research Sponsor: Clovis Oncology.

3060 **Poster Session**

Frequency of practice-changing findings identified by comprehensive genomic profiling in non-myeloid hematologic malignancies.

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Background: Comprehensive genomic profiling (CGP) is increasingly used to guide management of myeloid and advanced solid malignancies, but its role in non-myeloid hematologic malignancies is less clear. Studies have found a high rate of potentially actionable variants by CGP in this population, but these do not always translate into clinical practice changes. We aimed to determine the rate at which variants found on CGP changed clinical practice. **Methods:** We retrospectively reviewed a cohort of 101 consecutive patients with non-myeloid hematologic malignancies at Duke, comprising a total of 105 samples that were sent for CGP by FoundationOne Heme (104) or HemeComplete (1) in 2014–2021. We identified variants of clinical significance and classified them by evidence level according to the AMP/ASCO/CAP 2017 guidelines (e.g., for therapies, level A: FDA-approved / in guidelines; B: expert consensus; C: clinical trial / FDA-approved in different tumor type; D: preclinical data). We further identified documented changes in clinical practice that occurred in direct response to CGP results. **Results:** Commonly cited reasons for CGP included guiding therapy selection (27), identifying resistance mutations (19), refining prognosis (14), and clarifying diagnosis (11). Of the 105 samples sent for sequencing, 92 (88%) yielded at least one pathogenic or likely pathogenic variant. CGP resulted after death in 12 patients and within 1 month of death in another 11 patients. Seventy-three out of 101 patients (72%) had at least one variant with therapy sensitizing, diagnostic, or prognostic significance (levels A–C) or associated with therapy resistance (levels A/D). While 61 patients (60%) had a therapy sensitizing variant, only 6 patients (10%) were offered a biomarker-directed therapy. In contrast, the presence of a resistance mutation led to discontinuation of current therapy or influenced future therapy selection in 9 of 13 patients (69%). The absence of a resistance mutation influenced choice of therapy in another 4 patients. Sequencing results also helped clarify a previously uncertain diagnosis in 4 patients and led to medical genetics referrals in 3 patients. **Conclusions:** Comprehensive genomic profiling of non-myeloid hematologic malignancies identified variants of clinical significance in 72% of patients and led to changes in practice in 22% of patients. CGP was often sent late in the clinical course. Research Sponsor: U.S. National Institutes of Health.

	# Patients	# Therapy sensitizing (# acted on)	# Therapy resistant (# acted on)	# Diagnostic significance (# acted on)	# Prognostic significance
CLL	46	C: 32	A: 8 (6), D: 5 (3)	B: 1 (1)	A: 14
B-cell NHL	15	C: 11 (3)	0	B: 4, C: 7 (1)	C: 3
T-cell NHL	15	C: 8 (2)	0	C: 2	C: 2
Histiocytic Neoplasms	11	B: 3, C: 2 (1)	0	C: 1 (1)	0
Plasma Cell Neoplasms	5	C: 4	0	0	B: 1
Other	9	C: 1	0	B: 3, C: 2 (1)	A: 1
Total	101	B: 3, C: 58 (6)	A: 8 (6), D: 5 (3)	B: 8 (1), C: 12 (3)	A: 15, B: 1, C: 5

3061 **Poster Session**

Molecular typing and clinical characteristics of synchronous multiple primary colorectal cancer.

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Background: Synchronous multiple primary colorectal cancer (sMPCC) is clinically rare while its incidence was increasing in the past decade. However, little was known about molecular and clinical features of sMPCC, which might be different from single primary colorectal cancer (CRC). **Methods:** From November 2012 to April 2021, 239 sMPCC from a total of 13276 CRC patients operated in the 6th Affiliated Hospital of Sun Yat-sen University were enrolled in this study. Mismatch repair (MMR) status in each lesion of all 239 patients was examined by immunohistochemistry (IHC). Totally 78 sMPCC patients and 94 single primary CRC patients conducted an 831-gene panel based next-generation sequencing (NGS) (OncoPanscan, Genetronhealth). Somatic mutations and potential pathogenic germline variants were analyzed. Microsatellite instability (MSI) and tumor mutation burden (TMB) were calculated. **Results:** We found that dMMR/MSI-H frequencies in sMPCC were significantly higher than those in single primary CRC, which were confirmed by both IHC (50/239 vs 872/13037, $p < 0.001$) and NGS (17/78 vs 5/94, $p = 0.0022$). According to the MMR/MSI status at different lesion in sMPCC patients, they were further divided into all MSI-H, MSI-H & MSS and all MSS group, with incidences of 16.7%, 4.2% and 79.1%, respectively. With NGS analysis, we found that the most enriched gene mutation type in sMPCC patients was C > T (G > A), and their most frequently mutated genes were *APC* (65%), *KRAS* (46%), *TP53* (31%), *PIK3CA* (25%), *EGFR* (23%), *ARID1A* (18%), *NF1* (18%), *SOX9* (18%), *FAT4* (16%), and *TCF7L2* (15%), whereas those genes in single primary CRC patients were *APC* (71%), *TP53* (64%), *KRAS* (40%), *FBXW7* (20%), *PIK3CA* (13%), *SMAD4* (12%), *ARID1A* (11%), *FAT4* (11%), *CREBBP* (11%), and *NF1* (10%). Moreover, we found that higher TMB was correlated with higher MSI in sMPCC rather than single primary CRC patients. Furthermore, we found that the mutated genes were different among three subgroups. The top 5 mutated genes in MSI-H group were *APC* (68%), *FAT4* (64%), *TCF7L2* (59%), *KMT2B* (55%), *ARID1A* (45%), whereas those in MSI-H & MSS group were *APC* (57%), *KMT2B* (43%), *KMT2C* (43%), *ATM* (43%), *PRKDC* (43%), and those in MSS group were *APC* (66%), *KRAS* (49%), *TP53* (36%), *PIK3CA* (21%), *EGFR* (20%). Finally, we also found that patients with pathogenic/likely pathogenic germline mutations were comparable between sMPCC and single primary CRC, indicating that sMPCC may not be resulted from germline changes. **Conclusions:** Our results revealed that incidences of dMMR/MSI-H in sMPCC were significantly higher than those in single primary CRC. We proposed that MMR/MSI status of each lesion in sMPCC patients should be verified before treatment and these patients could be divided into three subgroups according to their MMR/MSI status. Our findings indicated that sMPCC patients with different MMR/MSI status might be treated with personalized therapies for better management of their disease. Research Sponsor: National Natural Science Foundation of China [Grant No. 81972885] and the 1010 project of the 6th Affiliated Hospital of Sun Yat-sen University [1010CG (2020)-20].

3062 **Poster Session**

Evaluating the utility of fluorine-18 fluorodeoxyglucose (^{18}F-FDG)-positron emission tomography (PET)/ computed tomography (CT) scan in cancer of unknown primary.

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Background: Cancer of unknown primary (CUP) represents a heterogeneous group of metastatic tumours where standardized diagnostic work-up fails to identify the tissue of origin (TOO). Small studies, to date mainly focused on cervical lymph node squamous cell CUP patients, have shown ^{18}F-FDG-PET/CT can change patient management and identify the TOO. We aimed to describe the Peter MacCallum Cancer Centre experience with ^{18}F-FDG PET/CT in CUP with respect to detection of a TOO and its impact on management. A secondary aim was to compare the overall survival (OS) in patients where TOO is detected with those without TOO detection. **Methods**: Retrospective analysis of CUP patients treated between 2014-2020. Patients were identified from medical oncology clinics and PET/CT records. Information regarding demographics, clinicopathological details, CUP subtype as per ESMO guidelines, genomic analysis (If known), suspected TOO as per clinician pre- and post-FDG PET/CT, treatment details pre- and post FDG PET/CT and follow-up were collated from electronic medical records. Clinical details and genomic analysis were used to determine the clinically suspected TOO and compared against independent blinded nuclear medicine specialist FDG-PET/CT reads to determine sensitivity, specificity, accuracy and detection rate of TOO. **Results:** One hundred and forty-seven patients were identified of whom 65% had undergone molecular profiling. The median age at diagnosis was 61 years (range 20-84) and the median follow-up time was 69 months (range, 26–83). The predominant histological subtype was adenocarcinoma (54%). Eighteen percent of patients had a prior cancer history and 29% had a 1st degree relative with a history of cancer. Ninety-three percent were ECOG 0-1, and the dominant metastatic site was lymph nodes (35%). Eighty-one percent were classified as unfavourable CUP subtype as per ESMO guidelines. FDG PET/CT demonstrated a TOO detection rate of 34% with high specificity (98%) and moderate accuracy (78%). FDG PET/CT resulted in a change in management in 22% of patients and identified occult disease sites in 37% of patients. The median OS for all patients was 17.8 months. Median OS was not reached and 12.5 months for favourable and unfavourable CUP subtypes, respectively ($p < 0.0001$). Median OS when a potential TOO was identified on an FDG-PET/CT scan was 25.4 months compared with 9.1 months when a TOO remained elusive. ($p < 0.0001$). Multivariable analysis of survival adjusted for age and sex remained significant for FDG-PET identification of TOO ($p = 0.004$), favourable CUP ($p < 0.001$) and ECOG ≤ 1 ($p < 0.001$). **Conclusions**: ^{18}F-FDG PET/CT plays a complementary role in CUP diagnostic work-up and was able to determine the likely TOO in a third of cases. OS is improved with TOO identification, demonstrating the value of access to a diagnostic PET/CT scan for CUP patients. Research Sponsor: None.

3063 **Poster Session**

Baseline tumor size as prognostic index in patients with cancer receiving experimental targeted agents.

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Background: Several studies showed that high baseline tumor size (BTS) is associated with worse outcomes in cancer patients treated with immunotherapy (IO). However, the prognostic impact of BTS for patients receiving targeted therapies (TT) remains uncertain. **Methods:** We collected clinical data for patients with solid tumors consecutively treated within early phase trials at our institution from 01/2014 to 04/2021. Treatments were categorized as IO-based (if any IO-agent was included) or TT-based (biomarker-matched or not). BTS was calculated as the sum of RECIST 1.1 baseline target lesions. Progression-free survival (PFS), overall survival (OS) and objective-response rate (ORR) were compared between patients with high BTS (> median) and low BTS (≤median). **Results:** 444 patients were eligible for the analysis (220 IO, 151 TT biomarker-matched, 73 TT biomarker-unmatched). Median age was 56 years (interquartile range, IQR 48-64) and median BTS was 69 mm (IQR 40-100). Most represented tumor types were breast (49%), lung (9%), melanoma (5%) stomach, colorectal, head and neck and ovarian (4% each). Patients with low BTS were more often female ($p < 0.001$), had a better performance status (PS, $p = 0.008$), lower LDH ($p < 0.001$), lower neutrophile/lymphocyte ratio (NLR, $p < 0.001$) and higher albumin ($p = 0.003$). OS was significantly longer for patients with low BTS (16.6 vs 8.2 months, $p < 0.001$), including when restricting at those receiving IO (12 vs 7.5 months, $p = 0.005$). Among patients receiving TT, those with lower BTS experienced longer PFS (4.7 vs 3.1 months, $p = 0.002$) and OS (20.5 vs 9.9 months, $p < 0.001$) as compared with those with high BTS. However, BTS was only prognostic among patients receiving biomarker-matched TT, with improved PFS (6.2 vs 3.3 months, $p < 0.001$) and OS (21.2 vs 6.7 months, $p < 0.001$) in the low-BTS subgroup, despite a similar ORR (28% vs 22%, $p = 0.57$). BTS was instead not prognostic among patients receiving unmatched TT, with similar PFS (3.7 vs 4.4 months, $p = 0.30$), OS (19.3 vs 11.8 months, $p = 0.20$) and ORR (33% vs 28%, $p = 0.78$) in the two BTS groups. Multivariate analysis confirmed that BTS was independently associated with PFS ($p = 0.03$) and OS ($p < 0.001$) but not with ORR ($p = 0.11$), regardless of tumor site, treatment category, PS, NLR, sites of metastases and number of prior lines. **Conclusions:** Patients receiving biomarker-matched TT experience longer PFS and OS if having a lower BTS, whereas response rate is not affected by this variable. This difference may reflect the faster emergence of molecular mechanisms of resistance among patients with higher baseline burden. Lower BTS is also confirmed to be associated with longer survival among patients receiving experimental IO. BTS has instead no prognostic value among patients receiving unmatched TT. Research Sponsor: None.

3064 **Poster Session**

A large-scale, multi-center molecular characterization of *MET* fusions in a real-world Chinese population.

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Background: *MET* is a driver gene notable in its diversity of clinically relevant aberrations, including exon 14 skipping, copy number gain, point mutations, and gene fusions. Compared with the former two, *MET* fusions are severely under-reported, leaving unanswered a series of fundamental questions. In this study, we addressed this knowledge gap by screening for and characterizing *MET* fusions in a real-world, multi-center population of Chinese cancer patients. **Methods:** We retrospectively included patients with solid tumors and available genome profiles acquired between August 2015 to May 2021. *MET* fusion-positive (*MET*+) patients were subsequently selected for clinical and molecular characterization. **Results:** A total of 79816 patients across 27 tumor types were screened. We detected 155 putative *MET* fusions from 122 patients, resulting in an overall prevalence of 0.15%. Lung cancer comprised the majority of *MET*+ patients (92, 75.4%). Prevalence was markedly higher in liver, biliary tract cancer, and renal cancer (range 0.52%-0.60%) and lower in ovarian cancer (0.06%). A substantial proportion (48/58, 82.8%) of unique partners were reported for the first time. The fusion partners also turned out to be highly heterogeneous, with *ST7, HLA-DRB1,* and *KIF5B* as the three most common partners. Mutational landscape analysis of lung adenocarcinoma patients (n = 32) revealed high prevalence of aberrant *TP53* in *MET*+ patients as well as *EGFR* L858R, L861Q and *MET* amplification as concurrent alterations. **Conclusions:** This study is, to our knowledge, currently the largest in characterizing *MET* fusions. Our findings warrant further clinical validation and mechanistic study that may translate into therapeutic avenues for *MET* fusion-positive cancer patients. Research Sponsor: Beijing Medical Award Foundation.

3065 **Poster Session**

Independent validation of a novel noninvasive 4-microRNA diagnostic model for multicancer early detection.

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Background: Cancer early detection is critical to reduce mortality as treating early stage cancers is more likely to have better outcomes. We previously developed a diagnostic model based on 4 serum cell-free microRNAs (miRNAs) capable of detecting 12 cancer types with high accuracy (AACR 2022, Poster 2890; Manuscript submitted). In the current study, we aimed to validate this diagnostic model using independent serum microRNA microarray datasets. **Methods:** Four microarray datasets assessing the expression of 2588 serum miRNAs in patients with esophageal squamous cell carcinoma, gastric cancer, prostate cancer and glioma, as well as non-cancer healthy controls with a standardized platform were identified from Gene Expression Omnibus (GEO). The datasets were combined, cases that were redundant among them or with the cases used in our previous study (correlation > 0.99) were excluded. The 4-miRNA model was applied to the final combined dataset to calculate a diagnostic index and make prediction of cancer vs. no-cancer using previously determined algorithm and cut-point. The performance of the diagnostic model was assessed using Receiver Operating Characteristic (ROC) analysis, sensitivity and specificity. **Results:** After excluding redundant cases, the final combined dataset consisted of 3877 subjects, including 447 esophageal, 1267 gastric, 769 prostate and 196 glioma cancer patients, as well as 1198 healthy controls. The 4-miRNA model demonstrated an area under the curve (AUC) of 0.986, 0.995, 0.992 and 0.990 in the ROC analysis, with a sensitivity of 85.0%, 99.6%, 90.6% and 86.7% for esophageal, gastric, prostate and glioma cancers, respectively, while achieving a 99.1% specificity. These performance metrics were highly consistent to those reported in our previous study (Table). **Conclusions:** The study provided an independent validation of the previously developed 4-miRNA model, further demonstrating that the diagnostic model we developed has the potential to be developed into a simple, inexpensive and noninvasive blood test for multi-cancer early detection with high accuracy. Research Sponsor: None.

Comparison of sensitivities of the 4-miRNA diagnostic model in the four cancer types between our previous study vs. the current study.

	Previous Study			Current Study		
Cancer Type	**N**	**AUC**	**Sensitivity**	**N**	**AUC**	**Sensitivity**
Esophageal Squamous Cell Carcinoma	124	0.990	84.7%	447	0.986	85.0%
Gastric Cancer	150	0.999	100%	1267	0.995	99.6%
Prostate Cancer	40	0.996	92.5%	769	0.992	90.6%
Glioma	40	0.996	87.5%	196	0.990	86.7%

3066 **Poster Session**

Comparative analysis of microsatellite instability-high (MSI-H) *BRAF* V600E-mutated versus MSI-H *BRAF* wild type colorectal cancers (CRC), including tumor microenvironment (TME), associated genomic alterations, and immunometabolomic biomarkers.

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Background: The *BRAF*^{V600E} mutation is associated with the hypermethylator phenotype CIMP, which can also lead to the MSI-H phenotype. *BRAF*^{V600E} mutation and MSI-H/dMMR status seem to be biologically intertwined; however, the impact of coexisting *BRAF*^{V600E} mutations on the TME and immunometabolomic features of MSI-H/dMMR CRC tumors is not well characterized. **Methods:** A retrospective review of deidentified records of patients with MSI-H/dMMR CRC tumors was conducted using next-generation sequencing data (Tempus lxT assay: DNA-seq of 595-648 genes at 500x coverage, and full transcriptome RNA-seq). Several immune markers of tumor immunogenicity in *BRAF* wild-type (*BRAF*^{wt}) vs. V600E-mutated (BRAF^{V600E}) tumors were assessed, including tumor mutational burden (TMB), neoantigen tumor burden (NTB, ScanNeo), PD-L1 expression, immune infiltration, and canonical immuno-metabolomic pathways (82 geneset signatures). **Results:** A total of 459 MSI-H/dMMR CRC tumors were analyzed, of which 123 (27%) tumors harbored *BRAF*^{V600E}mutations, and 336 (73%) were *BRAF*^{wt}. MSI-H/dMMR *BRAF*^{V600E} tumors were more frequently identified in females (69% vs. 55%; $P = 0.01$), non-Hispanic or non-Latino (100% vs. 73%; $P = 0.001$), and older patients (median age: 76 yrs vs. 62 yrs; $P < 0.001$). Compared to *BRAF*^{WT}, *BRAF*^{V600E} tumors exhibited significantly higher TMB (Median: 49 mut/MB vs. 36 mut/MB; $P < 0.001$) and were more frequently associated with TMB-High status (> 10 mut/MB; 100% vs. 95%; P = 0.008); however, no significant differences were observed with tumor NTB, immune score, or T cell infiltration (CD4 or CD8). NK cell infiltration was higher in the *BRAF*^{V600E}cohort (< 0.001). When compared to *BRAF*^{WT} tumors, *BRAF*^{V600E} tumors harbored a greater frequency of mutations in *MSH6*(42% vs. 20%), *B2M* (33% vs. 16%), *BRCA2* (31% vs. 12%), *ATM* (23% vs. 12%), and *TP53* (30% vs. 19%) but a lower frequency of *MSH2* (3.3% vs. 11%), all $P < 0.05$. Pathway enrichment analysis identified 10 significantly altered signaling pathways, most of which related to stromal/immune cell signaling and metabolism. Five were upregulated among *BRAF*^{V600E} tumors: glycerophospholipid, galactose, cyclin-dependent cell signaling; Nucleotide, and TH1 inflammation. Five pathways were downregulated (Wnt, Notch, TH17 inflammation, amino sugar, and cancer stem cell signaling). **Conclusions:** MSI-H/dMMR *BRAF*^{V600E} CRCs undergo broad metabolic reprogramming (e.g., glycerophospholipidgalactose, nucleotide). A rise in lipid metabolism, particularly with NK inflammation, suggests that *BRAF*^{V600E}mutated tumors may be associated with a non-classical immune component. *BRAF*^{V600E} and *BRAF*^{wt} CRCs exhibited similar NTB and T cell infiltration, suggesting that both are likely to benefit from immune checkpoint inhibitors. Research Sponsor: None.

3067 **Poster Session**

Impact of *RAS* mutations on immunologic characteristics of the tumor microenvironment (TME) in patients with microsatellite instability-high (MSI-H) or mismatch-repair–deficient (dMMR) colorectal cancer (CRC).

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Background: The KEYNOTE-177 trial demonstrated pembrolizumab's superiority over first-line chemotherapy in patients with MSI-H/dMMR mCRC. However, in a subgroup analysis, patients with *KRAS* or *NRAS* mutations did not show the same favorable PFS benefit with PD-1 blockade therapy (HR 1,19; CI 0.68-2,07). The impact of *RAS* mutations on the immunologic characteristics of the TME of MSI-H/dMMR CRC has not been well characterized. **Methods:** A retrospective review of deidentified records of patients with MSI-H/dMMR CRC tumors was conducted using next-generation sequencing data (Tempus lxT assay, DNA-seq of 595-648 genes at 500x coverage, and full transcriptome RNA-seq). MSI-H determined by assessment of 239 loci by NGS. Several immune markers were assessed, including tumor mutational burden (TMB), neoantigen tumor burden (NTB, ScanNeo), PD-L1 expression, immune infiltration, and canonical immune pathways (82 geneset signatures). **Results:** A total of 463 MSI-H/dMMR CRCs were analyzed, of which 110 (24%) tumors harbored *RAS* mutations (RAS^{mut}) [*KRAS*: 93%, *NRAS* 6% and *HRAS* 1%}, while 353 were *RAS*-wild-type (RAS^{WT}). Compared to MSI-H/dMMR RAS^{WT}, MSI-H/dMMR RAS^{mut} tumors were more frequently identified in males (53% vs. 38%; $P = 0.005$), and younger patients (median age: 57 yrs vs. 71 yrs, $P < 0.001$). Although there were no significant differences in median TMB (40 mut/MB for both, p = 0.9) or frequency of TMB-high status (≥10 mut/MB) between the two groups, RAS^{mut}tumors tended to have a lower tumor NTB (16 vs. 12 neoAg/Mb, $P < 0.001$) and lower % CD8 T cell but higher % CD4 T cell infiltration ($P < 0.05$). Significant differences were observed in genomic alterations co-occurring with RAS^{mut} compared to RAS^{WT} (e.g., *MLH1* (23% vs. 8.8%, P < 0.001), *MSH6 (36% vs. 24%, P = 0.017), APC* (60% vs. 20%, $P < 0.001$), *ARID1A* (54% vs 30%, $P < 0.001$), *PIK3CA* (36% vs 19%, $P < 0.001$), *and TP53* (32% vs. 19%, P = 0.014). Pathway enrichment analysis identified 14 differentially expressed pathways among RAS^{mut} tumors. Four pathways showed significant upregulation, including Hedgehog, Wnt, *TGFβ,* and cancer stem cell pathways. Ten pathways of interest showed significant downregulation among RAS^{mut} tumors. The majority (9/10) were immune-related, including cytokine signaling [*JAK-STAT, TGFβ, TH1*], innate immune [*NK cells*], and adaptive immune events *(CD8 T cell, Tregs*)]. **Conclusions:** MSI-H/dMMR CRCs harboring RAS^{mut} exhibited overall upregulated *WNT/SHH* pathway activity, coupled with reduced NTB, cytokine signaling, and innate and adaptive immune events. *TGFβ* is pleiotropic, and different members were associated with variable modulation. These data suggest that MSI-H/dMMR CRCs harboring *RAS* mutations are less immunogenic and appeared to contain a TME that is less sensitive to immune checkpoint blockade than MSI-H/dMMR RAS^{wt} CRCs. Research Sponsor: None.

3068 **Poster Session**

Lesion-specific radiomics analysis shows promising results for early-stage efficacy assessment of IOA-244 in uveal melanoma.

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Background: Radiomics is an image based approach that allows for characterization and quantification of tumor lesions in cancer patients. Radiomics has been proven capable of potentially adding value in the diagnostic and prognostic patient managment. In this study we evaluated the potential of Radiomics to bring additional insight also in early drug development. **Methods:** All the visible malignant lung and liver metastasis lesions of 7 uveal melanoma patients (86% of women, 60±11y) treated with IOA-244 (EudraCT 2019-000686-20) were manually segmented and analyzed in their size and shape *via* a radiomics approach. The CT scans at baseline and first follow-up (8 weeks) were included in the study and compared. Descriptive statistics and linear mixed effect (LME) models were used to quantify volumetric lesion-specific response to treatment. Response has been defined both as continuous variable and in three discrete categories (lesion shrinkage, stable and progressive disease for a volume change of [-100%;-0%];[0%-+25%] and > 25%, respectively). The influence of lesion shape at baseline (e.g. compactness, elongation or surface roughness among others) on the treatment response has been explore through LME models as well. **Results:** We identified and segmented 126 metastatic lesions (70 lung and 56 liver) from baseline scans and 122 lesions (71 lung and 51 liver) from post treatment scans. Of those, 64% could be consistently mapped between visits, resulting in a total of 147 matching lesions on which the radiomics analysis was performed. We found 19% of complete response and 16% of new lesions appearing. 8 weeks after treatment start, we observed non progressive disease in 61% of all lesions, of which 42% was shrinking. LME did not show a significant change in lesion volume between visits, but the mean difference between visits was negative. LME did show that lesion shape is significantly different between progressors and non-progressors at baseline for lung lesions (compact and irregular lesions are more likely to respond), and that there are moderate correlations (0.4-0.7) between tumor shape and volume change for liver lesions (compact lesions have a larger volume drop). **Conclusions:** This work demonstrates both the clinical potential of IOA-244 for treatment of Uveal Melanoma patients with lesions in the lung and in the liver and the potential of radiomics individual lesion analysis for clinical research in the very early stages of drug development. Lesion evolution volumetric assessment has allowed a more accurate and sensitive understanding of IOA-244 efficacy and impact across different lesions, in both lung and liver. Radiomics showed a promising response of selected population to IOA-244 over the first time point (W0-W8). A further radiomics analysis on next follow-up scans would allow a radiological proof of treatment-induced changes and long-term patient outcome prediction. Research Sponsor: None.

3069 **Poster Session**

The HERPET study: Imaging HER2 expression in breast cancer with the novel PET tracer [^{18}F]GE-226, a first-in-patient study.

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Background: Over-expression the human epidermal growth factor receptor-2 (HER2) is seen in 20% of breast cancers; this is an adverse prognostic factor and used to guide therapy selection. At present HER2 expression can only be determined using biopsy material using immunohistochemistry or fluorescence in situ hybridisation. Heterogeneous expression of HER2 is now being recognised as a cause of treatment resistance but is difficult to characterise. A non-invasive method for determining HER2 expression could have several advantages and help select appropriate therapy for patients. GE-226 is a novel radiolabelled GE-Affibody radioligand which binds to the HER2 receptor with high affinity at a different epitope than trastuzumab. **Methods:** Patients with locally advanced or metastatic breast cancer were recruited and scanned for 65 mins after iv injection of 200MBq of GE-226 (mean activity injected for each patient 202MBq (range 164-223MBq, mean radiochemical purity 94%) of radioligand, over one bed position for dynamic imaging, followed by a half-body scan. Blood sampling was used to measure metabolism of the tracer. Safety was assessed. HER2-extracellular domain (ECD) domain was measured in blood. Tumoural uptake was quantified by semi-quantitative and fquantitative parameters in HER2 positive and HER2 negative tumours. Patients had routine baseline FDG imaging. **Results:** Twenty patients completed the study. GE-226 scans were well tolerated. There were no serious adverse events. GE-226 was slowly metabolised into a single metabolite in the liver; 97% of parent remained at 60 minutes post injection (range 82-100). There was a significant difference in tumoural radioligand uptake between biopsy proven HER2 positive and HER2 negative tumoural patients as measured by SUV_{mean} and SUV_{max} ($p < 0.001$). Comparing HER2 positive to HER2 negative cases, there was also a significant difference between tumour to normal tissue uptake ratios SUV_{mean}. Heterogeneous uptake was observed in three patients, two with interlesional uptake variation and one with intralesional heterogeneity. Tumoural uptake increased over time. Normal physiological uptake in salivary glands and the thyroid gland was noted. GE-226 was able to differentiate between lymphadenopathy due to sarcoidosis and cancer in one patient and was superior to FDG which had shown widespread uptake in the benign and malignant nodes. **Conclusions:** [18F]GE-226 imaging is well tolerated and shows promise for imaging of HER2 positive breast cancer. Further studies with this agent are now planned. Clinical trial information: NCT03827317. Research Sponsor: Medical Research Council (UK), Pharmaceutical/Biotech Company, Medical Research Council.

3070 **Poster Session**

[^{18}F]Fluorothymidine(FLT)-PET imaging of thymidine kinase 1 pharmacodynamics in non-small cell lung cancer treated with pemetrexed.

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Background: Imaging of tumor proliferation has been studied with FLT-PET in various tumor types including NSCLC. Pemetrexed inhibits thymidylate synthase(TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT). TS inhibition upregulates the thymidine salvage pathway including relocalisation of ENT1 to membrane and TK1 activation as a transient "flare" response. We hypothesise that this can be detected as an increase in FLT tumoral uptake that subsequently decreases with reduced proliferation. This study was conducted to assess FLT uptake as an early pharmacodynamics(PD) marker of pemetrexed response. **Methods:** This was an open-label imaging study in 21 patients with Stage 3/4 NSCLC treated with pemetrexed and platinum-based chemotherapy. Patients underwent FLT PET/CT scan at baseline and 4h after administration of pemetrexed. Platinum component of treatment was administered on the day after second FLT scan for cycle 1. Plasma for TK1 activity expression were collected before each scan time point and analysed by ELISA. Percentage change in standardized uptake value (%ΔSUV) was calculated as [SUV(PET2) – SUV(PET1)]/SUV(PET1)*100. Treatment response calculated by RECIST 1. 1 and survival data were collected. **Results:** 17 patients had evaluable PET/CT scans for pemetrexed response. Median percentage difference for SUVmean and SUVmax in tumour lesions increased by 3% and 10.3% respectively. 5 patients showed homogeneous FLT flare at 4h after pemetrexed, 2 patients had decrease, 10 patients had heterogeneous FLT response (regardless of platinum doublet). There was no significant correlation between plasma TK1 activity and FLT flare. At 9 weeks, 4 patients had partial response, 9 stable disease and 4 progressive disease. Baseline and weighted average ΔSUVmax were not associated with survival. The 5 patients with FLT flare in all lesions showed a median OS of 31 months, unlike the group with heterogenous or decrease uptake(15 months). FLT uptake in bone marrow and small bowel significantly increased at 4h (t test $p = 0.004$, $p = 0.004$, respectively) indicating increased thymidine salvage activity. Early FLT uptake was not predictive for tumour RECIST response or OS. In multivariable cox regression analysis, pre-treatment TK1 activity, adjusted for performance status, smoking history and age, independently affected survival in this group ($p = 0.011$). **Conclusions:** Early FLT flare at 4h was seen in NSCLC post pemetrexed administration indicating activation of thymidine salvage pathway. Median overall survival of patients with an FLT flare response was more than twice longer than patients with mixed or no response. However, the small sample size lacked power to show statistical significance in the OS comparison. Further studies should evaluate this and the relationship to other prognostic variables in a larger cohort of patients. Clinical trial information: NCRI UK badge 9249. Research Sponsor: Medical Research Council, UK.

3071 **Poster Session**

Differential expression of somatostatin receptor (SSTR) subtypes across a spectrum of neuroendocrine neoplasms (NENs).

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Background: Targeted therapy of NENs based on the presence of SSTRs fills a unique niche in tumor biology and clinical treatment of patients with solid tumors. SSTRs have multiple isoforms and are collectively expressed in the majority of NENs. However, subtypes are still not routinely tested and thus not assessed for clinical decision-making, especially for patients meriting consideration of targeted radionucleotide therapy. Clarifying the landscape of SSTR subtypes using molecular techniques more sensitive than immunohistochemistry (IHC)-the standard of testing, and identifying associated genomic biomarkers that differ between them, will pave the way for more sophisticated decision-making in the future. Additionally, leveraging transcriptomics to better assess mitotic markers such as Ki-67 to assess tumor grade, would increase diagnostic accuracy. Here we provide initial validation across a spectrum of NENs. **Methods:** 1595 NENs were analyzed using Next Generation Sequencing (592 gene panel, NextSeq), Whole Exome and Transcriptome Sequencing (NovaSeq), and IHC at Caris Life Sciences (Phoenix, AZ). Significance was determined using chi-square, Fisher-Exact or Mann-Whitney U and p-adjusted for multiple comparisons ($q<0.05$) where applicable. **Results:** In a subset of 492 NENs with accompanying tumor grading information, a median *MKI67* (gene encoding Ki-67) TPM value of 2.27 for low-grade (LG-), and 38.7 for high-grade NENs (HG-NENs) was observed ($q<0.05$). Using ROC curve analysis, a threshold of *MKI67* expression (13.4375 TPM) differentiated LG- from HG-NENs, with a true positive rate of 86.84%, a false positive rate of 11.9% and an AUC of 95% and was subsequently applied to the entire cohort to infer HG/LG. Compared to HG-NENs (n = 862), LG-NENs(n = 733) expressed higher levels of SSTR 1(3.5-fold),2 (2.9-fold) and 5 (1.67-fold) and lower levels of SSTR4 (0.28-fold)($q<0.05$). Further, the expression of SSTRs 3 and 4 in HG-NEN ($r_s= 0.63$) and SSTRs 1 and 2 in LG-NENs ($r_s= 0.64$) were positively correlated. Overall, the prevalence of altered *TP53*, *RB1*, *PIK3CA*, *APC*, *KRAS* was higher and *MEN1* was lower in HG-vs LG-NENs ($q<0.05$). For each SSTR subtype, we established high and low cohorts based on median expressions. In LG-NENs, increased alterations in *TP53* and *RB1* were associated with increased expression of SSTRs 1 and 2 and reduced expression of SSTRs 3 and 4. In HG-NENs, increased alterations in APC were associated with increased expression of SSTR 1 and 4 and reduced expression of SSTRs 3 and 5. Additional subtype- and grade-specific alterations were also observed. **Conclusions:** This study provides evidence that WTS and NGS can be leveraged to predict grade of NENs and define characteristic differences in the genomic landscape across SSTR subtypes in HG and LG NENs. Incorporating the molecular profiling of NENs can thus aid in advancing the development of more tailored therapeutic strategies. Research Sponsor: Caris LLC.

3072 **Poster Session**

Image-based detection of *FGFR3*-fusion in urothelial bladder cancer.

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Background: Fibroblast growth factor receptor-3 (FGFR3) is a transmembrane protein, somatically altered in a large spectrum of cancer types. Chromosomal rearrangement resulting in *FGFR3* gene fusions leads to a constitutively active tyrosine kinase, mediating tumorigenesis. *FGFR3*-fusion is a prognostic and predictive marker as well as a validated therapeutic target in urothelial bladder cancer. Both FISH and RT-PCR assays can be used for the detection of *FGFR3* rearrangements while immunohistochemistry lacks sufficient sensitivity and specificity. In recent years advances in next-generation sequencing improved their ability to detect these alterations in clinical settings. However, systemic screening of these alterations is still expensive, time-consuming, and requires expertise personnel for data analysis and interpretation. In this study, we aimed to develop and validate an alternative machine learning (ML) based method for the detection of *FGFR3*-fusions directly from routine pathology hematoxylin and eosin (H&E) slides. **Methods:** A cohort of 388 H&E whole slide images of bladder urothelial carcinoma samples, obtained from the TCGA Research Network (https://www.cancer.gov/tcga) was used. Cases were randomly divided into training (n = 238) and testing (n = 150) sets. Advanced Convolutional Neural Network (CNN) was used to generate the *FGFR3*-fusion classifier on the training set following validation on the testing set. **Results:** Validation of the *FGFR3*-fusion classifier was performed on a cohort of 150 cases from 19 different centers, including three positive cases of *FGFR3-TACC3* fusions and 147 negative cases. The AI-classifier performance was measured in comparison to the TCGA dataset. The model demonstrated 100% sensitivity and 94% specificity, with an Area Under the Curve (AUC) of 0.96. **Conclusions:** Herein, we demonstrate a real-time ML-based genomic testing solution for *FGFR3*-fusion detection in bladder cancer directly from H&E stained slide images. Utilization of such an alternative method can facilitate fast, accurate, and systemic screening of patients if integrated within the routine pathological pipeline supporting targeted therapy treatment for these patients. Research Sponsor: Imagene-AI.

3073 **Poster Session**

Molecular therapy selection in treatment-refractory advanced cancers: A retrospective cohort study determining the utility of TOPOGRAPH knowledge base.

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Background: Comprehensive genomic profiling (CGP) is increasingly used to guide therapy selection in advanced cancer patients who have exhausted standard therapy options. Here we assess the utility of Therapy Oriented Precision Oncology Guidelines for Recommending Anticancer Pharmaceuticals (TOPOGRAPH) to guide matching of drug treatments based on CGP in this setting. **Methods:** This study was conducted in an Australia-wide precision oncology program, the Molecular Screening and Therapeutics Study (MoST, ANZCTR registration ACTRN12616000908437). All patients with advanced cancer after exhausting standard treatments underwent CGP in 2016-2021 were stratified into cohort A (no further therapy received) and B (received ≥1 therapy after CGP). The primary outcome was overall survival (OS) estimated by the Kaplan-Meier method, using the log rank test to assess between-group differences. TOPOGRAPH matched the treatment history to the CGP results, stratified into clinically active (Tiers 1-3, T1-3), investigational (T3B/4), inactive (R2) or unmatched groups. **Results:** Over a median follow-up of 21.7 months (mo) for 2852 patients (75% with rare cancers, n = 2150), the median OS (mOS) from the date of CGP result was 7.0 mo (95% CI 6.4-7.6) for cohort A (n = 1562) and 15.8 mo (95% CI 14.5-16.9) for cohort B (n = 1290). In both cohorts, patients with CGP results matching any TOPOGRAPH tier (T1-4) had shorter OS compared to patients without a matching tier (A: 6.4 v 20.5 mo, hazard ratio for death [HR] 2.15, p<0.001; B: 14.7 v 23.6 mo, HR 1.43, p<0.001). Patients in cohort B receiving matched therapy (n=342, 27%) had a longer mOS than 948 patients who received only unmatched therapy (16.9 v 10.4 mo, HR 0.70, p<0.001). For CGP results matched to T1-3, 122 patients who received a T1-3 therapy had a significantly longer mOS than those who received unmatched therapy (22.1 v 9.8 mo, HR 0.51, p<0.001). For CGP results matched only to T3B/4, a trend toward longer mOS was observed in patients receiving matched therapy in T3B/4 (n = 138, 14.5 v unmatched 10.0 mo, HR 0.81, P = 0.07). In tier-matched analysis, the mOS were not significantly different between patients who received genomics matched v unmatched therapy in T3B (matching outside cognate histotypes, n = 48 v 508, 11.9 v 9.7 mo, HR 0.84, p = 0.36) and T4 (n = 32 v 134; therapy with preclinical/early clinical evidence, 17.1 v 12.2 mo, HR 0.69, p = 0.17). **Conclusions:** TOPOGRAPH is prognostic and likely predictive of treatment effect based on CGP, supporting its utility in guiding molecular therapy selection in patients who have exhausted standard treatment options. Research Sponsor: Office for Health and Medical Research, State of New South Wales and Australian Federal Government.

OS from the next therapy after CGP in cohort B (n = 1290).

Therapy received post CGP	Overall Matched N	mOS (mo)	N	Tier-matched analysis Matched mOS (mo)	Unmatched N	mOS (mo)	HR	P
T1-3	122	22.1	122	22.1	296	9.8	0.51	<0.001
T3B/4	220	14.5	138	14.5	584	10.0	0.81	0.07
Untiered	913	10.5						
R2	35	9.4						

3074 **Poster Session**

Development and validation of Duoseq as a novel diagnostic and companion assay for lymphoma and other cancers.

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Background: While NGS applications of DNAseq and RNAseq have proven to be powerful tools for genomic discovery, NGS remains underutilized in the clinic. We hypothesized that the clinical translation of NGS would be greatly improved by addressing two critical issues: first, having a single assay for both DNA and RNA sequencing, and second, including all the bioinformatics to enable rapid analysis and reporting of clinically relevant findings within 2 days rather than 2-3 weeks which remains the widespread standard. We developed Duoseq to address these issues. **Methods:** In most cancer biopsies, RNA constitutes nearly 80% of the total nucleic acid and DNA only 20%. Duoseq incorporates interfering factors that make the ligation of sequencing barcodes to RNA much less efficient than that to DNA to, in effect, invert the proportion of DNA and RNA from the sample. This enables the efficient generation of high quality DNA and RNA libraries. The assay targets over 450 recurrently altered genes in hematologic cancers. We developed secure bioinformatics software that connects to an Illumina sequencer to render four major classes of clinical measurements: mutations, gene expression (cell of origin in DLBCL), Epstein Barr virus (EBV) status and and common translocations (BCL2, BCL6, MYC, IRF4, CCND1). **Results:** Technicians at three different CLIA labs were trained to perform Duoseq at the respective sites using a local Illumina sequencer. The assay was performed on 111 FFPE lymphoma cases including diffuse large B cell lymphoma, and other B and T cell lymphomas that were characterized using clinical standard assays. The standards included Sanger sequencing or Foundation One testing (mutations), in situ hybridization (EBV), immunohistochemistry or Nanostring (expression) and fluorescent in situ hybridization (translocation). The included Duoseq software provided the bioinformatics results as well as annotations. With a minimum input of 50ng of nucleic acid/sample, Duoseq generated a mean depth of coverage of 438X. We found that, compared to clinical standards, Duoseq performed accurately for mutations (95.9%), EBV status (96.5%), translocations (94.1%) and expression (100%). In addition, Duoseq provided information on clonality, specific translocation partners and identified novel fusions that were not available from standard assays. **Conclusions:** Duoseq accurately recapitulates the clinical workup of lymphomas replacing the need for single analyte tests such as FISH, while providing a wealth of additional data. The simplicity of the assay and the included bioinformatics software enables its performance at any clinical lab without the need for specialized personnel or computing infrastructure. We anticipate the application of Duoseq as a diagnostic assay, as well as in clinical trial selection and companion diagnostic applications owing to its high accuracy and short turnaround time. Research Sponsor: Data Driven Bioscience.

3075 **Poster Session**

Real-world utilization of ctDNA in the management of colorectal cancer.

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Background: The utilization of circulating tumor DNA (ctDNA) as a non-invasive biomarker for the detection of minimal residual disease, prediction of recurrence in the post-operative setting, and real-time monitoring of treatment efficacy has the potential to vastly improve the care and outcomes of patients with colorectal cancer (CRC). In August of 2020, ctDNA testing first gained approval for use in solid tumors and its prognostic benefit after curative intent surgery has been demonstrated to exceed that of prior standard of care clinicopathological criteria in CRC patients. The comprehensive integration of validated ctDNA approaches into the routine clinical care of patients with CRC would not only fundamentally change how risk of recurrence is assessed but could also reduce treatment with unneeded/unwarranted toxic therapies and allow for earlier recognition and treatment in cases with a high risk of relapse. This survey-based study aimed to evaluate the utilization of ctDNA testing in the management of CRC among practicing community oncologists in the U.S. **Methods:** Questions related to ctDNA utilization for patients with CRC were presented to community oncologists during a virtual meeting held in July 2021. Descriptive statistics were used to analyze the results. **Results:** Of 55 participating oncologists geographically distributed across the U.S., 49% indicated not using ctDNA to make treatment decisions in CRC. A proportion of physicians reported using ctDNA to detect recurrence (27% of physicians); make decisions around post-resection adjuvant therapy (25%); monitor disease progression/relapse (18%); and track tumor resistance during treatment (9%). The most frequently cited barriers to ordering ctDNA testing for patients with metastatic CRC were reimbursement issues (reported by 56% of oncologists), insufficient clinical evidence (46%), and limited familiarity with ctDNA use (28%). Oncologists reported that the following would increase their utilization of ctDNA testing: more clinical evidence of the utility of ctDNA (reported by 66% of physicians), increased education on methodology (60%), more education on the use of ctDNA (57%), more financial aid and reimbursement support for patients (49%), more decision support tools (47%), and better communication between physicians and vendors (26%). **Conclusions:** These findings demonstrate limited adoption of ctDNA testing by community oncologists in the care of CRC patients. Insufficient demonstration of clinical utility, limited familiarity with methodology, and reimbursement issues were cited as barriers to uptake. Education for community oncology providers about ctDNA testing and its demonstrated clinical utility, and increased financial support for patients may improve its utilization and adoption in CRC to improve patient outcomes and care. Research Sponsor: None.

3076 **Poster Session**

Repeat large panel genomic sequencing identifies actionable alterations and characterizes the genomic landscape in patients with metastatic solid tumors.

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Background: The implementation of genomic profiling with next generation sequencing has revolutionized the field of precision oncology. Comprehensive genomic testing of tumors to identify actionable genomic alterations is now commonly performed in the care of patients with advanced/metastatic disease. Although the genomic profile of tumors has been shown to evolve with progression and intervening treatments, the role of repeat genomic testing is not well established. We sought to determine the evolution of actionable genomic alterations in patients undergoing repeat genomic testing on the same comprehensive genomic panel. **Methods:** We retrospectively examined the molecular profiles and medical records of 262 patients with metastatic solid tumors treated in MD Anderson who underwent genomic testing on the same panel (Oncomine, Thermo Fisher) for the detection of somatic mutations in the coding sequence of 143 cancer-related genes, on at least 2 separate occasions. Genomic alterations were reviewed by a central Precision Oncology Decision Support (PODS) team in order to provide annotations at the alteration level on the functional significance. **Results:** 262 patients underwent repeat genomic testing using the same genomic panel on samples collected at different time points from July 2010 to Dec 2021 across tumor types. Changes in alterations (gain or loss) were identified on repeat testing in most patients (66%) We then specifically assessed changes in alterations that were categorized as actionable if annotated by the PODS team at the time of reporting. A gain or loss of an actionable alteration was detected in 38% (100/262) patients. New actionable alterations were frequently identified (73%; 73/100), while 41% had loss of an actionable alteration (41/100). 14% had both loss and gain of actionable alteration on repeat testing; 58% had new actionable alteration identified alone; 27% had loss of actionable alteration only. Actionable alterations identified on repeat testing included alterations in *PI3K/AKT* (27%), *EGFR* (15%), and *MAPK (*16%). On repeat testing, changes in ^{3}2 actionable alterations were frequently identified in the same test (43%). **Conclusions:** Repeat large panel genomic testing identifies both gain and loss of actionable alterations in patients with advanced metastatic cancers. Actionable aberrations frequently co-exist with alterations in a variety of other genes, which highlights the complexities of treating patients with metastatic cancer on progression of disease and suggests that tailored combination strategies may be necessary in these patients. Research Sponsor: None.

3077 **Poster Session**

Use of clinical RNA-sequencing in the detection of actionable fusions compared to DNA-sequencing alone.

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Background: While targeted DNA-seq can detect clinically actionable fusions in tumor tissue samples, technical and analytical challenges may give rise to false negatives. RNA-based, whole-exome sequencing provides a complementary method for fusion detection, and may improve the identification of actionable variants. In this study, we quantify this benefit using a large, real-world clinical dataset to assess actionable fusions detected from RNA in conjunction with DNA profiling. **Methods:** Using the Tempus Research Database, we retrospectively analyzed a de-identified dataset of ~80K samples (77.4K patients) profiled with the Tempus xT assay (both DNA-seq with fusion detection in 21 genes and whole exome capture RNA-seq). Only patients that had successful RNA- and DNA-seq were included. Fusions were detected using the Tempus bioinformatic and clinical workflow. Candidate fusions were filtered based on read support thresholds, fusion annotation (*i.e.,* breakpoints, reading frame, conserved domains), and manual review. OncoKB was used to select fusion alterations in levels 1 and 2 and to identify those indication-matched to targeted therapies. **Results:** We identified 2118 level 1 and 2 fusion events across 1945 patients across 20 different cancer types. Most fusions were observed in non-small cell lung cancer (NSCLC) (25%) and biliary cancer (9%) samples. Of the 2118 fusion events, 29.1% (616) were detected only through RNA-seq while 4.8% (101) of the events were identifiable only through DNA-seq. Notably, 69.4% of fusions in low-grade glioma and 58.2% in sarcomas were detected only by RNA-seq. When evaluating specific gene fusion events, RNA-seq consistently improved the detection of fusions compared to DNA-seq alone (Table) across all cancer types. A total of 1106 fusions were classified as targetable by OncoKB indication-matched therapies with 19% (214) of these identifiable through RNA-seq alone, 5% (54) by DNA-seq alone, and 76% (838) identifiable through RNA- and DNA-seq. Overall, fusions identified through RNA-seq alone led to a 24% increase in the number of patients who were eligible to receive matched therapies (214 / 892). This included imatinib for patients with CML/BLCL (69.8%), crizotinib for NSCLC (40.3%) and entrectinib for *NTRK* and *ROS1* fusions (32.5%). **Conclusions:** The addition of RNA-seq to DNA-seq significantly increased the detection of fusion events and ability to match patients to targeted therapies. Results support consideration of combined RNA-DNA-seq for standard-of-care fusion calling. Research Sponsor: None.

All fusion events.

Fusion	N	% Both RNA+DNA	% DNA only	% RNA only
ALK-*	386	78.0	4.1	17.9
FGFR2-*	384	69.3	9.1	21.6
FGFR3-*	307	73.6	2.9	23.5
BRAF-*	289	30.4	1.4	68.2
NTRK1/2/3-*	198	65.7	11.1	23.2
RET-*	191	85.3	4.2	10.5
BCR-ABL	130	87.7	1.5	10.8
ROS-*	113	70.8	1.8	27.4
Others	118	28.0	3.4	68.6
All	**2118**	**66.1**	**4.8**	**29.1**

3078 **Poster Session**

Pathogenic fusion detection in solid malignancies utilizing RNA-DNA based comprehensive genomic profiling (CGP) testing.

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Background: Gene fusions caused by chromosomal rearrangements comprise a key category of oncogenic driver mutations. However, given the diverse array of potentially novel loci where each proto-oncogene can translocate, many assays including DNA-based CGP have technical limitations that disallow the detection of all relevant fusion partners potentially leading to false negatives. Hybrid Capture RNA sequencing renders a more comprehensive evaluation of genes and allows detection of novel and known fusion partners. Here we assessed the impact of utilizing in-house CGP testing with a paired RNA-DNA hybrid assay in the identification of pathogenic fusions and their potential clinical actionability for patients with solid tumors across a large US health system. **Methods:** Patients in the Providence health system diagnosed with advanced solid tumor malignancies over a two-year period (2019-2021) received reflex CGP testing at the time of diagnosis utilizing an internally validated workflow. DNA/RNA sequencing results as well as histology and staging information were curated from deidentified electronic medical records and in-house databases, and tumor types were mapped to OncoTree tissue categories. Potential clinical actionability was assessed based on OncoKB therapeutic levels 1-3 and clinical trial eligibility matched to the biomarker inclusion criteria for ASCO TAPUR, NCI-MATCH and MyPathway studies (both without time limits and at time of testing). **Results:** The median patient age at diagnosis was 67 years, 52% of patients were female, and the majority (80%) were white. Across all tested advanced solid tumors, 6.7% (217/3218) were found to harbor a pathogenic fusion. The tumor types most enriched in this set of pathogenic fusions were prostate (30%), lung (27%), CUP (10%) and breast (9%). 29% (n = 64) of the identified pathogenic fusions were identified as actionable based on OncoKB criteria (levels 1-3), and 31% (n = 69) matched to one or more arms in the ASCO TAPUR, NCI-MATCH or MyPathway basket clinical trials. The most frequent actionable fusion driver genes identified were *ALK* (12%), *FGFR 1-3* (12%), *RET* (7%) *NTRK 1-3* (3%), and *ROS1* (2%) and a subset of these key drivers were fused with novel gene pairs. A subset of fusions cooccurred with other targetable biomarkers, with the most common comprising tumor mutational burden high (TMB-H) (13%), *PIK3CA* (7%) and high microsatellite instability (MSI-H) (2%). **Conclusions:** In-house CGP testing utilizing an RNA-DNA based assay identified actionable fusion targets across tumor types, with many novel fusion partners that may be undetectable by prior generation sequencing assays. While many of these actionable targets are rare individually, the expanding totality of actionable gene alterations supports the growing utility of CGP for identifying patients who are candidates for approved targeted therapies and clinical trials. Research Sponsor: Illumina grant.

3079 **Poster Session**

DNA methylation profiling to determine the primary sites of metastatic cancers using formalin-fixed paraffin-embedded tissues.

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Background: Metastatic cancers with uncertain primary sites account for a significant portion of new cases. Among them, 3-9% are eventually assigned to cancer of unknown primary (CUP) site after a comprehensive diagnostic workup. Accurate identification of the primary site is the starting point for cancer diagnosis worldwide, and it is critical to guide the subsequent treatments of metastatic cancers. Here we presented a new DNA methylation sequencing-based method to predict the tissues of origin for metastatic cancers, including CUP. **Methods:** Cancer diagnosis relies substantially on histological and immunohistochemical analyses of formalin-fixed paraffin-embedded (FFPE) tissues. To take advantage of sample accessibility, we developed an optimized and streamlined method that was particularly used to generate reduced represent bisulfite sequencing (RRBS) libraries for genome-wide DNA methylation profiling with degraded DNA fragments. After confirming that data quality generated using the new FFPE-RRBS method was comparable with regular RRBS, we created an RRBS database using 541 fresh frozen samples across ten most common cancer types and 58 tumor-adjacent normal tissues. By incorporating four distinct methylation summary scores and seven machine learning approaches, 28 models were trained and compared for multi-class classification using our database. Lastly, we selected the best classifier to predict the tissues of origin utilizing 249 FFPE samples across ten metastatic cancer types and 12 FFPE samples from CUP patients. Meanwhile, the classifier was also cross-validated using a DNA methylation microarray data set of 4702 patients diagnosed with corresponding primary cancers in the TCGA project. **Results:** FFPE-RRBS allowed to construct decent libraries with heavily degraded genomic DNA within 20 hours. Comparable DNA methylation metrics were obtained for the RRBS libraries of paired primary cancer tissues (fresh frozen vs. FFPE) and the libraries of paired FFPE samples derived from primary and metastatic tissues. Among the 28 methylation-based classifiers, the mean methylation-based LinearSVC model performed the best, achieving an overall accuracy of 81% with an AUC of 0.95 in determining the primary sites of 10 metastatic cancers. In a cross-validation assay using the TCGA data set of 4702 cancer patients, the overall prediction accuracy and AUC were 92% and 0.99, respectively. Lastly, our model successfully identified the tissues of origin in 10 of 12 CUP patients in a prospective study. **Conclusions:** The FFPE-RRBS is a novel method for efficient profiling of heavily degraded FFPE samples and the mean methylation-based LinearSVC model can predict the tissues of origin for metastatic cancers and CUP with high accuracy. Research Sponsor: Affiliated Hangzhou First People's Hospital, Cancer Center, Zhejiang University School of Medicine.

3080 **Poster Session**

A first-in-human phase I study of CTX-712 in patients with advanced, relapsed or refractory malignant tumors.

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Background: CTX-712 is a first in class, orally available, highly potent and selective small-molecular inhibitor of CDC2-like kinase (CLK), a key regulator of the RNA splicing process that plays a critical role in driving cell growth. CTX-712 demonstrated potent inhibition of proliferation in a variety of human tumor cell lines in vitro and elicited robust antitumor activity in vivo in multiple xenograft models. The objectives of this study are to determine the recommended dose (RD) by evaluating maximum tolerated dose (MTD) and dose limiting toxicity (DLT), safety, pharmacokinetics (PK) and pharmacodynamics (PD) profiles, and preliminary efficacy of CTX-712 in patients with solid tumors (ST) and hematologic malignancies (HM). **Methods:** This study consists of ST and HM dose escalation cohorts to identify MTD and ST dose expansion cohort to identify RD. The ST dose escalation cohort was initiated with accelerated titration and then switched to a 3+3 design (10, 20, 40, 70, 105, 140 and 175 mg/body twice a week in 28-day cycles). The initial dose of HM dose escalation cohort was decided from the safety information of ST dose escalation cohort. A 3+3 design was used in HM dose escalation cohort. **Results:** As of Dec. 31, 2021, 30 patients were enrolled (16 in the ST dose escalation cohort (10/20/40/70 mg [1], 105/175 mg [3], 140 mg [6]), 10 in the ST expansion cohort, and 4 in the HM dose escalation cohort). In the ST dose escalation cohorts, DLTs were observed in 2 patients (140 mg [platelet count decreased, hypokalemia], 175 mg [dehydration]) and MTD was determined to be 140 mg. Based on this safety information, the ST dose expansion cohort and the HM dose escalation cohort were initiated with the dose of 105 mg twice a week. Among all enrolled patients, the common any-grade Adverse Events (AEs) (≥30%) were nausea (97%), vomiting (63%), diarrhoea (63%), decreased appetite (57%), blood creatinine increased (40%), dysgeusia (37%), constipation (33%), pyrexia (33%) and white blood cell count decreased (30%). The most common Grade 3 or higher AEs were hypokalemia (10%), amylase increased and platelet count decreased (7%). In PK analysis, a dose-dependent increase in systemic exposure of CTX-712 was observed. PD response was assessed in RNA extracted from peripheral blood cells. Dose dependent increases of exon skipping in two marker RNAs were detected. Two Partial Responses and two Complete Responses were observed in ST and HM, respectively. **Conclusions:** CTX-712 demonstrated an acceptable safety profile with early signs of clinical antitumor activity, establishing the initial proof of concept of the CLK inhibitor. Observed DLTs included dehydration, platelet count decreased, and hypokalemia. Investigation is ongoing to determine RD. Clinical trial information: JapicCTI-184188. Research Sponsor: Chordia Therapeutics Inc.

3081 **Poster Session**

First-in-human phase 1/2 dose escalation and expansion study evaluating first-in-class eIF4A inhibitor zotatifin in patients with solid tumors.

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Background: Zotatifin (eFT226) is a first in class, potent and sequence selective inhibitor of RNA helicase eIF4A1 that promotes stable mRNA:eIF4A:drug ternary complex at specific polypurine motifs within the 5'-UTR, preventing ribosome docking and thus, efficient translation of select transcripts. In preclinical models zotatifin treatment simultaneously down-regulated translation of numerous oncogenes with complex 5' mRNA structures, including ERBB2, FGFR1/2, EGFR, KRAS, and CCND1. **Methods:** Patients (pts) with select advanced solid tumors harboring mutations/amplification of ERBB2, FGFR1, FGFR2, EGFR, or KRAS or with pancreatic cancer were enrolled into 3+3 dose escalation portion of the protocol (Part 1), and indication specific expansions continue to enroll at recommended phase 2 dose (RP2D; Part 2). The primary endpoints of Part 1 include determination of safety, tolerability, and maximum tolerated dose (MTD)/RP2D; additional endpoints include characterization of pharmacokinetic, pharmacodynamic (including from blood-based assay during escalation and from pre- and on-treatment biopsy at/near MTD with reverse phase protein array (RPPA)), and initial efficacy. **Results:** As of cut-off date Jan 13, 2022, Dose escalation phase (Part 1) included 37 patients treated with zotatifin at dose levels: 0.005, 0.01, 0.02, 0.035 mg/Kg IV weekly, and 0.035, 0.05, 0.07, 0.1 mg/kg IV 2 weeks-on and 1 week-off. DLTs were observed in 3 patients: Gr 2 thrombocytopenia (0.035 mg/kg weekly), Gr 3 anemia (0.1 mg/kg) and Gr 3 gastrointestinal bleed resulting in anemia (0.1 mg/kg). MTD/RP2D is 0.07 mg/Kg IV 2 weeks-on and 1 week-off. The most common treatment emergent adverse events (TEAEs) in Part 1 include: fatigue, anemia, diarrhea and dyspnea. The most common AEs at RP2D (n = 16 pts; Part 1 and Part 2) include: anemia (25% all gr 1 or 2), fatigue (25% all gr 1 or 2) and dyspnea (19%; 13% Gr 3) diarrhea (13%, all Gr 1 or 2). Pharmacokinetics were generally linear and dose proportional and exposures at MTD/RP2D are consistent with target pharmacologic levels in preclinical models. Blood based biomarkers showed dose- and time- dependent evidence of target engagement. Pre- and on-treatment biopsy data in expansion patients showed decreased expression of target proteins. No patient in dose escalation experienced an objective tumor response; initial efficacy data from Part 2 and at RP2D will be presented. **Conclusions:** eIF4A inhibitor zotatifin achieves pharmacologically relevant exposures with on-target AEs that are manageable at the MTD, with evidence of target knockdown from on-treatment biopsies. Part 2 indication-specific expansions (including in ER+ FGFR-amplified MBC as single agent, ER+ MBC in combination with fulvestrant and abemaciclib, and KRAS NSCLC in combination with sotorasib) are on-going. Clinical trial information: NCT04092673. Research Sponsor: eFFECTOR Therapeutics.

3082 **Poster Session**

Circulating tumor DNA (ctDNA) determinants of improved outcomes in patients (pts) with advanced solid tumors receiving the ataxia telangiectasia and Rad3-related inhibitor (ATRi), RP-3500, in the phase 1/2a TRESR trial (NCT04497116).

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Background: RP-3500 is a selective and potent oral ATRi in development for advanced solid tumors harboring loss-of-function (LOF) alterations in genes associated with ATRi sensitivity. We determined whether ctDNA can facilitate enrollment/monitoring of pts treated with RP-3500. **Methods**: Serial plasma samples collected at baseline (BL, 99 pts) and early timepoints on therapy (89 pts, 3-9 weeks [wks]) were profiled for ctDNA (Tempus xF or Guardant360). Targeted next generation sequencing (NGS) (SNiPDx panel) was performed on matched peripheral blood mononuclear cells and tumor samples collected at BL. Molecular ctDNA response (MR) was defined as ≥50% reduction in mean variant allele frequency (VAF) from BL to any timepoint ≤9 wks on-therapy. Clonal hematopoiesis (CH) or germline alterations were excluded from the analysis. Efficacy was assessed in pts treated with > 100 mg RP-3500/day with ≥1 post-BL response assessment. Endpoints included progression-free survival (PFS) and clinical benefit rate (CBR; CR/PR by RECIST1.1 or PSA/CA-125, or > 16 wks on treatment). **Results:** BL ctDNA was detected in 82% (81/99) of pts. Eligibility alterations were evaluable by the ctDNA panel in 61% (60/99) of pts, excluding structural/copy number variants and genes/exons not on the panel. Percent agreement between BL ctDNA and local eligibility NGS test was 93% (56/60). CH variants were identified in 26 pts (1-14 per pt); median VAF was 0.4% (0.1-12.4%). Two pts with pathogenic ataxia-telangiectasia mutated (*ATM*) alterations were determined to be from CH. MRs were observed in 44% (24/55) of pts with median time to MR of 3.3 wks and were across tumors harboring *ATM* (10/20), *BRCA2* (7/10), *BRCA1* (4/15), *CDK12* (1/3), *PALB2* (1/3) and *RAD51C* (1/1) pathogenic alterations. Four pts with BRCA1 mutant tumors had MRs, 2 of whom (breast cancer) had received prior PARPi and had confirmed BRCA1 reversion mutations and clinical benefit (CB). One pt with g*ATM* pancreatic cancer with CB had > 90% reduction in *KRAS* mutant VAF at 3 wks. MR was associated with longer mPFS (29 vs 12 wks, p = 0.0002) and significantly higher CBR (17/22 (77%) vs. 8/28 (29%); p = 0.001) than those without MR. Pts with MRs not achieving CB (N = 5) included 4 with RP-3500 dose interruptions/reductions and 1 who discontinued early (10 wks) due to clinical progression but with decreased target lesions and stable disease. **Conclusions:** ctDNA testing is a reliable method to detect DNA damage repair LOF alterations but is limited to alterations and genes/exons covered by the ctDNA test. CH alterations are frequent, especially for ATM, thus matched normal analysis is preferred. Changes in ctDNA as early as 3 wks were associated with improved outcomes and may be useful for evaluating drug activity in heterogenous tumors outside of traditional efficacy endpoints. Clinical trial information: NCT04497116. Research Sponsor: Repare Therapeutics.

3083 **Poster Session**

Pharmacokinetic and pharmacodynamic activity evaluation of MAK683, a selective oral embryonic ectoderm development (EED) inhibitor, in adults with advanced malignancies in a first-in-human study.

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Background: Polycomb Repressive Complex 2 (PRC2) regulates transcription via trimethylation of histone H3 at lysine 27 (H3K27me3). Its dysregulation and over-expression are associated with tumorigenesis in several conditions. MAK683 is a potent oral inhibitor of PRC2 activation, allosterically targeting the EED–H3K27me3 binding site. **Methods:** NCT02900651 is an ongoing first-in-human dose-escalation study of MAK683 in adults with advanced malignancies. MAK683 was administered fasted once (QD) or twice daily (BID) on a continuous schedule in 28-day treatment cycles. The pharmacokinetic (PK) profile of MAK683 was assessed in sequential blood samples on Days 1, 8 and/or 15 of Cycles 1–6. MAK683 pharmacodynamic activity in Cycle 1, measured by change in H3K27me3, was evaluated in peripheral blood monocytes on Days 1, 8, and 15 by flow cytometry and in tumor biopsies at baseline and Day 15 by H-score. **Results:** As of Aug 30, 2021, 125 patients had received MAK683 at doses of 10–800 mg QD or 60–450 mg BID. MAK683 was well absorbed with a median T_{max} of ~1-4 hours across cohorts. PK exposure (C_{max}, AUC) increased generally with dose over the entire dose range with no major deviation from dose proportionality, taking into account the sample size and PK variability. Apparent terminal half-life (geometric mean) was 2.5–6.6 hours across cohorts and constant over time. MAK683 accumulation of ~0.9-2.2-fold (QD) or ~1.3-2.0-fold (BID) was seen with repeat dosing. Peripheral monocytes showed substantial on-treatment reductions from baseline in the H3K27me3/H3 ratio across doses. Maximum percentage reduction was proportional to cumulative MAK683 AUC, with a trend towards greater reductions at higher baseline H3K27me3. H3K27me3 H-score reductions from baseline > 40 were observed in 7/10 patients with diffuse large B-cell lymphoma (n = 4) or epithelioid sarcoma (n = 6) and paired baseline–Day 15 biopsies. RNA-seq characterization of biopsy samples is ongoing. **Conclusions:** MAK683 has a PK profile supportive of QD or BID dosing in patients with advanced malignancies. Analysis of H3K27me3 in blood monocytes and tumor biopsy confirm the *in vivo* pharmacodynamic activity of MAK683. Clinical trial information: NCT02900651. Research Sponsor: Novartis.

3084 **Poster Session**

Phase 1 results of a phase 1/2 trial of CYT-0851, a first-in-class inhibitor of RAD51-mediated homologous recombination, in patients with advanced solid and hematologic cancers.

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Background: Homologous recombination (HR) is an essential, high-fidelity mechanism to repair DNA double strand breaks (DSBs) in cancer cells. CYT-0851 inhibits HR leading to an accumulation of unrepaired DSBs and tumor cell death. We are reporting the completed Phase 1 dose-escalation results and RP2D selection to support ongoing development of CYT-0851. **Methods:** Patients (pts) with advanced hematologic and solid tumors were treated with continuous 28-day cycles of increasing doses of CYT-0851 following a 3+3 design. The primary objective was determining the maximum tolerated dose. Secondary objectives included safety, pharmacokinetics, and anti-tumor activity. **Results:** As of a 15 Nov 2021 data cutoff (DCO), 73 pts with advanced cancers (NHL n = 18; Sarcoma n = 16; Pancreas n = 11; Breast n = 8; HNSCC n = 6; Ovarian n = 4; SCLC n = 4; Other n = 4; Myeloma n = 2) were treated in 12 cohorts (total daily doses: 30 mg to 1200 mg). One pt experienced a dose-limiting toxicity (DLT) of reversible metabolic acidosis at 1200 mg. Two of 3 pts at 800 mg experienced reversible DLT-like events in Cycle 2 of Gr3 dry skin and Gr3 myalgia and polyarthritis, respectively. Three of 10 pts treated at 600 mg experienced DLT-like events in Cycle 1: 1 pt experienced an SAE of Gr3 anorexia with Gr3 stomatitis, vomiting, and dehydration and 2 pts had Gr3 fatigue. No DLTs occurred at 400 mg daily which was selected as the RP2D. 42 pts (57.5%) experienced a CYT-0851-related adverse event (AE), including 12 (16.4%) with a Gr3/4 AE. There were no treatment-related deaths. AE leading to CYT-0851 withdrawal were reported in 2 pts (2.7%) treated with 600 and 800 mg. The most common CYT-0851-related AEs were primarily Gr1/2 and included fatigue (20.5%), hyperuricemia (11%), nausea (11%), alopecia (9.6%), constipation (8.2%) and headache (8.2%). CYT-0851 exposure was approximately dose-proportional across the evaluated doses with an effective half-life of ~3 days. Exposure at 400 mg daily was consistent with efficacy in preclinical models. 46 pts were evaluable for response at the DCO. 12 pts with NHL were evaluable by Lugano and included 1 CR in FL and 1 PR in DLBCL treated for 393+ and 244 days respectively. 34 pts with solid tumors were evaluable by RECIST v1.1 with 1 PR in a pt with myxofibrosarcoma treated for 313 days and 16 pts with stable disease. Fifteen pts were treated for 100+ days and 5 for 180+ days. **Conclusions:** CYT-0851 has demonstrated promising and broad clinical activity in a Ph 1 population of pts with advanced cancers. The safety profile is favorable as characterized by events that were infrequent, primarily Gr1/2, and reversible. Six expansion cohorts (DLBCL, Follicular Lymphoma, Myeloma, Pancreatic, Ovarian and Sarcoma) are enrolling to characterize activity at the RP2D. Ph 1 evaluation of CYT-0851 in combination with 3 chemotherapy backbones is also ongoing. Clinical trial information: NCT03997968. Research Sponsor: Cyteir Therapeutics.

3085 **Poster Session**

Interim phase 1 results for SQ3370 in advanced solid tumors.

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Background: SQ3370, a novel therapy, utilizes Shasqi's proprietary Click Activated Protodrugs Against Cancer (CAPAC) platform where mutually-reactive click chemistry groups release Doxorubicin (Dox) at the tumor site minimizing systemic exposure. In animals, SQ3370 enhanced survival, T-cell infiltration and antitumor responses in injected and non-injected tumors. Minimal to no toxicity, including no cardiotoxicity was seen in up to 9-fold dose increases in animals. Conventional Dox can induce cardiomyopathy at incidences of 1-20% for cumulative doses from 300-500 mg/m^2 in humans and re-treatment with Dox is less effective in heavily pre-treated patients (pts). Here we report interim results of the Phase 1 (NCT04106492). **Methods:** SQ3370 has 2 components: 1) Intratumoral injection of a protodrug-activating biopolymer (SQL70: 10 mL or 20 mL); 2) 5 consecutive daily IV infusions of an attenuated protodrug of Dox (SQP33). Key eligibility includes locally advanced or metastatic solid tumors, ≤300 mg/m^2 prior exposure to Dox, ECOG 0-1 and no limit to prior systemic therapies. Primary objectives include safety and determining Phase 2 dose. Dose escalation was assessed in 2 stages: 1) accelerated titration; 2) 3+3 design. **Results:** As of 31JAN2022 data cut, 26 pts were treated, 21 with 10 mL biopolymer (bp) and 5 with 20 mL bp over 9 dose escalation protodrug cohorts. MTD has not been reached. Median age was 61 years (26-84), 62% were females, and 69% were ECOG 1. Prior procedures included surgery (89%) and radiation (62%). At study entry, 77% of pts had metastases with a median number of metastatic sites being 2 (1-5); most frequently lung (50%). Tumors were sarcoma (73%), breast cancer (7.7%), gyne (7.7%) and other (11.5%). Twenty-four of 26 (92%) pts received prior systemic therapies with 50% receiving prior Dox. Median number of prior systemic therapies was 2 (1-7). Of the 26 pts, 62% received > 500 mg/m^2 cumulative Dox given as SQP33. Median duration of treatment was 2 cycles (1-12). Most frequent AEs, regardless of causality, for the 10 mL bp group included nausea (n = 11), fatigue (n = 9) and anemia (n = 6), and for the 20 mL bp group included anemia (n = 3) and nausea (n = 2). Ejection fraction (LVEF) remained normal during the study period. No AEs that led to discontinuation or death were related to SQ3370 by investigator. At a median follow-up of 9.2 wks (3-37), 21 pts were evaluable. SD was best response in 71%. Median duration of SD was 80-dys (37-186) corresponding to an overall disease control rate (CR+ PR+ SD x 30-dys) of 71% (68% in 10 mL bp; 100% in 20 mL bp). The remainder of pts had PD as best response. Over 38% of pts remain on drug. **Conclusions:** SQ3370 with 10 mL or 20 mL biopolymer was well tolerated in pts with half being re-treated with Dox. Although > 60% of pts received > 500 mg/m^2 cumulative Dox given as SQP33, LVEF remained normal. Preliminary evidence of disease control was observed in pts despite heavy prior pre-treatment and high cancer burden. Dose escalation is ongoing. Clinical trial information: NCT04106492. Research Sponsor: Shasqi, Inc, U.S. National Institutes of Health.

3086 **Poster Session**

Safety, tolerability, pharmacokinetics and preliminary efficacy of MIL93, an anti-Claudin18.2 monoclonal antibody, in patients with advanced solid tumors: A phase 1 clinical study.

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Background: Claudin18.2 (CLDN18.2) is specifically expressed in the tight junction of gastric epithelial cells, and has been identified as a promising target in gastric and pancreatic cancer as well as several other malignancies. MIL93 is a humanized IgG1 monoclonal antibody targeting CLDN18.2. From January 2021, we started a multicenter, dose escalation and expansion phase 1 study of MIL93, for the treatment of patients with advanced solid tumors (Protocol number MIL93-CT101, Beijing Mabworks Biotech Co. Ltd.) at 6 clinical study sites in China. Currently the study is still ongoing. **Methods:** We already enrolled 13 pts aged 18 years or older with advanced solid tumors whose disease had progressed after standard systemic treatments. Pts were required to have measurable lesion as per RECIST v1.1; ECOG PS score of 0-1 and adequate organ functions. In the dose escalation phase, 6 dose levels (0.3mg/kg, 1mg/kg, 3mg/kg, 10mg/kg, 20mg/kg and 30mg/kg, Q3W) of MIL93 were planned for assessment. Accelerated titration was adopted for the first 2 dose levels, and the 3+3 design was used afterwards. In the dose expansion phase, pts with CLDN18.2-positive cancers received the selected RP2D. The primary objectives were the safety and tolerability, dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) of MIL93. Secondary objectives included pharmacokinetics, immunogenicity and preliminary efficacy. **Results:** At the data cut-off date (February 14, 2022), 13 pts were enrolled between April 23, 2021 and February 9, 2022. MIL93 was well-tolerated for the dosages tested (0.3mg/kg through 20mg/kg Q3W) as no DLTs were observed, and dose escalation was ongoing at 30mg/kg. In particular, Grade 3 nausea and vomiting occurred in 2 cases in the third dose group, so preventive antiemetic treatment was given from the fourth dose group. 9 pts (69.2%) experienced at least one treatment-emergent adverse event (TEAE) with no Grade 4 or Grade 5 AEs. The most common treatment-related adverse events (TRAEs) occurring in ≥10% of pts were nausea (46.2%), vomiting (46.2%), fatigue (15.4%), anemia (15.4%). Serious adverse events (SAEs) were observed in 3 (23.1%) pts, and MIL93-related SAEs occurred in 1 pt (7.7%, Grade 3 nausea). Among the 10 pts who had at least one post-treatment radiological evaluation, 1 pt with CLDN18.2-positive gastric cancer achieved PR and 3 pts had SD, including 1 case of gastric cancer, 1 case of gastroesophageal junction cancer and 1 case of gallbladder cancer. **Conclusions:** MIL93 had a favorable safety profile with no DLTs observed through 20mg/kg Q3W. Pts with CLDN18.2-positive gastric cancer responded to the treatment. Dose escalation and expansion in selected tumor types is currently underway. Clinical trial information: NCT04671875. Research Sponsor: Mabworks Biotech Co.Ltd.

3087 **Poster Session**

Molecular landscape and actionable alterations in a genomic-guided cancer clinical trial: First analysis of the ROME trial.

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Background: The Rome Trial is a randomized, prospective, multicenter, multi-basket, Phase II clinical trial (EudraCT n° 2018-002190-21; NCT04591431). The aim is to evaluate the efficacy of Tailored Therapy (TT) vs Standard of Care (SoC) in patients (pts) with metastatic solid tumors who received at least one and no more than two lines of treatment. Pts with a molecular alteration were discussed in a Molecular Tumor Board (MTB), assigned to one or a combination of the 20 available treatments, and randomized to TT or SoC. **Methods:** Tissue (collected within 6 months) and blood samples from pts with refractory solid tumors were analyzed centrally with next generation sequencing (NGS, FoundationOneCDx and FoundationOneLiquid). MTB discussed all screened pts with any actionable genomic alterations using common mutational database and ESCAT. Genomic data, MTB reports and treatment outcomes were collected. The 3 outcomes of the MTB were: A) assignment of a TT and randomization, B) screening failure (SF) C) SF for the trial but with relevant information from the genomic test. Outcome C was divided into 3 groups: 1) indication to receive a personalized standard treatment different from the planned one, 2) indication to access to another clinical trial/compassionate use/expanded access, 3) indication to perform a germline test (GT). **Results:** From Oct 2020 to Dec 2021, 497 pts were enrolled in 38 Italian accrual sites, 303 (61.0%) had relevant genomic alterations and were discussed to the MTB. Molecular profiling was determined both on tissue and liquid biopsy in 262/303 (86.5%) pts, while in 11 (3.5%) and 30 (10.0%) only on tissue or liquid, respectively. After applying clinical and molecular exclusion criteria and considering multiple actionable or resistance-conferring mutations (detected in 95 and 70 out of 303 patients): 135 pts (45%) were randomized (outcome A), 19 (30%) were SF (outcome B), and 78 (25%) SF but with an additional indication (outcome C). Of them, 14 patients (18%) were group 1 and 42 (54%) had indication to a target therapy outside from the trial (group 2). MTB suggested a GT to 60/303 pts (20%, group 3). To date, 8 out of 9 GT performed confirmed a germline mutation (4 BRCA1/2, 2 PALB2, 1 MUTHY, 1 ATM). Finally, 213 pts, 71% of those discussed to MTB and 43% of the entire screened population, were randomized or received at least one specific indication following the extended molecular assessment with NGS. **Conclusions:** We demonstrated the feasibility of screening a large numbers of pts from numerous accruing sites in a complex trial to test investigational therapies for moderately frequent molecular targets. Co-occurring resistance mutations were common and endorse to investigate combination targeted-therapy regimens. The Rome trial MTB, even when no actionable alterations were detected, provided a therapeutic and diagnostic indication with a potential impact on patient's outcomes. Clinical trial information: NCT04591431. Research Sponsor: Roche, Bristol Myers Squibb, Incyte, Takeda, Pfizer, Novartis.

3088 **Poster Session**

Characterizing the genomic landscape of *PIK3CA* alterations from 121,221 adult patients with cancer: The next tissue-agnostic target?

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Background: The PI3K–AKT–mTOR signaling pathway is frequently dysregulated in cancer and small molecule inhibitors targeting various nodes in the pathway have been pursued for decades. Activating mutations in *PIK3CA* are recognized potent drivers of oncogenesis, though the landscape of *PIK3CA* fusions and amplifications has yet to be well-defined. The field has been hampered by issues such as resistance and poor tolerance, however several isoform-specific PI3K inhibitors have now received regulatory approval and allosteric pan-mutant and specific mutant selective Inhibitors of PI3Kα are being investigated in early phase clinical trials. Here, we present a comprehensive analysis of *PIK3CA* alterations in pan-cancer adult malignancies. **Methods:** We analyzed 136096 samples from 121221 patients available from AACR Project GENIE v.11 database for the prevalence of PIK3CA mutations, fusions and copy number alterations in a range of cancer types. **Results:** 15712 alterations in *PIK3CA* were detected in profiled tumor samples (12%), in 14774 of patients profiled (12%), most frequently in endometrial (44% of 4135 cases), anal (35% of 286 cases), breast (35% of 14218 cases), cervical (27% of 761 cases) and colorectal cancer (20% of 3743 cases).*PIK3CA* alterations identified included 17740 mutations (11%) (including duplicate mutations in patients with multiple samples). 16685 missense mutations were identified (12%);14953 were identified as missense in driver mutation (likely oncogenic)(90% of missense); 1,732 were missense of variants of uncertain significance (VUS) using OncoKB database (11%). Missense mutations most frequently involved codons 545(3347, 20% of missense), codon 1047 (3644, 22%) and codon 542 (1881, 11%). 237 truncating mutations were identified (0.2%), 442 in-frame deletions, 29 in-frame insertion mutations. PIK3CA fusions were observed in 0.06% of tumor samples and were most identified in breast, colorectal, lung, GBM and ovarian cancer (24%, 17%, 13%, 7% and 6% of identified *PIK3CA* fusions respectively). PIK3CA fusions were most commonly intragenic fusions(36%);common fusion partners included *TBL1XR1*, *FNDC3B* and *NAALADL2*(17%, 7%, 5% of identified *PIK3CA* fusions, respectively). *PIK3CA* fusions were identified as VUS, aside from *KMT2C-PIK3CA* (2%). *PIK3CA* amplification high level gain occurred in 0.5% of samples tested(662), deletion occurred in 0.16%(21). **Conclusions:** Activating *PIK3CA* mutations occur frequently across cancer types and could be considered for tissue-agnostic drug development. *PIK3CA* fusion and amplification events are extremely rare. Most *PIK3CA* missense mutation variants are described as oncogenic, while fusions are described as VUS, which may limit the impact of precision oncology for patients with this alteration. Further functional characterization of *PIK3CA* variants and basket trial enrollment are warranted. Research Sponsor: None.

3089 **Poster Session**

A phase I/II study of first-in-human trial of JAB-21822 (KRAS G12C inhibitor) in advanced solid tumors.

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Background: KRAS G12C mutation occurs in approximately 4% of non-small cell lung cancer (NSCLC), 1-2% of colorectal cancer (CRC) and other solid tumors in China. JAB-21822 (Jacobio, Beijing, PRC) is a highly selective, covalent oral inhibitor of KRAS G12C. **Methods:** NCT05009329 is an ongoing first-in-human, open label phase I/II study of JAB-21822 in patients with advanced solid tumors. The primary objective is to evaluate the safety and tolerability of JAB-21822. Other objectives include preliminary efficacy, pharmacokinetics, and biomarkers. Here we report the results from the dose escalation phase of the trial. **Results:** As of January 28th, 2022, 53 patients with a median age of 62 years (39-79) were enrolled in 5 different dose levels: 200mg QD, 400mg QD, 800mg QD, 400mg BID and 400mg TID. Most patients (55%) had ≥ 2 prior lines of therapy. No dosing-limiting toxicities were observed. Two treatment-related adverse events (TRAEs) were G4 neutropenia (1 in 400mg BID and 1 in 400mg TID). The most common TRAEs (≥ 10%) included anemia (24.5%), total bilirubin increase (20.8%), direct bilirubin increase (15.1%), proteinuria (13.2%) and indirect bilirubin increase (11.3%). Only Grade 1 and 2 TRAEs were observed in the QD cohorts. A total of 33 patients (22 NSCLC, 9 CRC and 2 pancreatic cancer) had at least 1 post-baseline tumor assessment; in the 800mg QD cohort, overall response rate (ORR) and disease control rate (DCR) were 50% (5/10) and 100% (10/10), respectively, including 4 non-confirmed partial response (PR); in the 400mg QD cohort had an ORR and DCR of 80% (4/5) and 100% (5/5) respectively, including 2 non-confirmed PR. Patients with NSCLC (400mg QD and 800mg QD), the ORR and DCR were 70% (7/10) and 100% (10/10), respectively, including 5 non-confirmed PR. With respect to the pharmacokinetics analysis, JAB-21822 was rapidly absorbed with an average T_{max} of 2 hr and reached higher plasma exposures (C_{max} and $AUC_{0\text{-}24h}$) after a single dose and multiple doses at C1D8. **Conclusions:** JAB-21822 was well tolerated with impressive preliminary efficacy in patients with heavily treated solid tumors harboring KRAS G12C mutation. The study is enrolling patients in the expansion phase. Multiple JAB-21822-based combination trials are also ongoing. Clinical trial information: NCT05009329. Research Sponsor: Jacobio Pharmaceuticals Co., Ltd.

3090 **Poster Session**

Dose optimization for MORAb-202, an antibody-drug conjugate (ADC) highly selective for folate receptor-alpha (FRα), using population pharmacokinetic (PPK) and exposure-response (E-R) efficacy and safety analyses.

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Background: MORAb-202 is an ADC consisting of farletuzumab (an antibody that binds to FRα) paired with eribulin mesylate (a microtubule dynamics inhibitor) conjugated via a cathepsin B-cleavable linker. A phase 1 dose-escalation and expansion study in patients with advanced solid tumors evaluated MORAb-202 doses ranging from 0.3 mg/kg to 1.2 mg/kg IV every 3 weeks (Shimizu 2021, *CCR*). The dose-expansion part included starting doses of 0.9 mg/kg and 1.2 mg/kg in an ovarian cancer (OC) cohort. Objective response rates (ORR) by investigator per RECIST v1.1 and rates of all-grade interstitial lung disease (ILD), an adverse event of interest, were lower at the 0.9 mg/kg dose vs the 1.2 mg/kg dose. To support dose optimization for clinical benefit while reducing the risk of ILD, a MORAb-202 PPK model was developed to characterize the pharmacokinetics and to obtain model-predicted exposure measures. **Methods:** Exposure was predicted for different dosing scenarios: flat dosing, bodyweight (BW)-based dosing with or without a dose cap, adjusted ideal BW dosing, and body surface area (BSA)-based dosing. E-R analyses for efficacy (ie, ORR) and safety (ie, ILD by expert review) were conducted using logistic-regression analysis. Simulations (N = 1000) were performed using a BW distribution from a previous phase 3 farletuzumab study in OC (Vergote 2016, *JCO*) to predict the probability of ORR and ILD in patients treated with MORAb-202. **Results:** MORAb-202 exposures were dose proportional, and the pharmacokinetics were described by a 2-compartment model with zero-order IV infusion and first-order elimination. Patients with higher BW had less-than-proportional increases in clearance (allometric exponent [AE] 0.571) and distribution volume (AE 0.524). MORAb-202 demonstrated a positive exposure (based on area under the curve [AUC]) dependence to ORR and ILD. The probability of achieving a tumor response was higher with higher AUC (odds ratio [OR] for an AUC unit change of 1000 μg•h/mL: 1.73 [95% CI 1.06–3.11]). The probability of an ILD event was higher with higher AUC (OR for an AUC unit change of 1000 μg•h/mL: 3.50 [95% CI 1.89–7.81]). Simulations across BW ranges (34.2–144 kg) indicated that BSA-based dosing (33 mg/m^2), compared with BW-based dosing (0.9 mg/kg), yielded similar predicted median (90% prediction interval) rates for ORR (33.7% [19.3–62.2] vs 37.9% [20.6–67.5]) and all-grade ILD (46.8% [18.2–88.2] vs 55.1% [20.7–91.9]). However, BSA-based dosing is predicted to reduce ILD in the highest BW quartile (> 80–144 kg) by approximately 35% compared with BW-based dosing. **Conclusions:** Based on this assessment, BSA-based dosing is predicted to lower the exposure-dependent ILD risk in patients with higher BW and is being further evaluated in ongoing clinical studies. Clinical trial information: NCT03386942. Research Sponsor: Eisai Inc., Nutley, NJ, USA.

3091 **Poster Session**

Adaptive response analysis of colorectal cancer cells to low-dose oxaliplatin as a tool to deciphering mechanisms of synergistic drug interaction.

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Background: Using an *in vitro* dose matrix approach, we previously showed in multiple colorectal cancer cell lines a striking cytotoxic synergism between oxaliplatin at very low concentrations and the ATR inhibitor VE-822. We confirmed this finding *in vivo*, and, surprisingly, in this setting the oxaliplatin-induced cell addiction to VE-822 persists over several days after oxaliplatin elimination. We tried to elucidate the molecular mechanism of the latter phenomenon. **Methods:** We evaluated by RNAseq the gene expression changes induced *in vitro* by low-dose oxaliplatin in the colorectal cancer cell line HCT-116 after 24 and 48 hours of treatment. In order to untangle the functional significance of the adaptive response to oxaliplatin, we performed on the RNAseq data an extensive gene set enrichment analysis (GSEA) using gene set from all Molecular Signature Database v7.4 collections with the exception of C7. For ontology-based gene set collections, we clusterized the enriched gene sets using the semantic similarity methodology in order to increase the readability of global functional response. **Results:** Extensive GSEA showed that after 24 hours of oxaliplatin treatment cancer cells upregulate several gene sets involved in aspecific responses to cellular stress or to various type of extracellular stimulations, including other organisms, oxygen-containing compounds, abiotic stimuli and hypoxia. In addition, several gene sets involved in proteolysis and autophagy are upregulated, suggesting a rewiring of cell machinery. After 48 hours of oxaliplatin treatment, we observed the activation of ribosome function, mitochondrial assembly and synthesis of aminoacids and ribonucleosides. Finally, a widespread negative enrichment of gene sets involved in DNA repair-related was detected both at 24 and at 48 hours, with a far greater negative enrichment at 48 hours, which suggest a commitment of cancer cell to a major limitation of DNA repairing capability lasting several days following a DNA damaging insult. Analysis of leading edge genes from the DNA repair gene sets showed a profound repression both at 24 and 48 hours of the transcripts of BRCA1, BRCA2, ATM, CHK1, WEE1, BARD1, BRIP1, NEHJ1, RAD51, XRCC2, CLSPN, GEN1, DNA2, EXO1, TOPBP1, POLE, RMI1. Interestingly, ATR mRNA was minimally repressed both at 24 and at 48 hours, which could explain the long-standing *in vivo* dependence of cancer cell to ATR after a brief oxaliplatin exposure. **Conclusions:** Extensive GSEA was able to elucidate the molecular mechanism underlying synergistic interaction between oxaliplatin and VE-822. The impact of profiling cancer cell adaptive responses by extensive GSEA should be further evaluated in the setting of rational development of drug combinations. Research Sponsor: None.

3092 **Poster Session**

^{64}Cu-SAR-Bombesin PET-CT imaging in the staging of ER+/PR+/HER2- metastatic breast cancer: Safety, dosimetry, and feasibility in a phase I trial.

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Background: Breast cancers are most frequently oestrogen receptor (ER) and progesterone receptor (PR) positive and ^{18}F-Fluorodeoxyglucose PET-CT (FDG) used in conventional staging of breast cancer has lower sensitivity for these subtypes. Gastrin releasing peptide receptors (GRPR) are a potential alternative diagnostic and theranostic target for ER+/PR+ breast cancers due to their overexpression of GRPR. This phase 1 study aims to assess the safety and potential of the novel radiotracer ^{64}Cu-Sarcophagine(SAR)-Bombesin (BBN) in the re-staging of recurrent metastatic ER+/PR+/human epidermal growth factor 2 negative (HER2-) breast cancer. **Methods:** Patients with confirmed recurrent or primary metastatic ER+/PR+/HER2- breast cancer undergoing staging prior to a new treatment underwent ^{64}Cu-SAR-BBN PET-CT with imaging at 1, 3 and 24 hours post-injection. Bloods and vital signs were acquired for patients at baseline, 1, 3 and 24 hours post-injection timepoints, and electrocardiogram (ECG) performed 1 hour pre and 1 hour post injection. Blood tracer-clearance and dosimetry was performed. GRPR receptor status was assessed in 4/7 patients from metastatic-site biopsy samples. Staging of the patients was assessed by conventional imaging (FDG, bone scan and diagnostic CT) within 3 weeks of ^{64}Cu-SAR-BBN imaging. All PET scans were assessed visually, and quantitatively using MIM Software. **Results:** 9 patients were enrolled. 7/9 patients underwent all imaging modalities, while 2/9 did not undergo BBN imaging. 1/7 patient who underwent all imaging had de- novo metastatic ER+/PR+/Her 2- breast cancer and 6/7 recurrent metastatic disease. 2/7 had lobular subtype. There were no adverse events reported, and ECG, vitals and haematological, biochemical and coagulation markers remained unchanged. All 7 patients were positive on conventional imaging, while 6/7 were positive on FDG. BBN was positive in 5/7 patients. Both BBN negative patients had disease identified on FDG. Conversely, 1 patient was BBN positive but FDG negative. 4/7 patients were BBN positive and FDG positive. In these 4 patients, mean SUVmax was higher for BBN than FDG (15 vs. 12). In classical lobular subtype (2/7), BBN was highly avid compared to FDG (SUV max 20 vs 11, and 20 vs <3) and with a higher tumor volume compared to FDG (2034 vs 504, and 634 mL vs FDG negative). **Conclusions:** ^{64}Cu-SAR-Bombesin is a novel tracer which appears safe and may have a diagnostic and theranostic role in patients with metastatic ER+/PR+/HER2- breast cancer, particularly lobular subtype. Further evaluation appears warranted. Research Sponsor: Clarity Pharmaceuticals.

3093 **Poster Session**

Theranostic pairing: ABY-025/251 targeting HER2 with ^{68}Ga and ^{188}Re—Minimized radioligands using Affibody peptide scaffold technology.

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Background: HER2 expressing tumors such as subsets of metastatic breast cancer and gastro-esophageal tumors can be targeted using specific antibodies or antibody-drug-conjugates (ADCs). However, some tumors remain refractory to treatment. External radiation therapy is unsuited to advanced metastatic disease. Targeted molecular radiation therapy has proven useful in other tumors such as neuroendocrine tumors or prostate cancer using ^{177}Lu. ^{188}Re is a beta emitting isotope that when chelated to the ABY-251 Affibody molecule has the potential to precisely target HER2 expressing tumors locally. The ABY-251 Affibody molecule is a very small, structured protein scaffold with a molecular weight of only 7 kDa targeting HER2 with high affinity (K_D = 100pM). ABY-251 can be manufactured by chemical synthesis. A diagnostic analog molecule ABY-025 was also developed with chelation to ^{68}Ga ideal for PET visualization. **Methods:** A pre-clinical study in mice was conducted to investigate tumor/tissue uptake, followed by a clinical diagnostic study for visualization in HER+ patients with metastatic breast cancer, to be followed by a theranostic study in humans. **Results:** Pre-clinical Study: A preclinical study in mice has previously demonstrated high contrast uptake in HER2 tumor tissue using the diagnostic analog ABY-025. Off target accumulation was seen in kidney tissue using the diagnostic ABY-025, which in the ABY-251 therapeutic molecule has been reduced by further engineering of the molecule. This molecule has now been proven to increase survival in mice bearing HER2+ tumors. Median survival in the treated animals was 68 days as compared to 29 and 27.5 days in animals treated with vehicle and non-labelled peptide respectively. Clinical diagnostic study ph1/2: ABY-025 was studied in HER2+ patients with metastatic breast cancer. In a study of 16 women with refractory metastatic breast cancer (>2 prior lines of therapy, 12 IHC positive and 4 IHC negative) 9 out of 10 patients showed high HER2 expression levels as measured with ABY-025 PET despite ongoing treatment with HER2 targeted therapy. Persistent high ^{68}Ga-ABY-025 tumor uptake in patients despite treatment with standard HER2-targeted therapies is a sign of therapeutic drug resistance. These patients would be eligible for treatment with the therapeutic analog ABY-251 using ^{188}Re generated beta radiation for tumor eradication. Clinical therapeutic study (planned): ABY-251 is in development to soon enter therapeutic clinical Ph1/2a trials in patients with refractory HER2+ tumors and positive tumor imaging using ABY-025 as a theranostic pair. **Conclusions:** A radiopharmaceutical theranostic approach diagnosing HER2+ patients with metastatic disease using ^{68}Ga-ABY-025 for targetability and subsequent treatment using ^{188}Re-ABY-251 seems feasible and is currently in clinical trials. Clinical trial information: NCT01858116. Research Sponsor: Uppsala University and Affibody AB.

3094 **Poster Session**

Tumor agnostic efficacy of selpercatinib in patients with *RET* fusion+ solid tumors: A global, multicenter, registrational trial update (LIBRETTO-001).

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Background: Selpercatinib, a first-in-class highly selective and potent RET kinase inhibitor, is approved in multiple countries for the treatment of lung and thyroid cancer with *RET* fusions and medullary thyroid cancer with *RET* mutations. We provide an efficacy and safety update with more patients (pts) and longer follow-up (data cut-off: 24Sep2021) in *RET* fusion+ solid tumors with histologies other than lung/thyroid. **Methods:** The phase 1/2 LIBRETTO-001 trial (NCT03157128) enrolled pts with locally advanced/metastatic *RET* fusion+ solid tumors. Following dose escalation, pts received the recommended dose of 160 mg orally twice daily. The efficacy analysis set consisted of pts enrolled ≥6 months (mo) prior to the cut-off date. If a pt achieved response, an additional ≥6 mo follow-up from the initial response was required. There was no additional follow-up required for non-responders. Response was assessed per RECIST 1.1. Primary endpoint was objective response rate (ORR) by independent review committee (IRC). Secondary endpoints included ORR by investigator (INV), duration of response (DoR), progression-free survival (PFS), time to response (TTR), and safety. **Results:** Forty-five pts with 14 unique *RET* fusion+ tumor types received ≥1 dose of selpercatinib: 12 pancreatic, 10 colon, 4 salivary, 3 unknown primary, 3 sarcoma, 2 each of breast, carcinoma of the skin, xanthogranuloma, and cholangiocarcinoma, and 1 each of lung carcinoid, rectal neuroendocrine, small intestine, ovarian, and pulmonary carcinosarcoma. Median age was 53 years (range 21-85). Forty-one pts received prior systemic therapy (median prior lines: 2, range 0-9); 31% received ≥3 lines. In 41 efficacy-evaluable pts, confirmed ORR by IRC was 44% (18/41, 95% CI: 29-60). Clinical benefit was observed in 63% (26/41) of pts: 2 complete responses (breast, small intestine), 16 partial responses, and stable disease ≥16 weeks in 8 pts by IRC. Responses were observed across a variety of fusion partners. Median TTR was 1.9 mo by IRC. Median DoR was 24.5 mo (95% CI: 9.2-NE) with 50% (9/18) of responses ongoing at a median follow-up of 14.9 mo by IRC. Median PFS by IRC was 13.2 mo (95% CI: 7.4-26.2), with 34.1% alive and progression-free at a median follow-up of 16.4 mo. No new safety signals were identified in this cohort compared to broader safety database. Three grade 5 AEs were observed (unrelated to treatment by INV), and 4 pts discontinued treatment due to AEs (1 deemed related to treatment by INV). **Conclusions:** Selpercatinib continued to demonstrate durable antitumor activity in pts with *RET* fusion+ cancers across multiple tumor types. No new safety signals were identified. These results emphasize the importance of comprehensive genomic profiling to identify actionable oncogenic drivers, including *RET* fusions. The LIBRETTO-001 study continues to enroll pts. Clinical trial information: NCT03157128. Research Sponsor: Eli Lilly and Company.

3095 **Poster Session**

A phase Ia/Ib, dose-escalation/expansion study of BI 907828 in combination with BI 754091 (ezabenlimab) and BI 754111 in patients (pts) with advanced solid tumors.

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Background: Preclinical data show that combining a murine double minute 2–tumor protein 53 (MDM2–p53) antagonist with immune checkpoint inhibitors produces anti-tumor effects in multiple tumor types. This Phase Ia/Ib study (NCT03964233) is assessing BI 907828, a MDM2–p53 antagonist, combined with immune checkpoint inhibitors in *TP53* wild-type cancers. **Methods:** In Phase Ia (dose escalation), pts with advanced/metastatic solid tumors received escalating doses of BI 907828 guided by a Bayesian Logistic Regression Model (starting dose 10 mg orally) plus ezabenlimab 240 mg (anti-PD-1 antibody) and BI 754111 600 mg (anti-LAG-3 antibody) every 21 days (q3w). Primary endpoint was the maximum tolerated dose (MTD) of BI 907828 based on the number of pts with dose-limiting toxicities (DLTs) during cycle one. During Phase Ia, other studies indicated a lack of added efficacy when BI 754111 was combined with ezabenlimab; therefore, the study design was updated to switch the dose escalation to the doublet combination of BI 907828 plus ezabenlimab. **Results:** A total of 11 pts received the triplet combination at 10/20/30/45 mg dose levels (DL; n = 3/3/3/2 respectively); all have discontinued treatment. No DLTs were reported in cycle one; MTD was not reached. As of 20th January 2022, 15 pts have received the doublet combination at 30/45 mg DLs (n = 10/5 respectively). One pt (45 mg) had a DLT during cycle one: G2 neutropenia. Four DLTs were reported after cycle one: G3 anemia (30 mg); G2 thrombocytopenia (45 mg); and G3 neutropenia and G4 thrombocytopenia (45 mg). G≥3 adverse events occurred in eight pts; most commonly anemia (n = 6), thrombocytopenia (n = 4) and lymphopenia (n = 3). There were no notable safety findings with BI 907828 45 mg q3w, the recommended dose for expansion (RDE) for BI 907828 monotherapy. Nine of the 15 pts who received doublet therapy were evaluable for response; four had a confirmed partial response (PR; 30 mg, n = 1; 45 mg, n = 3), two biliary tract carcinoma, one urothelial carcinoma, and one myxoid liposarcoma; one had an unconfirmed PR (30 mg) with adenocarcinoma (primary site intrahepatic cholangiocarcinoma). Four pts with liposarcoma and gastric cancer had stable disease. MTD will be reported. In Phase Ib, pts will receive the RDE of BI 907828 plus 240 mg ezabenlimab (q3w). Pts will be recruited to two cohorts: soft tissue sarcomas (liposarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, synovial sarcoma and leiomyosarcoma) and selected MDM2-amplified tumors (NSCLC, gastric adenocarcinoma, urothelial carcinoma, and biliary tract carcinoma). Primary endpoints are progression-free survival and objective response (RECIST 1.1). **Conclusions:** The doublet combination of BI 907828 plus ezabenlimab showed a manageable safety profile and early signs of anti-tumor activity. Eleven pts remain on treatment; recruitment is ongoing. Clinical trial information: NCT03964233. Research Sponsor: Boehringer Ingelheim.

3096 **Poster Session**

Interim safety and efficacy results from a phase 1 study of NT219 in adults with advanced solid tumors.

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Background: NT219 is a small molecule, effecting IRS1/2 degradation and inhibiting STAT3 phosphorylation. IRS1/2 and STAT3 are major signaling junctions regulated by various oncogenes, altered during epithelial to mesenchymal transition (EMT) and drug resistance, and play an important role in the tumor and its microenvironment. A Phase 1/2 study (NCT04474470) includes a dose escalation of NT219 administered weekly for the treatment of relapsed and/or refractory cancer patients. **Methods:** In the dose escalation part of the study involving a conventional 3+3 design, patients with recurrent and/or metastatic solid tumors were administered intravenously with NT219 at 3, 6, 12 and 24mg/kg. Safety was assessed according to CTCAE v5 and anti-tumor activity was assessed by the investigators according to RECISTv1.1 using CT/MRI. The primary objectives of this part of the study are to evaluate safety, tolerability, PK and determine the recommended Phase 2 dose (RP2D). The study includes evaluation of potential biomarkers including measurements of STAT3, IRS1/2 phosphorylation, and TILs in biopsy specimens. **Results:** As of data cutoff date of February 8, 2022, a total of 13 patients were enrolled to 4 NT219 dose levels (3 - 24mg/kg) in the dose escalation phase, of which 11 were evaluable for dose limiting toxicity (DLT) determination, including 4 with colorectal cancer (CRC), 2 with pancreatic cancer, 2 with breast cancer, and one of each of the following cancers: gastroesophageal junction (GEJ), esophageal, appendiceal, papillary thyroid, and mesothelioma. Median number of prior treatment regimens for metastatic disease was 4 (2-11). Six Grade 3 adverse events (AEs) were observed, including alkaline phosphatase increase, aspartate aminotransferase increase, toxic encephalopathy, worsening back pain, abdominopelvic ascites, closed displaced fracture of right femoral neck, with the first 2 considered as possibly related to NT219. No Grade 4 AEs or treatment related deaths were reported. For the 11 evaluable patients, best overall response included one confirmed PR (GEJ patient, 5.5 months duration of response), and 3 SD (3 of 4 CRC patients; duration of 5.2, 4, and 2 months with ongoing follow up) with two patients awaiting follow up MRI/CT scans. As of the cutoff date, 9/11 patients that completed the DLT period are either on treatment or in follow up (range 1.1 to 14.7 months). **Conclusions**: Interim analysis of safety results obtained in 4 NT219 dose levels found NT219 to be well tolerated without DLTs in advanced cancer patients. The observed durable PR in a GEJ patient and SDs in 3 CRC patients are an encouraging initial signal of efficacy. Combination treatment of cetuximab with escalating NT219 doses in patients with recurrent/metastatic CRC and squamous cell carcinoma of the head and neck (SCCHN) has begun. An expansion cohort in patients with recurrent/metastatic SCCHN will be initiated at the conclusion of this part. Clinical trial information: NCT04474470. Research Sponsor: Purple Biotech Ltd.

3097 **Poster Session**

A phase 1, first-in-human, dose-escalation and biomarker trial of liposomal gemcitabine (FF-10832) in patients with advanced solid tumors.

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Background: FF-10832 is a stable liposomal formulation of gemcitabine (GEM) shown to overcome resistance through increased plasma stability and enhanced tumor drug delivery. Macrophage uptake and immune activation in the tumor microenvironment (TME) play a role in the superior efficacy of FF-10832 compared to GEM, with selective, marrow-sparing biodistribution contributing to an improved safety profile. **Methods:** A 3+3 design determined the safety, maximum tolerated dose (MTD), dose-limiting toxicities (DLT), pharmacokinetics (PK), and recommended Phase 2 dose (RP2D). FF-10832 was administered IV once or twice per cycle on a 28 or 21-day schedule until disease progression or unacceptable toxicity. Circulating immune cell populations were measured over time by flow cytometry. **Results:** Patients (pts) [n = 73, 26M/47F; median age, 64 (range, 26–84); # prior therapies, 3 (1–11); prior GEM, 60%] received FF-10832 on Day 1 and 15 Q28 days (1.2–30 mg/m^2), Day 1 and 8 Q21 days (12–23 mg/m^2), or Day 1 only Q28 or 21 days (30–55 mg/m^2); median # cycles = 2 (1–14) & time on study = 8.3 (4–60) weeks. Common drug-related adverse events were Grade (Gr) ≤2 rash (22%), nausea (22%, 1 Gr 3), and pyrexia (21%, 2 Gr 3). Dose-limiting Gr ≥3 cellulitis/skin ulcers were observed at ≥23 mg/m^2 with twice per cycle dosing and those regimens discontinued. Dose frequency was reduced to Day 1 only, which was well-tolerated without significant skin toxicity. Gr ≥3 thrombocytopenia and pneumonitis were observed at 55 mg/m^2 Q21 days and the MTD confirmed at 40 (Q21) and 48 mg/m^2 (Q28). Median OS = 25.3 (95%CI: 16–27.1) weeks and PFS = 9.6 (95%CI: 7.9–17.6) weeks. Three of 35 evaluable pts achieved a partial response (PR): one pt with gallbladder cancer who previously progressed on GEM achieved a 50%↓ by Cycle 13 at 40 mg/m^2 Q28 days & maintains response on study at 60 weeks; two pts with pancreatic cancer had ≥30%↓: one adenocarcinoma after 2 cycles at 4.8 mg/m^2 Days 1 & 15 Q28 days, and one acinar cell after 7 cycles at 40 mg/m^2 Q28 days who remains on study. Stable disease (SD) was observed in 16 pts; 9 for ≥20 weeks. AUC increased in proportion to dose without accumulation. An extended plasma $t_{1/2}$ (hrs) for released (39) & total GEM (26) with a free fraction < 1% of total GEM concentrations suggests continuous release in the TME. Pts with PR or SD had dose and time-related log decreases in Ki67+ regulatory T cells relative to total CD4+ cells with increases in anti-tumor CD8+ cells, suggesting a shift to a more immunocompetent environment. **Conclusions:** FF-10832 was well-tolerated in heavily pre-treated pts with solid tumors, with evidence of anti-tumor activity in pts who progressed on prior GEM. Prolonged, continuous exposure and enhancement of anti-tumor immunity may contribute to improved efficacy. Expansion is ongoing in biliary tract cancer pts treated at the RP2D/schedule of 40 mg/m^2 Day 1 of a 21-day cycle. Clinical trial information: NCT03440450. Research Sponsor: FUJIFILM Pharmaceuticals U.S.A., Inc.

3098 **Poster Session**

The bi-steric mTORC1-selective inhibitor RMC-5552 in tumors with activation of mTOR signaling: Preclinical activity in combination with RAS(ON) inhibitors in RAS-addicted tumors, and initial clinical findings from a single agent phase 1/1b study.

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Background: RMC-5552 is a potent bi-steric mTORC1-selective inhibitor that activates the downstream tumor suppressor 4EBP1, thereby inhibiting initiation of protein translation. This novel therapeutic moiety addresses a key limitation of rapalogs, which do not effectively inhibit phosphorylation of 4EBP1. RMC-5552 has previously demonstrated significant anti-tumor activity in preclinical models of human cancers with mTOR pathway activation. Additionally, mTOR signaling plays a key role in therapeutic response and resistance in RAS-addicted cancers, which represent a significant unmet medical need. **Methods:** We examined the combination of bi-steric mTORC1 inhibitors (RMC-5552 and the research tool compound RMC-6272) with direct inhibitors of active RAS (RAS(ON) inhibitors) in mutant KRAS-driven models. To enable the clinical testing of RMC-5552 as a companion inhibitor for RAS(ON) inhibitors, a Phase 1/1b dose-escalation trial of RMC-5552 monotherapy is currently testing a once-a-week IV schedule. **Results:** RMC-5552 and RMC-6272 demonstrated marked combinatorial anti-tumor activity with RAS(ON) inhibitors across a series of preclinical models of KRAS mutated non-small cell lung cancer. The combination enhanced tumor apoptosis and resulted in durable tumor regressions as compared to tumor growth inhibition resulting from single agents alone. As of 13 January 2022, a total of 14 patients with solid tumors have been evaluated in an ongoing Phase 1/1b trial over 5 dose levels ranging from 1.6 to 12 mg IV weekly. Median age was 62 years and the majority received ≥3 prior therapies. The most common (> 25%) drug-related adverse events were mucositis/stomatitis (43%) and decreased appetite (29%). The most common grade 3 drug-related adverse events were mucositis/stomatitis observed in 3 patients in dose levels ≥ 10 mg (21%) and were dose-limiting. The dose of 6 mg IV weekly was well tolerated. Plasma exposures of RMC-5552 were dose-proportionate at lower dose levels up to 6 mg but increased above dose proportionality with higher dose levels. Plasma exposures at 6 mg and above were consistent with those resulting in inhibition of tumor p4EBP1 in preclinical models. Of 5 patients evaluable for efficacy at doses of 6 mg and higher, one confirmed PR was observed in a patient with head and neck cancer with a pathogenic mutation in *PTEN* (ORR 20%) and 3 patients had a best response of SD. Dose-optimization is ongoing. **Conclusions:** RMC-5552 is clinically active in tumors with mTORC1 signaling activation at a tolerable dose and schedule and has the potential to be a companion inhibitor of choice for RAS(ON) inhibitors in RAS-addicted tumors. Clinical trial information: NCT04774952. Research Sponsor: Revolution Medicines.

3099 **Poster Session**

Updated analysis of the efficacy and safety of entrectinib in patients (pts) with locally advanced/metastatic *NTRK* fusion-positive (*NTRK*-fp) solid tumors.

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Background: *NTRK* gene fusions, coding for chimeric TRK proteins, are oncogenic drivers in many solid tumors. In an integrated analysis of three phase 1/2 trials (ALKA-372-001 [EudraCT 2012-000148-88]; STARTRK-1 [NCT02097810]; STARTRK-2 [NCT02568267]), entrectinib, a potent CNS-active TRK inhibitor, showed durable systemic and intracranial responses in pts with *NTRK*-fp solid tumors. We report updated data from a larger cohort with longer follow-up (clinical cutoff 2 Aug 2021). **Methods:** Pts with locally advanced/metastatic *NTRK*-fp solid tumors and ≥12 months' follow-up from first tumor assessment were efficacy evaluable. The safety cohort also included pts from TAPISTRY (NCT04589845). Tumor responses were assessed by blinded independent central review (BICR) per RECIST v1.1 at Week 4 and every 8 weeks thereafter. Primary endpoints: objective response rate (ORR) and duration of response (DoR). Progression-free survival (PFS), overall survival (OS), intracranial (IC)-ORR and safety were also assessed. **Results:** The efficacy-evaluable cohort comprised 150 adults (vs 121 previously) with 17 different solid tumor types. Median age was 58.5 years; 91% of pts had ECOG PS 0–1 and 37% had received ≥2 prior lines of therapy. Median survival follow-up was 30.6 months. ORR was 61.3% (n = 92/150; 95% CI: 53.1–69.2), including 25 complete responses. Responses were observed in all tumor types with n>1 (Table). Median DoR, PFS and OS were 20.0 months (95% CI 13.2–31.1), 13.8 months (95% CI 10.1–20.0), and 37.1 months (95% CI 27.2–not estimable [NE]), respectively. In pts with and without investigator-assessed baseline CNS metastases (n = 31 / n = 119), ORR was 61.3% (95% CI 42.2–78.2) and 61.3% (95% CI 52.0–70.1) respectively. IC-ORR was 69.2% (n = 9/13) in pts with BICR-assessed measurable CNS metastases; median IC-DoR was 17.2 months (7.4–NE). In the safety population (N = 235: all treated pts), most treatment-related adverse events (TRAEs) were grade 1/2 and not serious; the most frequent were dysgeusia (36.6%), diarrhea (29.8%) and weight increase (28.5%). TRAEs led to dose interruption, reduction and discontinuation in 32.8%, 24.3% and 7.2% of pts, respectively. **Conclusions:** In this updated analysis, entrectinib continued to demonstrate deep and durable responses and was well tolerated in pts with *NTRK*-fp solid tumors with or without baseline CNS metastases. Clinical trial information: STARTRK-2 [NCT02568267]. Research Sponsor: F. Hoffmann-La Roche Ltd.

NTRK-fp tumor type (N ≥ 5)	ORR, n/N (%)
Sarcoma	19/32 (59.4)
Non-small cell lung cancer	20/31 (64.5)
Mammary analogue secretory carcinoma	22/26 (84.6)
Thyroid	10/16 (62.5)
Colorectal	3/11 (27.3)
Breast	6/9 (66.7)
Head and neck	3/5 (60.0)
Neuroendocrine	2/5 (40.0)

Other tumor types included in efficacy-evaluable population: pancreatic (N = 4); carcinoma of unknown primary (N = 3); gynecological (N = 2); adrenal, cholangiocarcinoma, gastrointestinal tract, neuroblastoma, penile and prostate (N = 1 each).

3100 **Poster Session**

Long-term efficacy and safety of larotrectinib in a pooled analysis of patients with tropomyosin receptor kinase (TRK) fusion cancer.

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Background: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in multiple tumors. Larotrectinib is a highly selective, central nervous system (CNS)-active tropomyosin receptor kinase (TRK) inhibitor, approved to treat adult and pediatric patients (pts) with TRK fusion cancer. In an integrated analysis of 206 pts with non-primary CNS TRK fusion cancer, larotrectinib demonstrated an investigator-assessed objective response rate (ORR) of 75%; median progression-free survival (PFS) was 35.4 months (mo; Hong et al, ASCO 2021). We report updated efficacy and safety data based on central review assessments in an expanded dataset. **Methods:** Data were pooled from three clinical trials (NCT02576431, NCT02122913, and NCT02637687) of pts with non-primary CNS TRK fusion cancer treated with larotrectinib. Larotrectinib was administered until disease progression, withdrawal, or unacceptable toxicity. ORR was assessed by independent review committee (IRC) per RECIST v1.1. Data cut-off was July 20, 2021. **Results:** As of data cut-off, 244 of 269 larotrectinib-treated pts were evaluable for efficacy by IRC. There were 25 different tumor types. The most common were soft tissue sarcoma (STS [43%], including infantile fibrosarcoma [18%] and other STS [25%]), thyroid (11%), lung (10%), salivary gland (9%), and colorectal (7% [colon, n = 18; rectal, n = 1]). Ninety-four (35%) pts were aged < 18 years; 175 (65%) were ≥18 years. Pts had gene fusions involving *NTRK1* (46%), *NTRK2* (3%), or *NTRK3* (51%). A total of 27%, 28%, and 45% of pts had 0, 1, and ≥2 prior lines of systemic therapy, respectively. The ORR was 69% (95% confidence interval [CI] 63–75): 64 (26%) complete response (CR), including 13 (5%) pathological CR, 104 (43%) partial response**,**41 (17%) stable disease, 20 (8%) progressive disease, and 15 (6%) not determined. Median time to response was 1.8 mo (range 0.9–16.2). Median duration of response (DoR) was 32.9 mo (95% CI 27.3–41.7); median follow-up was 28.3 mo. Median PFS was 29.4 mo (95% CI 19.3–34.3); median follow-up was 29.3 mo. At a median follow-up of 32.2 mo, median overall survival (OS) was not reached; the 48-mo OS rate was 64% (95% CI 55–73). Treatment duration ranged from 0.1 to 67.9 months. Treatment-related adverse events (TRAEs) were mainly Grade 1–2; 50 (20%) pts had Grade 3–4 TRAEs. Five (2%) pts discontinued treatment due to TRAEs. To exclude the possible confounding effect of ongoing enrollment on median DoR, we conducted an exploratory analysis in the subset of 164 pts who were analyzed as of July 2019. The ORR was 74% (95% CI 67–81) and median DoR was 34.5 mo (95% CI 27.6–43.3); median follow-up was 34.1 mo. **Conclusions:** With longer follow-up, larotrectinib continued to demonstrate rapid and durable responses, extended survival benefit, and a favorable safety profile. These results highlight the importance of testing for *NTRK* gene fusions in cancer pts. Clinical trial information: NCT02576431, NCT02122913, NCT02637687. Research Sponsor: Bayer HealthCare and Loxo Oncology.

3101 **Poster Session**

A first-in-human phase 1 dose escalation study of FF-10850 (liposomal topotecan) in patients with advanced solid tumors.

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Background: FF-10850 (liposomal topotecan) was developed using a unique dihydrosphingomyelin-based carrier to enhance tumor drug delivery and retention, leading to improved efficacy and safety. Preclinical studies demonstrated superior anti-tumor activity with less myelosuppression compared to topotecan, with a pharmacokinetic (PK) profile supporting a twice-monthly dosing schedule. **Methods:** Accelerated titration followed by a 3+3 dose escalation design was used to determine the safety, maximum tolerated dose (MTD), dose-limiting toxicities (DLT), PK, and recommended Phase 2 dose. FF-10850 was administered IV on Day 1 and 15 of a 28-day cycle until disease progression or unacceptable toxicity. **Results:** Patients (pts) [n = 29; 4M/25F; median age, 64 (range, 37–79) and # prior therapies, 4 (range, 1–8)] received FF-10850 at doses of 1, 2, 2.5, 3, 3.5 and 5 mg/m^2; median # of cycles, 2 (range, 1–11). FF-10850 was well-tolerated at doses up to 2 mg/m^2. Common drug-related adverse events (AEs) included anemia (83%, 51% Gr≥3), thrombocytopenia (62%, 35% Gr≥3), neutropenia (59%, 45% Gr≥3), nausea (38%), fatigue (24%, 7% Gr≥3), alopecia (24%), and hypokalemia (17%, 3% Gr≥3). Dose-limiting Gr≥3 thrombocytopenia, neutropenia, anemia, and fatigue were observed at doses ≥2.5 mg/m^2. Eight pts required dose reductions due to AEs. The median time on study was 8.3 (1.6–45) weeks, with a median PFS of 9.4 weeks and median OS at least 26 weeks. Of 24 pts evaluable for response, two achieved a partial response (PR). One pt with ovarian cancer treated at 3.5 mg/m^2 achieved a complete response in target lesions by Cycle 2 with stable non-target lesions, and maintained response for > 30 weeks (8 cycles) before progressing; dose was reduced in this pt to 2.6 mg/m^2 at Cycle 2 due to Gr 4 thrombocytopenia. Another pt with refractory metastatic Merkel cell carcinoma tolerated therapy well at 2 mg/m^2 and achieved a 48% reduction in target lesions that was maintained for > 30 weeks (8 cycles). Stable disease was observed in an additional 9 pts for ≥10 weeks (5 ovarian, 2 uterine and 2 cervical); five who maintained disease control for ≥24-45 weeks including one (ovarian) who had previously progressed on topotecan. An extended plasma $t_{1/2}$ for topotecan of 25-30 hours was observed with no apparent dose-dependency or accumulation; < 1% of circulating topotecan was in the free (released) form. **Conclusions:** FF-10850 was well-tolerated up to 2 mg/m^2 with anti-tumor activity demonstrated in heavily pre-treated pts with solid tumors including ovarian cancer, and an improved PK profile allowing less frequent dosing compared to topotecan. Expansion is ongoing in pts with ovarian and Merkel cell carcinoma at the RP2D of 2 mg/m^2 IV on Day 1 & 15 of a 28-day cycle. Clinical trial information: NCT04047251. Research Sponsor: FUJIFILM Pharmaceuticals U.S.A., Inc.

3102 **Poster Session**

A study of senaparib in combination with temozolomide for the treatment of patients with advanced solid tumors and extensive-stage small cell lung cancer.

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Background: Senaparib (or IMP4297) is a PARP inhibitor with a novel chemical structure. Preliminary data demonstrate senaparib has significant anti-tumor activity with good tolerability in some patients with advanced solid tumors. DNA damage caused by temozolomide, a non-classic oral alkylating agent, can sensitize tumors to the effects of PARP inhibitors. In a xenograft model, synergistic antitumor effect was observed with the combination of senaparib and temozolomide, supporting this trial (NCT04434482). **Methods:** This is a phase Ib/II dose-escalation and dose-expansion study. Patients with advanced solid tumors were enrolled for dose escalation to evaluate the safety, tolerability using a modified "3+3" design. Low dose temozolomide (20 to 30 mg, once daily, days 1 to 21) in combination with continuous senaparib (40 to 80 mg, once daily, days 1 to 28) of each 28-day cycle was evaluated. Dose expansion will establish anti-tumor activity and safety of the combination in patients with extensive stage small cell lung cancer (ES-SCLC). **Results:** A total of 14 patients were enrolled for dose escalation as follows: Cohort 1 (1 patient; senaparib 40 mg plus temozolomide 20 mg), Cohort 2 (3 patients; senaparib 60 mg plus temozolomide 20 mg), Cohort 3 (7 patients; senaparib 80 mg plus temozolomide 20 mg), Cohort 4 (3 patients; senaparib 80 mg plus temozolomide 30 mg). One DLT (Grade 4 thrombocytopenia) was observed in Cohorts 3 and 4. The MTD and RP2D were determined as: senaparib 80 mg plus temozolomide 20 mg. Anaemia, neutropenia and thrombocytopenia were the only Grade $\geq$3 TEAEs occurring in > 1 patient. All AEs were manageable, and no treatment related deaths were reported. The ORR was observed in 3 of 12 (25.0%) evaluable patients, including 2 confirmed PR and 1 unconfirmed PR. The DCR was 83.3% (10 of 12 evaluable patients). Two patients remain on treatment for more than 1 year. **Conclusions:** Preliminary results suggest that low dose temozolomide (D1-21 of a 28-day cycle) in combination with continuous senaparib is generally well tolerated with encouraging anti-tumor activity. Recruitment for dose expansion for ES-ECLC patients has commenced (Sep 2021). Clinical trial information: NCT04434482. Research Sponsor: None.

3103 **Poster Session**

A CRUK first-in-human phase I trial of LY3143921, a novel CDC7 inhibitor, in patients with advanced solid tumors.

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Background: CDC7, a protein with key roles in regulating cell-cycle progression is often over-expressed in malignant cells, particularly those with *TP53* mutations. LY3143921, an orally administered ATP-competitive CDC7 inhibitor, demonstrated favorable pre-clinical anti-cancer activity in colorectal cancer (CRC) and squamous non-small cell lung cancer (sqNSCLC), particularly in *TP53* mutant models. **Methods:** Phase Ia (dose escalation) recruited patients (pts) with advanced solid tumors enriched for malignancies associated with *TP53* mutation. Pts received LY3143921 OD or BD continuously on a 21-day schedule, using an accelerated 3+3 escalation design, starting at 30 mg OD. Phase Ib recruited pts with CRC or sqNSCLC treated continuously at RP2D, or pts with other advanced tumors treated at RP2D on days 1-3 every 7 days. Radiological assessment was performed every 2 cycles initially. Pts in phase Ib could consent to pre- and on-treatment skin +/- tumor biopsies. Primary objectives: assess safety/tolerability and determine MTD and RP2D of LY3143921. Secondary objectives: evaluate preliminary efficacy and pharmacokinetic (PK) profile of LY3143921. Exploratory objective: correlate efficacy to baseline molecular/genetic alterations, including *TP53* mutation and measure markers including pMCM2 in pre- and on- treatment tumor and skin samples. **Results:** 68 pts were recruited and 67 treated (38 phase Ia, 29 phase Ib). Most frequent drug-related CTCAEs (all grades): nausea (75%), orthostatic hypotension (50%), vomiting (47%), fatigue (45%) & diarrhea (44%). Grade 3-4 LY3143921 related AEs occurred in 17 pts. In phase Ia 8 DLTs occurred in 5 pts (G3 nausea, vomiting, fatigue & hyponatraemia and G2 diarrhea, anorexia & lethargy). RP2D was 360 mg BD (continuous non-fasted dosing schedule). 37 pts were evaluable for radiological response with no complete or partial responses seen, and stable disease (SD) was observed in 24 pts (65%). In phase Ia 3 pts achieved long term SD of 1, 2.5 and 3+ years duration. For evaluable pts treated in phase Ib, SD was seen in 8/12 CRC pts, 1/2 sqNSCLC pts and 2/2 pts treated with the intermittent schedule (median duration 15 weeks, range 6-18+). 2 pts remain on-study. Recruitment ceased due to lack of radiological response according to RECIST. Dose-dependent increases in LY3143921 exposure (C_{max} & AUC_{0-24}) were seen. IHC analyses of skin biopsies demonstrated reductions in pMCM2, indicating on-target activity of LY3143921. Pre-clinical testing of combination with standard of care agents is ongoing. Additional PD and PK data will be presented. **Conclusions:** LY3143921 is well tolerated, exhibits dose-dependent increases in plasma exposure and demonstrates evidence of target inhibition. Significant monotherapy clinical activity was not observed; further analyses should investigate potential predictive response biomarkers and rational combination approaches. Clinical trial information: NCT03096054. Research Sponsor: Cancer Research UK.

3104 **Poster Session**

Mechanisms of acquired resistance to TRK inhibitors.

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Background: First-generation TRK tyrosine kinase inhibitors (TKIs) are approved in a tumor-agnostic fashion in more than 40 countries for patients with *NTRK* fusion-positive adult and pediatric cancers. While resistance to these agents has previously been described, the exact frequency with which major mechanisms of resistance emerges is not clearly understood. **Methods:** Patients with an *NTRK*-fusion-positive tumor who received a first-generation TRK TKI were eligible. We retrospectively identified those patients that had post-progression tumor tissue analyzed by next-generation sequencing (NGS). The pattern of serial resistance to a second-generation TKI was analyzed when available. **Results:** Eighteen patients were identified. The median age was 46 years (range 2-67). Nine unique fusions were detected in ten different tumor types. *NTRK1*, *NTRK2*, and *NTRK3* fusions were found in eight (44%), one (6%), and nine (50%) patients, respectively. Thirteen patients (72%) were treated with larotrectinib and five patients (28%) received entrectinib. NGS (MSK-IMPACT n = 17, Foundation One n = 1) carried out on post-progression tissue revealed the following profile of acquired resistance: on-target resistance (83%, n = 15/18), off-target resistance (11%, n = 2/18), and no identifiable mechanism (6%, n = 1/18). Among patients with on-target resistance, the most common mutation involved the solvent front (87%, n = 13/15: n = 7 *NTRK3* G623R, n = 4 *NTRK1* G595R, n = 1 *NTRK2* G639L, n = 1 *NTRK3* G623E) followed by the gatekeeper region (13%, n = 2/15: n = 1 *NTRK1* F589L, n = 1 *NTRK3* F617I). Two patients developed off-target alterations. One acquired *BRAF* V600E mutation and the other *MET* amplification. Interestingly, solvent front mutation loss was observed in two patients who transitioned to and progressed on a second-generation TRK TKI. One patient with a baseline *NTRK1* G595R mutation developed polyclonal resistance with acquisition of *KRAS* G12A and *NTRK1* G667A alterations as well as *NTRK1* G595R loss. The other patient with *NTRK3* G623R developed an *NTRK3* F617I gatekeeper mutation with *NTRK3* G623R loss. **Conclusions:** In *NTRK* fusion-positive cancers, on-target resistance preferentially involving the solvent front is more frequent than off-target resistance to first-generation TKI therapy. Furthermore, the sequential use of second-generation therapy appears to alter the evolutionary kinetics of mutation retention and acquisition. Research Sponsor: U.S. National Institutes of Health.

3105 **Poster Session**

A phase 1 dose-escalation study of the ABN401 (c-MET inhibitor) in patients with solid tumors.

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Background: *MET* is a proto-oncogene encoding a receptor tyrosine kinase c-MET for hepatocyte growth factor (HGF). Dysregulated MET signaling by *MET* exon14 skipping, *MET* gene amplification and c-MET overexpression in cancer plays a critical role in the development of primary oncogenesis, acquired drug resistance and metastasis. This is a first-in-human trial, phase 1 dose-escalation study of the highly selective MET kinase inhibitor, ABN401. ABN401was evaluated in subjects with advanced solid tumors in South Korea and Australia. **Methods:** Patients with advanced solid tumors were enrolled in escalating dose cohorts using an accelerated titration design. ABN401 was orally administered daily with 21-day cycle. The primary objective was to evaluate safety and tolerability to define dose-limiting toxicity (DLT), maximum tolerated dose (MTD) according to CTCAE v5. Secondary objectives included pharmacokinetic, recommended phase II dose (RP2D), and preliminary efficacy assessments. Tumor assessment was determined using Response Evaluation Criteria in Solid Tumors (RECIST 1.1). **Results:** Out of 28 screened patients, 16 patients with 6 different tumor types were treated with ABN401 at daily dose levels of 50, 100, 200, 400, 800 and 1200 mg, 15 patients were evaluated for DLT and one unevaluable. No DLT was observed in all 6 dose levels and the MTD has not been reached. No drug related grade $\geq$ 3 AEs were observed: only one drug-related SAE (transient peripheral edema) was reported. For treatment response, 5 patients with stable disease, and 2 with partial response were observed. These two patients with partial response had non-small cell lung cancer (NSCLC) with c-MET overexpression and had been treated with ABN401 for 10 and 18 months, respectively. **Conclusions:** ABN401 dosed up to 1200 mg QD was well tolerated with an acceptable safety profile and promising preliminary antitumor activity in patients with advanced solid tumors. The extension (pilot expansion) for additional efficacy assessment is under way at 800 mg daily dose with c-MET altered NSCLC patients in South Korea and Australia. In addition, a phase 2 expansion study is to start in the United States and South Korea. Clinical trial information: NCT04052971. Research Sponsor: None.

3106 **Poster Session**

Safety, pharmacokinetics (PK), and clinical efficacy of ICP-723, a highly selective next-generation pan-TRK inhibitor, in patients with solid tumor.

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Background: NTRK gene fusion resulting from NTRK1/2/3 genetic alterations occurs in various adult and pediatric cancers, which is one of the most defined driving factors of carcinogenesis. Patients with NTRK fusion positive cancers treated by earlier generation TRK inhibitors achieve rapid and durable responses but can develop on-target resistance. ICP-723 is a highly selective next-generation TRK inhibitor. In preclinical studies, ICP-723 not only markedly inhibits the activity of the wild type TRKA/B/C, but also shows robust activity against resistant mutations, e.g., G595R, F589L or G667C/A/S. A first-in-human clinical study is currently ongoing to evaluate the safety, tolerability, pharmacokinetics (PK) characteristics and efficacy of ICP-723. **Methods:** This is a multi-center, open-label phase I/II clinical trial, which includes a phase I dose escalation part and a phase II dose expansion part. In the phase I dose escalation, patients with advanced solid tumor, who failed from clinical standard of care or for whom there is currently no effective therapy, will be enrolled. The modified "3+3" method is followed for dose escalation. **Results:** As of 11Feb2022, a total of 17 patients in phase I dose escalation were treated with ICP-723 at doses of 1 mg QD to 8 mg QD. The median age of the enrolled patients was 54 yrs, (range: 31 to 69 yrs) and ECOG performance status was between 0-1 (58.8% had ECOG PS of 1). Six of 17 patients were confirmed as NTRK gene fusion positive tumors by either prior gene test reports or the central lab gene test. There is no DLT observed in the 6 dose groups. Most AEs were manageable and grade 1-2. The most common TRAEs (> 20%) were asthenia (23.5%), increased ALT (29.7%), increased AST (29.7%) and anemia (29.7%). Gr ≥3 TRAEs were increased ALT (5.9%), increased AST (5.9%), increased CPK (11.8%), neutrophil count decreased (5.9%) and pain (5.9%). The plasma exposure to ICP-723 increased in a dose proportional manner across the observed dosage levels. According to RECIST 1.1 criteria, among the 6 patients with NTRK fusion, the overall response rate (ORR) was 66.7% (4 patients with partial response (PR)), the disease control rate (DCR) was 100%. It is worth noting that one patient with measurable brain metastasis achieved PR with the target brain lesion shrunk from 10 mm to 3 mm. All patients who achieved PR responded to ICP-723 at the first tumor assessment after 4-week treatment and maintained sustained responses to the date of data cutoff. **Conclusions:** ICP-723 is safe and well-tolerated in patients with advanced solid tumors. Encouraging clinical efficacy including intracranial activity was demonstrated in patients with NTRK gene fusion in various tumor types. Enrollment in phase I is ongoing until the final RP2D is determined, then phase II expansion will be conducted in patients with defined gene alterations. Clinical trial information: NCT04685226. Research Sponsor: InnoCare Pharma Limited.

3107 **Poster Session**

First-in-human (FIH) phase I study of the highly selective phosphoinositide 3-kinase inhibitor delta (PI3Kδ) inhibitor IOA-244 in patients with advanced cancer: Safety, activity, pharmacokinetic (PK), and pharmacodynamic (PD) results.

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Background: T regulatory (Tregs) cells contribute to immune suppression in cancer. The highly selective inhibitor of PI3Kδ, IOA-244, blocks the activity of Tregs among other things, thus reprograms the anti-tumor immune response. **Methods:** IOA-244 was investigated in a two-part FIH study. Part A explored the continuous daily dosing of IOA-244 at 10, 20, 40 and 80 mg. Part B consists of expansion cohorts of specific tumor indications, including pre-treated uveal melanoma patients (pts). Primary objective: safety of the anticipated biologically effective dose (BED), or the recommended phase 2 dose (RP2D). Secondary objectives: PK; PD (e.g., inhibition of CD63 expression on basophils, changes in immune cell subsets in peripheral blood); RECIST 1.1.-based responses; PFS and OS. Exploratory studies: changes in circulating immune cells by Cytometry by Time of Flight (CyTOF); response assessments by radiomics **Results**: Part A Solid Tumor (completed): Sixteen pts were treated in 4 cohorts each with 4 pts. Pts characteristics: uveal melanoma (9/16; 56%), cutaneous melanoma (5/16; 31%) and pleural mesothelioma (2/16; 13%). Four pts had at least one serious TEAE, none considered related to IOA-244. There was no treatment-emergent adverse events (TEAE) leading to study drug discontinuation, immune related toxicity or Dose Limiting Toxicity. CTCAE v5 Grade 1 and 2 were observed, including 2 cases of transient diarrhoea and 2 of AST/ALT elevation. Part A (Completed) – Subgroup Uveal Melanoma Pts (progressed $\geq$1 line prior therapy): 9 pts treated (3/9 pts ongoing). Mean time on treatment: 7.7 mo (range: 1.8-16.0 mo with 3 pts ongoing). ORR (RECIST 1.1): CR+PR: 0/9 (0%); SD: 6/9 (67%). Median OS: 5.4 mo - not determined (% alive at 1 year: 44% with 3 pts ongoing). CT images from 7/9 patients were assessed for changes in their metastatic lesions by radiomics (baseline and Week 8). Based on 147 matched lesions, 19% had complete responses and 16% had new lesions. In the liver, non-progressive disease was observed in 61% of all lesions, including 42% with either complete response or volume reduction of more than 30%. Using CyTOF, circulating Tregs were reduced while CD8 and NK cells were increased. Part B Uveal Melanoma Expansion Cohort (ongoing): 7 patients (7/7 pts ongoing); mean time on treatment 3.7 mo. ORR (RECIST 1.1): SD in 4/7 pts (57%). Part A Follicular Lymphoma Cohort (ongoing): At 20 mg: 4/4 pts. No DLT. At 80 mg: recruiting. **Conclusions:** In addition to being well tolerated, IOA-244 at the 80 mg dose shows reduction in peripheral blood Tregs and anti-tumor responses based on radiomics. Therefore, RECIST 1.1.-derived SD may underestimate anti-tumor activity of IOA-244 in treatment-resistant uveal melanoma. Additional patients will be treated to further refine this radiomics-based observation. Clinical trial information: NCT04328844. Research Sponsor: iOnctura SA.

3108 **Poster Session**

Phase Ib study of selinexor and eribulin combination in advanced solid tumors and triple-negative breast cancer.

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Background: Selinexor (KPT-330) is potent inhibitor of Exportin-1. *In vitro*, Selinexor was found to be synergistic with eribulin in triple negative breast cancer (TNBC) cell lines and enhanced antitumor activity of eribulin in TNBC patient-derived xenografts (PMID 28810913). **Methods:** We conducted a phase Ib trial in combination of selinexor and eribulin using 3 + 3 design in dose escalation for patients with advanced solid tumors and in TNBC in dose expansion cohort. Eribulin could be discontinued after combination for 6 cycles at physician discretion. Primary objectives: Safety, Recommended Phase 2 Dose (RP2D). Secondary Objectives: Objective Response Rate (ORR), Duration of Response (DOR), Disease Control Rate (DCR), Overall Survival (OS) and Progression Free Survival (PFS). **Results:** 31 patients, TNBC (n = 19), sarcoma (n = 8), others (n = 4) enrolled in dose escalation (n = 10) and dose expansion phases (n = 21). Median prior therapies:4 (1–6). Study initiated selinexor at 60mg twice weekly and eribulin 1.4mg/m^2 on Day1, Day8 every 3 weeks which led to 1 Dose Limiting Toxicity (DLT) and hence, selinexor 80mg once weekly and eribulin 1mg/m^2 was elected as RP2D due to efficacy and tolerability. As of 01/15/2022, of 29 patients (94%) who have discontinued treatment, 24 (77%) were due to progressive disease, 3 (10%) withdrew consent and 2 (6%) due to toxicities (G1 pneumonitis; G3 neutropenia) while 2 (6%) remain on trial. All 31 patients had at least one treatment emergent adverse event (TEAE) while most prevalent TEAEs (all grades) were leukopenia (77%), nausea (71%), anemia and neutropenia (68%) and fatigue (48%). The most common G3/4 TEAE were leukopenia (26%) and neutropenia (29%). 2 DLTs occurred; 1 in first dose level (DL); 1 in second DL dosed at selinexor 80 mg once weekly due to G3 neutropenia. ORR for all was 10% while DCR (SD+PR+CR) > 6 months seen in 3 (15%) TNBC and 2 (20%) sarcoma patients. The median OS and PFS for all were 12.3 (7.3, 27.3) months and 2.3 (1.6, 4.1) months. In dose escalation cohort, ORR was 10% where one patient (3%) with vaginal SCC had confirmed PR (-44%) for 2.1 months. Five patients (62.5%) with sarcoma had stable disease (SD). One patient with high grade sarcoma has SD for 68 months and remains on selinexor after 4 months of eribulin and selinexor. In TNBC dose expansion (n = 19), ORR was 10.5% with 2 confirmed PRs and median duration of response (DOR) of 10.8 months. One patient who has remained on treatment for 18 months, and after receiving 8 months of eribulin and selinexor, remains on selinexor with 100% target regression and an indeterminate brain lesion. **Conclusions:** Selinexor with eribulin is safe with manageable toxicity profile and modest overall clinical efficacy. Durable responses and disease control were observed with metastatic TNBC. Further study is needed to examine the determinants of response to this combination. Clinical trial information: NCT02419495. Research Sponsor: Karyopharm Therapeutics, U.S. National Institutes of Health, Clinical and Translational Sciences Award (1UL1TR003167) (NIH/NCATS), and MD Anderson Cancer Support Grant (P30CA016672) (NIH-NCI).

3109 **Poster Session**

Central nervous system (CNS) outcomes and progression patterns in patients with *RET* fusion-positive lung cancers treated with selpercatinib.

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Background: Selpercatinib, a potent/selective RET inhibitor, is approved for the treatment of *RET* fusion-positive non-small cell lung cancers. While the drug is known to have substantial intracranial activity (intracranial ORR 82%) in patients with existing brain metastases, (1) central nervous system (CNS) outcomes in patients without brain metastases and (2) CNS progression patterns in patients with brain metastases have not been explored. **Methods:** Patients with advanced *RET* fusion-positive lung cancers were prospectively treated with selpercatinib on the registrational LIBRETTO-001 trial (NCT03157128) or the LIBRETTO-201 multi-center expanded access program (EAP, NCT03906331). Key overall and CNS eligibility criteria were previously presented. Patients with and without pre-selpercatinib brain metastases who underwent serial CNS and extracranial imaging were eligible for analysis. The data cutoff was November 24, 2020. Cumulative incidence rates (CIRs) were calculated using a competing risk model with systemic progression of disease (PD) or death as competing risks; patients with simultaneous CNS and systemic PD were treated as having had CNS PD. **Results:** Sixty-two patients (48 LIBRETTO-001, 14 EAP) were identified. Median age was 64. Thirty-two (52%) were female and 47 (76%) were never smokers. The most common 5' fusion partner was *KIF5B* (68%). The median number of prior therapies was 2 (range 1-11); 34% received prior multikinase inhibitor therapy. The median time on treatment was 21.8 months. Thirty-one (50%) patients had no baseline brain metastases. In these patients, the CIR of CNS metastasis was 0% at 6 months and 12 months; none of these patients developed CNS metastasis during selpercatinib treatment. The 9 patients that progressed did so extracranially. Of the 31 patients with baseline brain metastases, 12 (39%) had prior CNS radiation and 3 (10%) had prior CNS surgery. At the time of data cut-off, 23 patients had some evidence of progression, including 8 in both the CNS and systemically, 6 only in the CNS, and 9 only systemically. Overall, 17 of the 31 patients with baseline brain metastasis did not develop evidence of CNS progression as of the data cut. Among patients with baseline brain metastasis, the CIR for evidence of CNS PD was 6.7% at 6 months and 27.4% at 12 months. **Conclusions:** In patients with *RET* fusion-positive lung cancers without baseline brain metastases, new CNS metastases were not observed during selpercatinib therapy. Among patients with baseline brain metastasis, a substantial number did not experience progression in the CNS on treatment. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

3110 **Poster Session**

Phase I dose-escalation study of IBI351 (GFH925) monotherapy in patients with advanced solid tumors.

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Background: IBI351(GFH925) is an irreversibly covalent inhibitor of $KRAS^{G12C}$. In this first-in-human dose-escalation study, we report the preliminary safety and anti-tumor activity of IBI351 (GFH925) in patients (pts) with advanced solid tumors harboring the KRAS p.G12C mutation. **Methods:** Pts with locally advanced, recurrent or metastatic solid tumors with $KRAS^{G12C}$ mutation for whom standard therapy had failed were enrolled. Phase I dose escalation had an accelerated titration design for dose level 250mg QD and a BOIN design with 450/700/900mg QD. The primary end points were safety and tolerabilityThe secondary end points were pharmacokinetics (PK) and anti-tumor activity of IBI351(GFH925) monotherapy per RECIST v1.1. **Results**: As of Feb 07 2022, 15 pts (13 men, 2 women; median age: 62 yrs, range: 48–74 yrs) were enrolled, among whom 12 had non-small cell lung cancer (NSCLC), and 3 had colorectal cancer (CRC). 4 pts had ≥3 prior lines of treatment (tx). Median tx duration was 66.5 ds (range: 21–98 ds). No dose-limiting toxicity (DLT) or any ≥grade 3 treatment-related adverse events were observed in any dose cohorts. A total of 12 patients (80.0%) had treatment-related adverse events (grade 1, n = 6; grade 2, n = 6). By investigator-assessment, tumor response was evaluated in 9 pts (4 with ≥2 assessments); 6 pts had not reached their first assessment. 2 pts had PR (1 NSCLC at wks 12, 450mg, tx ongoing; 1 CRC at wks 6, 700mg, tx ongoing), 4 pts (NSCLC) had SD, and 3 pts had PD (1 NSCLC at wks 12, 2 CRC at wks 6). As data cut-off date, 11 pts were continuing to receive IBI351 (GFH925). **Conclusions**: IBI351(GFH925) was well-tolerated without unanticipated adverse events across all doses explored in pts with advanced solid tumors harboring the KRAS p.G12C mutation. The data also demonstrated the preliminary efficacy signal of IBI351 (GFH925) in previously treated advanced NSCLC and CRC. Clinical trial information: NCT05005234. Research Sponsor: Innovent Biologics, Inc., China.

3111 **Poster Session**

Baseline predictors of hematological toxicity in patients with advanced cancer treated with ATR inhibitors in phase I/II clinical trials.

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Background: Ongoing trials are exploring ATR inhibitors (ATRi) in genomically selected contexts. However, myelosuppression, particularly anemia, has limited the therapeutic window of this class of drugs. We sought to discover clinical biomarkers predicting severe hematological toxicity from ATRi. **Methods:** We retrospectively analyzed clinical parameters and peripheral blood cell indices retrieved from complete blood count (CBC) reports of patients (pts) pre- and during treatment with an oral ATRi on phase I/II trials at our center. Pts received ATRi monotherapy or in combination with a PD1 inhibitor (PD1i) or a PARP inhibitor (ATRi+PARPi) in dose-escalation and expansion cohorts, which included ATRi at potentially toxic doses. **Results:** 37553 indices from 2209 CBC reports of 141 pts treated with an ATRi from 10/2017 to 1/2022 were analyzed. 132 (93.6%) pts received ATRi +/- PD1i; 9 (6.4%) pts received ATRi+PARPi. The incidences of ≥ grade (G) 3 anemia, neutropenia and thrombocytopenia were 47.5%, 31.9% and 11.4%. 73/141 (51.8%) pts received red cell transfusion. Baseline risk factors predicting ≥G3 anemia on univariate analysis included: lower median (med) hematocrit (Hct) (hazard ratio (HR) (95% confidence interval) = 3.05 (1.82, 5.13) ≤med vs > med; $p < 0.0001$), hemoglobin (Hb) (HR = 2.74 (1.64,4.57) ≤med vs > med; $p = 0.0001$), mean corpuscular Hb concentration (HR = 1.85 (1.11,3.10) ≤med vs > med; $p = 0.019$); and higher median immature reticulocyte fraction (HR = 0.43 (0.25,0.71) ≤med vs > med; $p = 0.0012$), reticulocyte count (ct) (HR = 0.59 (0.35,0.97) ≤med vs > med; $p = 0.037$) and red cell distribution width (RDW) (HR = 0.54 (0.33,0.88) ≤med vs > med; $p = 0.015$). On multivariate analysis, lower median Hct (HR = 3.76 (2.15, 6.6) ≤med vs > med; $p < 0.0001$), higher immature granulocyte ct (HR = 1.71 (1.30, 2.25) per 1 fold increase; $p = 0.0001$), higher RDW (HR = 7.83 (1.70, 36.03) per 1 fold increase; $p = 0.0082$) and higher ATRi starting dose (HR = 1.40 (1.05, 1.86) per 1 fold increase; $p = 0.022$) significantly predicted ≥G3 anemia risk. Baseline risk factors for ≥G3 neutropenia on univariate analysis included: lower median absolute neutrophil ct (ANC) (HR = 2.26 (1.18, 4.33) ≤med vs > med; $p = 0.015$) or white blood cell ct (WBC) (HR = 2.73 (1.40, 5.33) ≤med vs > med; $p = 0.0032$). On multivariate analysis, lower median WBC (HR = 2.85 (1.45, 5.59) ≤med vs > med; $p = 0.0024$) was associated with higher risk of neutropenia, while ATRi+PARPi increased risk of neutropenia (ANC < 0.75) (HR = 4.15 (1.40, 12.3); $p = 0.01$) and thrombocytopenia (HR = 3.90 (1.47, 10.4); $p = 0.0064$). **Conclusions:** ≥G3 anemia was frequent in pts receiving ATRi. At baseline, lower median Hct and higher RDW predict severe anemia, while lower WBC predicts neutropenia from ATRi. ATRi+PARPi has increased risk of neutropenia and thrombocytopenia vs ATRi +/- PD1i. These indices may inform patient selection and CBC monitoring for future ATRi trials. Research Sponsor: None.

3112 **Poster Session**

A phase Ib study of the combination of alisertib (Aurora A kinase inhibitor) and MLN0128 (dual TORC1/2 Inhibitor) in patients with advanced solid tumors, final expansion cohort data.

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Background: In prior work, senescence and up-regulation of genes in the PI3K/AKT/mTor pathway were observed in patient-derived xenograft models treated with alisertib to resistance, and tumor growth inhibition was observed when MLN0128 (sapanisertib) was added to alisertib. In a previously reported dose escalation cohort of patients with advanced solid tumors treated with the combination of alisertib and MLN0128, the maximum tolerated dose (MTD) was alisertib 30mg BID days 1-7 of a 21-day cycle and MLN0128 2mg daily on a continuous schedule. Presented here are final results from the dose expansion portion of this clinical trial. **Methods:** Three cohorts of patients were treated with the combination at the MTD. Patients with advanced solid tumors, refractory to standard therapy, were assigned to either single-agent treatment with alisertib (Group 1) or MLN0128 (Group 2) on days 1-7 of Cycle 1. For the remainder of the study, patients received combination treatment. Group 3 enrolled patients with refractory pancreatic adenocarcinoma who were treated with standard dosing of the combination. Biopsies were performed in Groups 1 and 2 prior to treatment initiation and after both the single-agent lead-in and 7 days of combination treatment, with assessment of pharmacodynamic markers. Functional imaging was performed pre-treatment and after Cycle 1. **Results:** A total of 31 patients with refractory cancers were treated. Group 1 included patients with breast (5), colorectal (2), ovarian (2), and pancreatic (1) cancers. Group 2 included patients with breast (4), colorectal (2), pancreatic (2), uterine (1), and kidney (1) cancers. Eleven patients with refractory pancreatic cancer were treated in Group 3. Median time on study was 11.6 weeks in Group 1, 6 weeks in Group 2, and 9 weeks in Group 3. One partial response was documented in Group 1. One patient with pancreatic cancer in Group 1 continued on study for 47 weeks, and another pancreatic cancer patient in Group 3 continued on study for 28 weeks. Toxicity was similar across cohorts, with mucositis, fatigue, hyperglycemia and neutropenia reported as most common. Biopsy results were significant for increased apoptosis and tumor-infiltrating immune cells noted in tissues from 4 patients treated with the MLN0128 lead-in. Decreased F18-FDG uptake on PET/CT, often with increased ADC values in diffusion MRI, was observed in metastatic liver lesions in 4 patients after Cycle 1. **Conclusions:** In an expansion cohort of 31 patients treated with the combination of MLN0128 and alisertib at the previously defined MTD, treatment was tolerable with an expected toxicity profile. Prolonged stable disease was observed in 2 patients with pancreatic cancer. Increased apoptosis and tumor-infiltrating immune cells were noted in tissues from patients treated with a lead-in of MLN0128. Clinical trial information: NCT02719691. Research Sponsor: Investigator Initiated Trial Agreement between Dr. Jennifer Diamond and Takeda Pharmaceutical Company.

3113 **Poster Session**

Pan-cancer analysis of exogenous (microbial) sequences in tumor transcriptome data from the ORIEN consortium and their association with cancer and tumor microenvironment.

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Background: The tumor microbiome holds great potential for its ability to characterize various aspects of cancer biology and as a target for rational manipulation. For many cancer types, little is known about the role of microbes and in what contexts they affect clinical outcomes. Non-human (i.e. exogenous) sequences can be observed in low abundance within high throughput sequencing data of tumors. Here, we describe a collaboration among members of The Oncology Research Information Exchange Network (ORIEN) to leverage tumor biopsy RNAseq data collected under a shared protocol and generated at a single site to better understand the tumor microbiome, its association with prognostic features of the tumor microenvironment (TME) such as hypoxia, and how it may be used to improve clinical outcomes. **Methods:** Tumor RNAseq samples from 10 primary source locations including the tissues colon, lung, pancreas, and skin from ORIEN and similar cancers from The Cancer Genome Atlas (TCGA) were processed through the exoTIC (exogenous sequencing in tumors and immune cells) pipeline to identify and count exogenous sequences, filter contaminants, and normalize across datasets. Gene expression signatures of the TME, such as hypoxia, were calculated using 'tmesig'. Microbe relative abundances were modeled with primary tumor location and hypoxia score using a gamma-distributed generalized linear regression via the stats package in R. **Results:** We analyzed RNAseq data of 2892 and 2720 tumors from ORIEN and TCGA, respectively. Patients' ages were significantly greater in the ORIEN than the TCGA dataset (62 vs 58 yo, t-test $p<0.001$). The ORIEN data contained more sarcoma samples than TCGA (n = 691 vs 259) with roughly equivalent numbers in other cancer types. Fewer microbes were significantly associated with the hypoxia score than with cancer type (n = 32 vs 210). This trend was observed in both the ORIEN and TCGA datasets. The largest effect sizes were observed between microbes and small cell lung cancer. **Conclusions:** We found microbial sequences in all ORIEN and TCGA tumor RNAseq samples tested. Cancer type showed more significant associations with microbes than a hypoxia signature. These observations merit further investigation into the interaction between microbes and the TME. Research Sponsor: None.

Cohort summary.

	ORIEN	TCGA	p
n	2892	2720	
Age (mean (SD))	58.49 (14.49)	62.02 (14.36)	<0.001
Sex = male (%)	1418 (49.0)	1371 (50.5)	0.297
Top Cancers (%)			<0.001
Thyroid Carcinoma	539 (18.6)	502 (18.5)	
Colon Adenocarcinoma	500 (17.3)	478 (17.6)	
Sarcoma	691 (23.9)	259 (9.5)	
Metastatic (%)	643 (22.2)	0 (0.0)	<0.001
Treatment Naive (%)	2284 (79.0)	2695 (99.2)	<0.001

3114 **Poster Session**

Temsirolimus (T) in patients (pts) with solid tumors with mTOR mutation: Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study.

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Background: TAPUR is a phase II basket study evaluating anti-tumor activity of commercially available targeted agents in pts with advanced cancers with genomic alterations. Results in a cohort of solid tumor pts with *mTOR* mutation (mut) treated with T are reported. **Methods:** Eligible pts had solid tumors, no standard treatment (tx) options, measurable disease, ECOG Performance Status (PS) 0-2, and adequate organ function. Genomic testing was performed in CLIA-certified, CAP-accredited site selected labs. Pts matched to T had various solid tumors with *mTOR* mut. After antihistamine pre-treatment, 25 mg T was infused over 30-60 minutes weekly until disease progression. Primary endpoint was disease control (DC), defined as complete (CR) or partial (PR) response, or stable disease at 16+ weeks (wks) (SD 16+) (RECIST v1.1). Low accruing histology-specific cohorts with the same genomic alteration and tx were collapsed into a single histology-pooled cohort for this analysis. For histology-pooled cohorts with sample size $\leq$28, the results are evaluated based on a one-sided exact binomial test with a null DC rate of 15% vs. 35% (α = 0.10 and power=0.86 for N = 26) and one-sided 90% confidence interval (CI). Other efficacy endpoint estimates are presented with two-sided 95% CIs. Secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. **Results:** 29 pts with solid tumors (11 histologies) with *mTOR* mut were enrolled from June 2016 to June 2020. 3 pts were not evaluable (2 pts, no post-baseline tumor eval; 1 pt, no measurable disease) and excluded from efficacy analyses. The Table shows demographics and outcomes. 2 PR and 10 SD16+ were observed for a DC rate of 46% (one-sided 90% CI: 32% to 100%) and an objective response (OR) rate of 8% (95% CI: 1% to 25%); the null hypothesis of a 15% DC rate is rejected (p<0.001). 5/10 pts with SD16+ had CRC or biliary cancer. Of the 2 pts with PR, one had uterine cancer and T1977R mut and the other had head and neck cancer and I1636V mut. The durations of PR were 12.3 and 23.9 wks, respectively, and median duration of SD was 34.5 wks (range: 18.7, 90.0) for pts with SD16+. 8 pts experienced grade 3 or grade 4 AEs or SAEs at least possibly related to T, including acute kidney injury, epistaxis, hyperglycemia, hypertension, hypertriglyceridemia, mucositis, leukopenia, thrombocytopenia, and pneumonitis. **Conclusions:** Monotherapy T showed evidence of anti-tumor activity in pts with advanced solid tumors with *mTOR* mut. Additional study is warranted to confirm the efficacy of T in pts with *mTOR* mut. Clinical trial information: NCT02693535. Research Sponsor: Pfizer, Pharmaceutical/Biotech Company.

Demographics and baseline characteristics (n = 29) and efficacy outcomes (n = 26).

Median age, yrs (range)		61 (36, 78)
ECOG PS, %	0	52
	1	45
	2	3
Prior systemic regimens, %	1-2	21
	≥3	79
DC rate, % (OR or SD16+) (one-sided 90% CI)		46 (32, 100)
OR rate, % (95% CI)		8 (1, 25)
Median PFS, wks (95% CI)		13.6 (8.1, 27.7)
Median OS, wks (95% CI)		45.3 (27.4, 61.4)

3115 **Poster Session**

Genomic and clinical characteristics of *MET* alterations in solid tumors among the 10,475 Chinese patients.

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Background: Somatic alterations of the MET oncogene are emerging as an attractive target in human cancers, thus, understanding the molecular epidemiology of MET alterations is essential. While the occurrence of MET exon 14 skipping mutations (MET ex14) in US lung cancer patients is well defined, it is not widely published for Chinese patients. In addition, reports on the occurrence of METex14 outside lung cancer and other clinically relevant MET alterations across all cancers are limited. **Methods:** The *MET* ex14 alterations and amplification data of 10475 Chinese cancer patients from 16 types of cancer were obtained in Acronmed database, including non-small cell lung cancer (NSCLC, n = 5719), Hepatocellular carcinoma (HCC, n = 511), colorectal cancer (CRC, n = 1779), renal cell carcinoma (RCC, n = 1169), Gastric carcinoma (GC, n = 679), etc. Genomic profiling of DNA was performed through a next-generation sequencing. **Results:** Of all pan-cancer patients, 141 cases (1.3%) with *MET* alterations were identified, including *MET* Amp (0.9%) and *MET* ex14 (0.7%). Compared to Western population (~3%), the frequency of *MET* alterations is much lower in Chinese cancer patients (1.3%). *MET* Amp were most commonly found in HCC (1.7%), GC (1.3%), NSCLC (0.7%), RCC (0.7%), CRC (0.2%). *MET* ex14 occurred most in NSCLC (0.5%), HCC (0.3%), CRC (0.2%). HCC were significantly to have *MET* Amp than NSCLC (P = 0.01), while *MET* ex14 mutations were more likely to be observed in NSCLC (p = 0.02). We further analyzed the *MET* mutation characteristics of NSCLC. The most frequently co-mutated genes in *MET* ex14 cohort were *TP53* (48%,15/31), *KMT2B* (23%,7/31) and *EGFR* (16%, 5/31). Except for *TP53* (65%,22/34) and *EGFR* (56%,19/34) mutations. Interestingly,other gene mutations were rare in the patients with *MET* Amp. In addition, *MET* ex14 patients showed significant lower *EGFR* mutation comparing to the *MET* amp patients (P = 0.002). **Conclusions:** Our study demonstrated a landscape of *MET* alterations among the Chinese population. *MET* mutations occurs in a variety of solid tumors, indicating that these patients may benefit from *MET* inhibitors. Research Sponsor: None.

3116 **Poster Session**

Variable detection of actionable alterations across racial groups and association with testing patterns.

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Background: Molecular landscape studies are critical to biomarker discovery and precision oncology research. However, non-White patients (pts) have historically been under-represented. In this study, we examine clinico-genomic data from a network of community oncology clinics to evaluate real-world mutational frequencies in Black, White, and Asian pts with cancer. **Methods:** We utilize Genospace, a precision medicine software, to harmonize clinical data from the Sarah Cannon research network of U.S. community oncology practices with genomic data from commercial NGS vendors. Pts with known race and NGS test results from September 2015 to November 2021 are assessed. Variants of uncertain significance (called by NGS vendor) are excluded. Asian pts are not evaluable in all instances because of low pt number. Statistical analyses include Chi squared and two sample test of proportions with Benjamini-Hochberg false discovery rate correction. **Results:** A total of 18,399 pts are assessed, with 7% Black (n = 1,319), 92% White (n = 16,903), and 1% Asian (n = 177) pt representation. The most common tumor types include non-small-cell lung (NSCLC; 27% of Black pts, 30% of White pts, 33% of Asian pts), colorectal (15% of Black pts, 12% of White pts, 14% of Asian pts), breast (14% of Black pts, 11% of White pts, 9% of Asian pts), and prostate (6% of Black pts, 5% of White pts, 3% of Asian pts) at roughly equal proportions across racial groups. In NSCLC, EGFR mutations and ALK fusions significantly enrich in Asian pts while KRAS G12C is detected more frequently in Black patients (see table for details; Black: n = 353, White: n = 5,127, Asian: n = 58). In both prostate and breast cancers, plasma-based NGS is less common in Black pts than White pts (plasma-to-tissue ratio = 1.1 (Black prostate: n = 82); 1.5 (White prostate: n = 863); 0.6 (Black breast: n = 178); 0.9 (White breast: n = 1,918)). In prostate, AR mutations are detected less frequently in Black pts. However, when considering plasma-NGS results alone the detection frequency is roughly equal. Similarly, the gap in ESR1 detection frequencies in breast decreases when considering plasma-NGS results alone. **Conclusions:** Actionable alterations are detected across racial groups at variable frequencies with potential biological and technical underpinnings. In scenarios where plasma-NGS is commonly used to monitor for resistance mutations, discrepancies in NGS ordering patterns likely affect detection frequencies. Research Sponsor: None.

Select gene alteration frequencies across racial groups.

	Black	White	Asian
NSCLC EGFR mutation*	9%	9%	43%
NSCLC KRAS G12C	11%	9%	5%
NSCLC ALK fusion*	1%	1%	5%
Prostate AR mutation	13%	17%	-
Prostate AR mutation (plasma)	22%	22%	-
Prostate AR mutation (tissue)*	3%	8%	-
Breast ESR1 mutation	11%	18%	-
Breast ESR1 mutation (plasma)	20%	25%	-
Breast ESR1 mutation (tissue)	3%	11%	-

*$p < 0.05$.

3117 **Poster Session**

Stress keratin 17 as a novel biomarker of response in immune checkpoint blockade–treated head and neck squamous cell carcinoma.

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Background: Low response rates in immune checkpoint blockade (ICB) treated head and neck squamous cell carcinoma (HNSCC)drive a critical need for robust clinically validated biomarkers that can predict response to ICB. Stress keratin 17 (K17) is a known prognostic marker in various types of cancer, including HNSCC; however, its predictive value for ICB response has not been investigated. Preclinical studies suggest K17 suppresses macrophage-mediated CXCL9/CXCL10 chemokine signaling involved in attracting activated CD8+ T cells into tumors. Furthermore, knocking out K17 results in restored response to ICB in a HNSCC mouse model. Here, we evaluated if K17 protein expression predicts response to ICB in human HNSCC patients. **Methods:** We conducted a retrospective analysis of 26 HNSCC patients that received at least one cycle of pembrolizumab at the University of Wisconsin-Madison Carbone Cancer Center. Pretreatment, archival, formalin-fixed, paraffin-embeded samples were stained by immunohistochemistry using a K17 monoclonal antibody. Clinical outcomes were investigator-assessed for all patients with at least one post-treatment scan or evidence of clinical progression after treatment initiation. Based on independent pathology review, cases were categorized into K17 high vs K17 low based on a cut-off of > 5% strong cytoplasmic staining intensity of tumor cells in the invasive carcinoma component. Correlation between K17 expression and clinical outcomes was assesed using Fischer's exact test and log rank test. **Results:** The 26 patients included in this study were 85% male, median age 60.5 years, 74% ECOG performance status < 2, with 80% having received prior chemotherapy. Primary site included oral cavity (54%), oropharynx (23%), larynx (4%), or other (19%). Seventeen tumors (65%) showed high K17 expression, and 9 tumors (35%) showed low K17 expression. Eleven patients (42%) had programmed death ligand 1 (PD-L1)+ tumors as determined by combined positive score. Six patients (23%, all K17 low) achieved clinical benefit, while 20 patients (77%, 17 K17 high and 2 K17 low) had progressive disease. High K17 expression was associated with lack of clinical benefit ($p < 0.001$), shorter time to treatment failure ($p < 0.001$), progression-free ($p = 0.004$) and overall survival ($p = 0.02$). PD-L1 expression by immunohistochemistry (clone 22C3) did not correlate with K17 expression or clinical outcome. **Conclusions:** Our findings suggest that K17 expression may predict clinical benefit from ICB in HNSCC patients, thus supporting further validation studies. Research Sponsor: U.S. National Institutes of Health.

Response Status	K17 High		K17 Low		Total	
Clinical benefit	0	(0.0%)	6	(75.0%)	6	**(23.1%)**
Progressive disease	18	(100.0%)	2	(25.0%)	20	**(76.9%)**
All	**18**		**8**		**26**	

3118 **Poster Session**

Genomic landscape of SMARCA4-deficient lung tumors by clinical RNA sequencing.

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Background: SMARCA4-deficient lung cancer is an undifferentiated lung cancer subtype associated with poor prognosis and morphological features that make them challenging to distinguish from sarcoma. These tumors are known to be resistant to standard of care surgery, radiation, and chemotherapy. Recent case reports suggest that these tumors might be resistant to immunotherapy. An assessment of the genomic and transcriptomic features of *SMARCA4*-deficient thoracic tumors may identify potential novel targets and treatment strategies for this new WHO lung cancer classification. **Methods:** We retrospectively analyzed de-identified NGS data from 8,484 thoracic formalin-fixed, paraffin-embedded tumor biopsies from lung cancer patients sequenced using the TempuslxT solid tumor assay (DNA-seq of 595-648 genes at 500x coverage; whole-exome capture RNA-seq). Tumor-normal match sequencing was performed for all tumors, enabling the detection of incidental germline alterations across 46 genes. SMARCA4-deficiency was defined as tumors with a pathogenic or likely pathogenic *SMARCA4* single nucleotide variant, insertion/deletion, or copy number alteration. Statistical significance was determined using Fisher's exact test and Wilcoxon rank-sum tests. **Results:** *SMARCA4*-deficiency was detected in 370 (4.4%) tumors, of which over 80% were stage III or IV. *SMARCA4*-deficient tumors included more male patients (63% vs 49%, $p < 0.001$) and younger age at diagnosis (median 64 vs 68 years, $p < 0.001$). There were more patients with high tumor mutational burden (TMB-H, ≥10 mutations per megabase) (34% vs 15%, $p < 0.001$), and fewer patients with positive PD-L1 immunohistochemical staining (44% vs 54%, $p = 0.009$) compared to *SMARCA4* wild-type tumors. Microsatellite instability status occurred at similar low frequencies across SMARCA4-deficient vs wild-type tumors (0.8% vs 0.5%, $p = 0.5$). *SMARCA4*-deficient tumors showed enrichment for somatic mutations in *TP53* (71% vs 47%, $q < 0.001$), *STK11* (22% vs 6.8%, $q < 0.001$), *KEAP1* (15% vs 4.2%, $q < 0.001$), and *CDKN2A* (15% vs 5.9%, $q < 0.001$) compared to wild-type. Tumor normal-match sequencing identified incidental germline mutations in *MUTYH* (2.2%), *ATM* (1.1%), *ATP7B* (0.5%), and *MSH6* (0.5%) for *SMARCA4*-deficient tumors. RNA-sequencing analysis confirmed reduced transcriptional expression of *SMARCA4* ($p < 0.001$), *CD274* (PD-L1; $p < 0.001$), *TNFRSF18* ($p < 0.001$), and *TNFRSF4* ($p = 0.035$) in deficient tumors vs wild-type. Furthermore, *SMARCA4*-deficient tumors revealed reduced infiltration of CD4+ T cells (19% vs 22%, $p < 0.001$). **Conclusions:** This study reveals the unique genomic and transcriptional characteristics of *SMARCA4*-deficient lung tumors. Further studies are needed to assess the impact of immunotherapies and targeted therapies among this patient population. Research Sponsor: Tianhong Li.

3119 **Poster Session**

Clinical utility of tumor next-generational sequencing (NGS) panel testing to inform treatment decisions for patients with advanced solid tumors.

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Background: There is limited information about the clinical utility of targeted NGS panel testing to inform decision-making for patients with advanced solid tumors. The Ontario-wide Cancer Targeted Nucleic Acid Evaluation (OCTANE) is an ongoing prospective study that enrolled over 4,500 solid tumor patients for NGS panel testing. We performed a retrospective survey of 21 medical oncologists enrolling OCTANE patients at a single academic institution to evaluate the impact of NGS testing on treatment decisions. **Methods**: Patients and treating oncologists were identified at the Princess Margaret Cancer Centre between 2016-2021. Tumor-only sequencing was performed using a custom hybridization capture panel of 555 cancer genes (Hi5) or a commercial 161-gene amplicon DNA/RNA panel (Oncomine Comprehensive v3). Oncologists were asked to review testing results for individual patients and complete a survey indicating whether NGS testing impacted treatment decisions. Mutations were defined as actionable based on clinical judgment and compared to classifications provided by OncoKB, an FDA-recognized precision medicine knowledgebase. The primary outcome of this study was rate of treatment change based on mutation results. Patient, test, and physician factors were evaluated for association with treatment changes using univariate analyses and a mixed effects model. **Results:** Two cohorts were surveyed, the first between 2017-2019 and the second in 2021. Of the 582 surveys sent, 394 (67.7%) were completed. Each physician completed a median of 19 surveys (range, 9-48). We found that 188 (47.7%) patients had a mutation classified as actionable by the oncologist, of whom 134 (71.3%) had $\geq$1 OncoKB-defined actionable mutation(s). 62/394 (15.7%) patients were matched to a treatment, of whom 37 were enrolled in a clinical trial, 13 received an approved drug, 4 were prescribed off-label therapy and 8 avoided ineffective treatment. 127/188 (67.5%) patients with actionable mutations did not receive treatment due to lack of available therapy, stability on current regimen, clinical deterioration or patient decision. Rate of treatment change was highest for bowel (15/37, 40.5%), breast (14/52, 27.5%), biliary tract (6/22, 27.3%) and lung (4/17, 23.5%) cancers. Treatment decisions were not associated with patient age, gender, physician clinical experience, physician gender, testing experience, OncoKB mutation level or time from biopsy to sequencing. There was no difference in overall survival between patients with matched vs. no matched treatment ($p = 0.55$, median survival not reached). **Conclusions:** OCTANE testing led to a change in drug treatment in 15.7% of patients, supporting the clinical utility of NGS panel testing for patients with advanced solid tumors. Patient, test, and physician characteristics were not significantly associated with treatment change. Research Sponsor: This study was conducted with the support of the Ontario Institute for Cancer Research through funding provided by the Government of Ontario and by the Princess Margaret Cancer Foundation.

3120 **Poster Session**

Pan-cancer association between increased iron utilization and poor prognosis highlights potential of transferrin receptor-targeting therapies in multiple tumor types.

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Background: The cell-surface transferrin receptor TFR1 imports iron-bound transferrin into cells via clathrin-mediated endocytosis. Tumors require constitutive iron import to drive proliferation, and several studies establish TFR1 as a target able to facilitate intracellular delivery of cytotoxic therapeutic molecules. Our own work previously revealed association between high expression of *TFRC*, the gene encoding TFR1, and high risk for poor outcome in diffuse large B-cell lymphoma (DLBCL). We showed therapetuic targeting of TFR1 in DLBCL results in significant anti-tumor benefit. Systematic analysis of *TFRC* expression as a prognostic marker across tumor types, however, has not been investigated. **Methods:** Tissue samples underwent comprehensive molecular profiling at Caris Life Sciences. Analyses included next generation sequencing of DNA (592 Gene Panel, NextSeq, or whole exome sequencing, NovaSeq), RNA (NovaSeq, whole transcriptome sequencing, WTS) and immunohistochemistry. Overall survival (OS) was calculated from date of tissue collection to last contact from insurance claims data and employed Kaplan-Meier analysis by Wilcoxon statistics, with $p < 0.05$ defined as significant. **Results:** Amongst 47 cancer types included, colorectal cancer (CRC) displayed the highest level of *TFRC* mRNA, followed by gastric cancer. In an all-tumor cohort (n = 93248), patients with higher *TFRC* expression (cutoff = median) had significantly worse OS (HR = 1.348, 95% CI [1.317-1.38], $p < 0.00001$). This was statistically significant in 23 individual tumor types. Drilling down further, *TFRC* adverse prognostic value was mainly driven by cohorts with larger number of samples in the database, including non-small cell lung cancer (n = 17309), CRC (n = 12860), breast cancer (n = 8632), ovarian carcinoma (n = 7998), uterine neoplasms (n = 6097), prostate adenocarcinoma (n = 3411), glioblastoma (n = 2821), gastric cancer (n = 1579), and others. Surprisingly, *TFRC* overexpression correlated with improved outcome in vulvar squamous cell carcinoma (VSCC, n = 297). *TFRC* was found to be most prognostic in prostate adenocarcinoma with median OS 1139 days in pts with high vs 3230 days in pts with low *TFRC* (HR = 2.556, 95% CI [2.213-2.951], $p < 0.00001$). **Conclusions:** Our study is the first to combine modern molecular profiling with a large cohort of clinical tissue samples to reveal a prognostic role for *TFRC* expression in a variety of solid tumor types. We found *TFRC* overexpression to be prognostic in a large proportion of histologies, though surprisingly association with improved OS in VSCC. Highest expression occured in CRC and gastric cancer, diseases with needs for new therapies. A number of TFR1-targeting therapeutics are currently at various stages of development, and warrant further investigation in disease cohorts identified from our study. Research Sponsor: None.

3121 **Poster Session**

Molecular characterization of cancers with *ALK* gene fusions in nonlung tumors.

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Background: *ALK* gene rearrangement is known as "diamond mutation". Targeted tyrosine kinase inhibitors have perfect therapeutic effects on *ALK* fusion lung cancer patients (pts), but the molecular characteristics of *ALK* fusions in other cancers have not been systematically elucidated. **Methods:** We retrospectively analyzed the NGS data of *ALK* fusion-positive Chinese tumor pts (n = 1068) to characterize *ALK* fusions in pan-cancer (excluding lung cancer) pts. **Results:** A total of 66 *ALK* fusion-positive pts with 13 types of cancer (excluding lung cancer) were screened, including 0.4% (24/5800) of brain tumor pts, 0.1% (11/7725) of gastrointestinal cancer pts, 0.4% (7/1741) of thyroid cancer pts, 0.5% (8/1732) of sarcoma pts, 0.2% (4/2031) of liver cancer pts, 0.6% (3/540) of melanoma pts, 9% (2/22) of inflammatory myofibroblastic tumor pts, 2.5% (2/79) of embryonal tumor pts, 0.4% (1/282) of lymphoma pts, 3.2% (1/31) of parotid carcinoma pts, 0.1% (1/985) of breast cancer pts, 0.4% (1/241) of prostatic cancer pts and 0.3% (1/320) of ovarian cancer pts. Herein, we reported 28 *ALK* fusion patterns, of which the most common partners were *EML4* (n = 24) and *STRN* (n = 8), and mainly occurred in brain tumors (14/24, 58.8%) and thyroid cancers (6/8, 75%), respectively. In addition, there were 8 *ALK* fusion modes that were never reported before. Of the *ALK* fusion patterns described above, 92.4% (61/66) of fusions were located at the most canonical site of *ALK* (exon20), preserving the intact kinase domain. Meanwhile, rare fusion positions in the *ALK* gene were also found, such as *PPP1CB-ALK*(ex2:ex4), *NUP107-ALK*(ex20:ex3), *COL14A1-ALK*(ex8:ex4), *BRAF-ALK*(ex9:-ex4), which preserve the extracellular and transmembrane domains, as well as *RASD2-ALK*(ex2:ex24), of which the breakpoint in *ALK* gene may disrupt the formation of kinase domain. **Conclusions:** We demonstrated the rarity of *ALK* gene fusions in nonlung cancers. Analyzing the *ALK* fusion characteristics of these cancer may help to clarify their pathogenesis and provide ideas for new drug treatment. Research Sponsor: None.

Partners of *ALK* gene fusions.

	Partners	Counts	Partners	Counts	Partners	Counts	Partners	Counts
Known fusions	*EML4*	24	*KIF5B*	2	*FN1*	1	*TIMP3*	1
	STRN	8	*PPP1CB*	2	*KLC1*	1	*TPM3*	1
	DCTN1	3	*TPM4*	2	*PLEKHH2*	1	*LCLAT1*	1
	NPM1	3	*CLIP2*	1	*PRKAR2A*	1	*PABPC1*	1
	ATIC	2	*CLTC*	1	*RANBP2*	1	*HMBOX1*	1
Unreported fusions	*AMN*	1	*GTF2I*	1	*RASD2*	1		
	BRAF	1	*NUP107*	1	*TBC1D16*	1		
	COL14A1	1	*ZKSCAN1*	1				

3122 **Poster Session**

Results of a phase II trial of the PARP inhibitor, niraparib, in BAP1 and other DNA damage response pathway deficient neoplasms.

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Background: BRCA1-Associated Protein 1 (BAP1) acts as a tumor suppressor and critical regulator of the cell cycle and DNA damage response (DDR). PARP inhibitors (PARPi) demonstrate synthetic lethality in BAP1 mutant (mBAP1) preclinical models, independent of underlying germline BRCA status. mBAP1 leads to a loss of functional protein in several solid tumors. This study aimed to explore the clinical activity of niraparib in patients (pts) with advanced tumors likely to harbor mBAP1. **Methods:** Eligible adult pts with measurable metastatic solid tumors having exhausted approved therapies, adequate organ function, and ECOG PS 0-1 were assigned to Cohort A (histology-specific): tumors likely to harbor mBAP1 (i.e., cholangiocarcinoma, uveal melanoma, mesothelioma, or clear cell renal cell carcinoma) with tissue available for mBAP1 confirmation; or Cohort B (histology-agnostic): tumors with other known non-BRCA confirmed DDR mutations. Known BRCA1 or 2 mutations or prior PARPi exposure were excluded. All pts received niraparib 200-300mg daily, depending on weight and/or platelet count. Radiographic response was assessed by RECIST v1.1 measured every 8 weeks while on treatment. The primary endpoint was ORR with secondary endpoints of PFS, OS, clinical benefit (CR+PR+SD), toxicity, and exploratory biomarker determinations. Cohort A employed Simon's optimal two-stage design to assess a 30% ORR increase ($a = 0.05$; power = 90%). Cohort B aimed to assess a 40% ORR increase for this molecularly selected/enriched patient population. **Results:** From 08/13/2018 to 12/21/2021, 37 pts enrolled from two different centers, with 32 evaluable for response (Cohort A n = 18; Cohort B n = 14). In Cohort A, best ORR was 1 PR (6%), 8 SD (44%; median 5.7 mo; range 2 - 9.4 mo), and 9 PD (50%). Cohort A was stopped at the first stage following the pre-specified Simon's design. mBAP1 was confirmed in 7/9 pts (78%) with PR or SD but in only 2/9 (22%) in those with PD. In Cohort B, best ORR was 6 SD (43%; median 7.5 mo; range 3.3 - 8.6 mo) and 8 PD (57%). Mutations in those with SD included ATM, CHEK2, PTEN, RAD50, and ARID1A. Common grade 3/4 AEs observed were anemia (16%), thrombocytopenia (16%), nausea (11%), and vomiting (8%). There were no unexpected nor grade 5 toxicities. **Conclusions:** The use of niraparib was well tolerated in pts with advanced treatment refractory solid tumors but failed to meet pre-specified efficacy threshold of ORR. However, clinical benefit was identified in 78% of patients in cohort A who had a confirmed mBAP1 tumor. Further correlative analyses are ongoing and additional clinical development restricted to mBAP1 tumors may be justified. Clinical trial information: NCT03207347. Research Sponsor: University of Florida Health Cancer Center and GlaxoSmithKlein.

3123 **Poster Session**

Inference of sample-specific genetic interactions to increase accuracy of indication prioritization in oncology clinical trials and facilitate exploration of combined therapy opportunities.

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Background: Precision oncology is growing rapidly in parallel with advances in high throughput sequencing. Development of new anti-cancer therapies is, however, still associated with low efficacy issues, leading to phase II and III clinical trial failures. Improved methodologies are required to identify clinical and molecular patient profiles associated with good drug response to inform decisions on indication prioritization. **Methods:** We used a sample-specific Genetic Interaction Graph Inference (ssGI^2) algorithm, integrating bulk tumor transcriptomic data as well as data collected from 120 public databases and scientific literature in oncology, to infer genetic interactions (GI). More than 10,000 genes from 17,000 samples, covering 195 oncology ICD10 codes, were used to infer GIs for each individual sample. GIs involving a given drug target are selected from a compendium of 17,000 networks of 2M GIs each, and ranked based on their prevalence in the patient cohort and data-support. The mean Z-scored expression of genes from the top ranked GIs were subsequently used to predict drug response for each patient and to calculate the response rate for each indication. Detailed information on each drug target's genetic interactors was used to characterize the drug's mechanisms of action and explore opportunities for combined therapies. We investigated our method's ability to predict good responders using four FDA approved immune and targeted therapies (pembrolizumab, nivolumab, ipilimumab and sorafenib) across seven clinical studies. Importantly this methodology is suitable for drugs with no clinical studies available. **Results:** Our results show that the prediction of good responders can be achieved with Precision-Recall AUC on average 13% higher than predictions based on drug target expression level solely, in five out of seven studies. Also, for each drug target, between 30 to 140 genetic interactors with good performance (Precision=0.92; Recall=0.61) were identified, suggesting potential synergistic effects of drugs, some of which have already been confirmed by clinical studies on combined therapies. **Conclusions:** Our ssGI^2-derived signatures are powerful predictors of good response to a drug even without available clinical data. Applying this methodology at a pre-clinical stage will significantly de-risk clinical trials, particularly for novel therapies, and could also support investigation of new combined therapies. Research Sponsor: My Intelligent Machines Inc.

3124 **Poster Session**

Comprehensive genomic profiling to identify gene alterations in DNA repair pathway across solid tumors.

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Background: Deleterious events in DNA damage response (DDR) are hallmarks of cancer associated with sensitivity to PARP inhibitors (PARPi) and immune checkpoint inhibitors (CPI). This study investigated DDR pathway alterations across solid tumors. **Methods:** Samples were sequenced with the Oncomap ExTra assay using tumor-normal paired whole-exome DNA sequencing to detect single base substitutions, indels, and copy number alterations that were clinically actionable, defined as associated with FDA approved drugs or clinical trial enrollment. Here, we report the frequency of MSI-high and TMB-high (>10 mutations/Mb), and clinically-actionable alterations for the following 49 DDR genes: *ARID1A, ATM, ATR, ATRX, BAP1, BARD1, BLM, BRCA1/2, BRIP1, CDK12, CHEK1/2, EPCAM, ERCC1/2/3/4/5, FANCA/C/D2/E/F/G/I/L/M, MLH1, MRE11A, MSH2/6, MUTYH, NBN, PALB2, PMS2, PPP2R2A, PTEN, RAD21/50/51/51B/51C/51D/52/54L, XRCC1/2/3*. **Results:** Of the 6055 patient samples profiled, 1633 (27.0%) had clinically actionable alterations in DDR genes; DDR alterations varied from 0-64.3% across tumor types. For the 5657 samples with TMB/MSI data, 429 (7.6%) had high TMB and 193 (3.4%) were MSI-high; MSI-high samples were usually TMB-high (n = 180; 93.2%). The percent of cancers that were TMB-high or MSI-high varied from 0-64.8% and 0-20.8% respectively. Actionable *BRCA1/2* gene alterations were present in 319 patients (5.3%, range 0-15.3%). Three cancers (biliary, brain and liver) had *BRCA1/2* alterations in less than 2% of patients but across the 49 DDR genes alterations were present in more than 20% of patients, representing a greater than 10-fold difference. Across solid tumors, this analysis identifies a group of 1314 patients (21.7%) who harbor a DDR gene alteration other than *BRCA1/2*. **Conclusions:** Defective DNA repair as detected by deleterious alterations in DDR genes along with TMB/MSI status has the potential to guide clinicians to FDA-approved therapy or clinical trial enrollment in a large percentage of patients across solid tumor types. Research Sponsor: Exact Sciences Corporation.

Number (percent) of patients with alterations in DDR, TMB-High and MSI-High.

Tumor Type	Total	All DDR genes	BRCA1/2	TMB-high	MSI-High
ALL	6055	1633 (27.0%)	319 (5.3%)	429 (7.6%)	193 (3.4%)
Biliary	89	28 (31.5%)	1 (1.1%)	0	0
Brain	264	102 (38.6%)	5 (1.9%)	3 (1.6%)	2 (1.1%)
Breast	1103	246 (22.3%)	69 (6.3%)	16 (1.5%)	2 (0.2%)
Endometrial	184	115 (62.5%)	13 (7.1%)	41 (23.0%)	37 (20.8%)
Epithelial Ovarian	275	90 (32.7%)	42 (15.3%)	5 (2.0%)	4 (1.6%)
Melanoma	188	65 (34.6%)	4 (2.1%)	69 (37.7%)	1 (0.5%)
Prostate	313	91 (29.1%)	22 (7.0%)	9 (2.9%)	8 (2.6%)
Stomach	156	51 (32.7%)	8 (5.1%)	21 (14.4%)	21 (14.4%)

3125 **Poster Session**

Molecular and immune landscape of *FH*-mutated cancers.

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Background: Fumarate Hydratase (FH) encodes an essential enzyme in the TCA cycle. Inactivating germline mutations in FH lead to hereditary leiomyomatosis and renal cell cancer syndrome with risk of development of certain cancers. Sporadic FH mutations have been described in different cancers but implications of somatic mutations on cancer outcomes and survival are not well described. Here, we characterize the molecular landscape of FH-mutant cancers. **Methods:** Tumors analyzed using NGS (NextSeq, 592 genes; NovaSeq, WES), IHC, and WTS (NovaSeq) (Caris Life Sciences, Phoenix, AZ). PD-L1 tested by 22c3, 28-8 (Agilent) and SP-142 (Spring Biosciences) IHC (>1%). MSI tested by FA, IHC, and NGS. TMB measured by totaling somatic mutations per tumor (TMB-h > 10 mutations/MB). Real-world overall survival was extracted from insurance claims data and calculated from first treatment to last contact using K-M survival curves for molecularly defined cohorts. Statistical significance was determined using chi-square and Wilcoxon rank-sum test, adjusted for multiple comparisons ($q<0.05$). **Results:** 3239 *FH* mutations were seen in 45 tumor types in 3149 FH-mutated tumors. NSCLC, colorectal and endometrial cancers harbored the most mutations. There were 839 pathogenic (P) or likely pathogenic (LP) and 2400 variants of unknown significance (VUS). Some tumors had multiple mutations. The most common mutations: R233H (P; 37), K477dup (LP; 555), and A41V (VUS; 70). VUS had increased TMB-H (40.4% vs 29.8%, q=0.004) and *CREBBP* mutations (5.1% vs 1.6%, q=0.012) compared to P+LP. A41V-mt tumors had significantly lower TMB-H than other VUS (8.8% vs 41.5%, q=0.002) and lower MSI-H (3.13% vs 3.69% vs 29.4%, q=0.003) and *DICER1*, *PRKDC*, *FBXW7* mutations ($q<0.05$) compared to K477dup and R233. The A41V-mt patients had worse survival compared to patients with P+LP (HR: 1.4, 95% CI: 1.0-2.0, p = 0.049) and a trend toward worse survival compared to K477dup and R233H. In patients treated with chemotherapy, A41 was associated with worse survival compared to P+LP (HR: 4.6, 95% CI: 2.0-10.3, $p<0.0001$) and compared to K477dup and R233 ($p<0.01$). There was a trend towards worse survival after IO of A41-mt compared to P+LP (HR: 1.99, 95% CI: 0.88-4.5, p = 0.093). **Conclusions:** FH alterations are found in multiple cancers. A41V was the most common VUS mutation and is associated with a distinct molecular profile compared to K477dup-mt and R233-mt tumors; it was associated with worse survival in all-comers and after chemotherapy compared to P+LP mutations. This highlights the significance of this mutation and the need for further investigation into how this specific and other FH mutations contribute to cancer progression and treatment outcomes. Research Sponsor: None.

3126 **Poster Session**

Insights of clinical significance from solid tumor profiles with FoundationOne CDx.

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Background: FoundationOne CDx (F1CDx) is a US FDA-approved companion diagnostic test to identify patients who may benefit from treatment in accordance with the approved therapeutic product labeling for 28 drug therapies. Tumor profiling with F1CDx detects genomic findings with evidence of additional clinical significance. This study analyzes the breadth and impact of clinical decision insights from F1CDx clinical reports across solid tumors. **Methods:** F1CDx consecutive reports (n = 109,695) were retrospectively analyzed for the type and frequency of clinically significant predictive, prognostic, and diagnostic genomic alterations and signatures in common cancer types and across solid tumors. Predictive markers were defined as therapeutically relevant markers in drug labels or NCCN guidelines or targets of ESCAT evidence Tier I/II (Mateo et al., 2018; PMID: 30137196). Prognostic and diagnostic markers were determined in accordance with NCCN, ESMO, or WHO guidelines. We also describe the frequency and targets of interventional clinical trials with targeted therapies or immune checkpoint inhibitors that were matched to tumor profiles based on clinical or strong preclinical evidence. **Results:** Predictive genomic findings of clinical significance were identified in more than half of non-small cell lung cancer (NSCLC), colorectal cancer (CRC), breast cancer (BC), and melanoma (MEL) tissue samples; over a third of ovarian cancer (OC), urothelial carcinoma (UC), and head and neck squamous cell carcinoma (HNSCC); approximately a fourth of prostate cancer (PC), gastro-esophageal adenocarcinoma (GEA), cholangiocarcinoma (CA), and glioma (GL) samples; and one in 18 pancreatic adenocarcinoma (PA) samples (Table). Prognostic markers were reported for patients with NSCLC (18%), CRC (10%), BC (16%), PC (25%), CA (8.1%), MEL (24%), GL (74%), or HNSCC (7.1%). Diagnostic markers were frequently detected for patients with GL and noted for patients with BC, GEA, or MEL (Table). Interventional clinical trials were evidence-matched to most F1CDx tumor profiles (89%, range 82% in PC to 99% in PA), with the targets of approved therapies accounting for a small subset of targets in clinical development. **Conclusions:** F1CDx reports support clinical decision making by interpreting predictive, prognostic, and diagnostic markers according to professional guidelines as well as investigational markers for the enrollment in clinical trials. Research Sponsor: Foundation Medicine, Inc.

Frequency of predictive, prognostic, and diagnostic markers of clinical significance by cancer type in F1CDx reports (N total reports, na not applicable).

Cancer Type	N	Predictive	Prognostic	Diagnostic
NSCLC	22152	59.8%	18.4%	na
CRC	13193	64.7%	10.3%	na
BC	11016	54.2%	16.3%	14.4%
OC	6999	36.2%	na	na
PC	6513	27.3%	24.7%	na
PA	6168	5.5%	na	na
GEA	4762	22.8%	na	6.2%
UC	3236	46.7%	na	na
CA	2901	24.0%	8.1%	na
MEL	2743	79.7%	24.1%	3.6%
GL	2350	24.1%	74.0%	80.6%
HNSCC	1787	38.4%	7.1%	na

3127 **Poster Session**

Molecular reflex testing in non-small cell lung cancer: An optimal approach?

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Background: Molecular testing of non-squamous non-small cell lung cancer (NSCLC) tumors can guide appropriate treatment decisions and improve patient outcomes, but guideline complexity and frequent revision may negatively affect adherence. To assist oncologists in making timelier informed treatment decisions, we implemented a pathologist-directed molecular reflex pathway for non-squamous NSCLC at our clinical laboratory. Testing patterns and adherence to NCCN testing guidelines before and after implementation were reviewed. **Methods:** This retrospective cohort analysis included patients with diagnosed NSCLC who had molecular testing performed without a molecular reflex testing pathway in place (April 2016-March 2018, cohort A) and after the pathway was implemented (April 2018-March 2020, cohort B) at our clinical laboratory. TATs were calculated using dates of biopsy specimen submission and of molecular testing completion. Molecular testing methods (e.g., polymerase chain reaction, next-generation sequencing [NGS]), genetic alterations tested for and identified, PD-L1 by immunohistochemistry, and specimen quantity not sufficient (QNS) for testing were obtained from patients' clinical laboratory reports. NSCLC diagnosis and cancer stage were obtained from electronic medical records, and adherence to NCCN guidelines (i.e., under-tested, over-tested genetic alterations) was evaluated according to specimen submission. **Results:** The mean TAT was 35.1 days for cohort A (n = 123) and 15.8 days for cohort B (n = 168), though the median in both was 14 with a range of 6 – 674 days in cohort A and 9 – 44 in cohort B (Table).Targetable genetic alterations were identified in 12.4% of patients in cohort A and 61.3% in cohort B; 46.3% in cohort A and 60.1% in cohort B had ≥1% positive *PD-L1* staining. QNS results declined from 16.7% (n = 20) in cohort A to 12.5% (n = 21) in cohort B. Non-NCCN guideline testing was observed in 86.7% of patients in cohort A and 25.6% in cohort B, with those in cohort A being primarily under-tested (70%) and those in cohort B being over-tested. Only 13.3% of cohort A had alignment with NCCN guidelines for appropriate time of testing. **Conclusions:** Implementation of a pathology-driven molecular reflex pathway for non-squamous NSCLC was associated with increased identification of potentially targetable genetic alterations and improved adherence to NCCN NSCLC testing guidelines, along with reduction in QNS results. Though the TAT mean decreased after pathway implementation, the median did not change, offsetting the often increased lab TAT for NGS methodology vs. PCR and FISH alone. Research Sponsor: Quest Diagnostics.

	TAT (mean)	Targetable mutations identified	Non-NCCN guideline testing
Total N reviewed (data missing)	291 (3)	291 (6)	291 (3)
2016-2018 cohort A	35.1 days (n = 120)	12.4% (n = 120)	86.7% (n = 120)
2018-2020 cohort B (reflex testing panel)	15.8 days (n = 168)	61.3% (n = 165)	25.6% (n = 168)
Change for cohort B vs cohort A	*-55.1%*	*+48.9%*	*-61.1%*

3128 **Poster Session**

Molecular correlates of *MAEA* expression in colorectal cancer (CRC).

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Background: Macrophage Erythroblast Attacher (MAEA) plays an important role in actin cytoskeleton rearrangement in macrophages and erythroid cells. We previously reported that MAEA suppresses migration, invasion and enhances chemosensitivity in CRC cell lines. Here we aimed to characterize the molecular features associated with *MAEA* gene expression in CRC. **Methods:** 14416 CRC were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (592 genes or WES) and RNA (WTS). Top quartile transcripts per million (TPM) for *MAEA* expression were considered high (Q4) while bottom quartile low (Q1). Consensus molecular subtypes (CMS) were assessed using RNAseq. Cell infiltration (CI) in the tumor microenvironment (TME) was estimated by QuantiSEQ. X^2 and Fisher-Exact tests were used and significance was determined as *P*-value adjusted for multiple comparisons ($Q < 0.05$). **Results:** *MAEA* expression was highest in rectal tumors (13.6 median TPM) followed by transverse and right-sided tumors (13.0 and 12.8, respectively) and lowest in left-sided tumors (12.5). Overall, *MAEA* TPM were associated with higher tumor mutational burden (≥ 10 Mut/Mb) (11.8% vs. 8.2%) and dMMR/MSI-H (8.7% vs. 5.1%) ($Q < 0.0001$); however, the association with TMB was not observed in MSS tumors. In the MSS cohort, *MAEA* expression was the highest in CMS4 (14.9 median TPM) followed by CMS1 (12.5), CMS2 (11.9), and the lowest in CMS3 (10.3, all intergroup $Q < 0.05$). *MAEA* high was associated with lower mutation rates of *APC* and amplification of *FLT1*/*FLT3* while higher mutation rates of *ASXL1*, *KMT2A/C/D*, *SMARCA4*, *FBXW7*, *PTEN*, *RNF43*, *BRCA2*, *HNF1A* in the overall cohort ($Q < 0.05$). In the MSS cohort, *FBXW7* mutation significance with *MAEA* high expression held true ($Q < 0.05$) while *MAEA* high expression trended to associate with higher mutation rates of *KMT2D*, *SMARCA4*, *PTEN*, *BRCA2* mutations, and a lower frequency of *FLT1*/*FLT3* CNA ($P < 0.05$ but $Q > 0.05$). High *MAEA* was associated with higher immune CI in the TME, including B cells, macrophages (M1 and M2), neutrophils, NK cells, Tregs, CD4+ T cells and myeloid dendritic cells both in the overall cohort and in MSS tumors (fold change: 1.11-1.33, all $Q < 0.001$). **Conclusions:** Our data show a strong association between *MAEA* gene expression and distinct molecular features (including CMS and immune biomarkers) and TME cell infiltration in CRC. These findings suggest that targeting MAEA may have relevant clinical applications in selected CRC subgroups and MAEA may be an important player in determining the composition of the TME. Research Sponsor: Partly supported by NCI P30CA014089, Gloria Borges WunderGlo Foundation, Dhont Family Foundation, Ming Hsieh research fund, San Pedro Peninsula Cancer Guild, V foundation for cancer research, Fong research project.

3129 **Poster Session**

Comprehensive profiling of clock genes expression in colorectal cancer (CRC).

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Background: Disruption of the circadian clock has been linked to cancer risk, development and progression. Core clock proteins are emerging as novel therapeutic targets in cancer. We previously showed that polymorphisms in clock genes were associated with anti-VEGF treatment outcome in metastatic CRC. Here we further evaluated the molecular landscape of clock pathway alterations in CRC. **Methods:** 7591 CRC tested at Caris Life Sciences (Phoenix, AZ) with WTS (Illumina NovaSeq) and NextGen DNA sequencing (NextSeq, 592 Genes and NovaSEQ, WES) were analyzed. Clock gene Score (CS) was determined using expression of core clock genes Z scores (positives of *CLOCK*, *ARNTL*, *RORA/B/C* and negatives of repressors *CRY1/2*, *PER1/2/3*, *REVERBA/B*) stratified by quartiles. xCell was used to quantify cell infiltration in the tumor microenvironment (TME). Consensus molecular subtypes (CMS) were assessed by RNAseq. Significance was determined as *P*-values adjusted for multiple testing (*q)* of <.05. Real world survival was obtained from insurance claims data and Kaplan-Meier estimates were calculated for comparison. **Results:** CS was higher in primary tumors than metastases and in right- than left-sided CRC (P <.001). Liver metastases were associated with lower CS (23% Q1 vs 19% Q4, P <.001). CS was positively associated with CMS1 and 3 (21 vs 11% and 23 vs 9%, respectively, Q4 vs Q1) and negatively correlated with CMS2 and 4 (22 vs 32% and 34 vs 48%) (all P <.001). These associations were confirmed in mismatch repair proficient (pMMR) tumors. Overall, TMB-H and dMMR/MSI-H were positively associated with CS (11 vs 6% and 8 vs 4%, Q4 vs Q1, q <.0001) and PD-L1 showed a similar trend (P <.01, q =.06); the association with TMB-H was not significant in pMMR. High CS was associated with alterations of genes in WNT signaling, RAS, PI3K, TGF-β, and NOTCH pathways, while negatively associated with *TP53* mutations, *HER2* expression and *CDX2* copy numbers, confirmed in pMMR (all q <.05). CS negatively correlated with the angiogenesis pathway signature (Q1 vs Q4 Z score: 6.6 vs -4.6, P <.001). B cells, M1 and M2 macrophages, neutrophils, NK, Tregs, CD4+ and CD8+ T cells, and myeloid dendritic cells were more abundant in the TME of tumors with high CS while cancer associated fibroblasts were lower, regardless of MMR status (all q <.001). Individually, *ARNTL* tumor expression below median was associated with better OS (overall: HR 0.88, 95% CI [0.82-0.94]; pMMR: HR 0.88 [0.81-0.94]) and longer time on treatment of bevacizumab (overall: HR 0.91 [0.83-0.99]; pMMR: HR 0.91 [0.83-0.99]). **Conclusions:** This is the most extensive profiling study to investigate the expression of clock genes in CRC. Our data show that clock genes expression is strongly associated with distinct molecular features, immune cell infiltration, angiogenesis pathway enrichment and patient outcomes. These findings support the clock pathway as a therapeutic target in CRC, with a major role in CRC biology and TME modulation. Research Sponsor: Partly supported by NCI P30CA014089, Gloria Borges WunderGlo Foundation, Dhont Family Foundation, Ming Hsieh research fund, Daniel Butler Research Fund, Victoria and Philip Wilson Research Fund.

3130 **Poster Session**

Increasing targeted therapy options for patients with relapsed cancer with broader somatic gene panel analysis from the primary tumor: The Profiler02 randomized phase II trial.

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Background: PROFILER-02 is a multicenter randomized prospective study comparing the proportion of metastatic cancer patients (pts) with Targeted Agent (TA) recommendation provided by large NGS panel (FOne panel, 324 genes) *vs* home 87-gene NGS panel (CTRL) (PMID 30865223). **Methods:** Adult pts with advanced/metastatic cancer during 1st or 2nd line of therapy without known targetable gene alteration were eligible and randomized (1:1) to FOne *vs* CTRL panel. Both panels were performed for each patient. The randomization arm defined the first panel reviewed by dedicated Molecular Tumor Board (MTB) at disease progression while the 2nd panel remained blinded. The primary objective was the pts rate with at least one TA recommendation by the MTB using either FOne or CTRL panel. The study was designed in order to detect difference in proportions of 10% between the two panels. A sample size of 289 pts with both panels were requested to show this difference with an expected proportion of discordant pairs of 20% using a McNemar's test with 98% power and 5% two-sided significance level. Secondary endpoints included number of pts receiving at least one TA, progression free survival (PFS) and overall survival (OS). **Results**: From June 2017 to June 2019, among the 339 included pts 171 and 168 pts were randomized in FOne or CTRL panels' first use, respectively. Median age was 57 years [19.0 - 85.0]; 54.9% were female. The median time from randomization to first MTB was 7.62 months [range 0.80 - 48.1]. Among the 339 pts, 147 pts (43.4%) had no TA recommendation, 108 pts (31.9%) had at least one TA recommendation according to both panels, 67 pts (19.8%) had one or more TA recommendation according to FOne panel only and 17 pts (5%) according to CTRL panel only (McNemar $p < 0.001$). At the time of the analysis, 51/339 (15%) pts started recommended treatment: 27 pts (8%) with TA recommendation from both panels, 21 pts (6.2%) from FOne only and 3 pts (0.3%) from CTRL only. Main initiated TA were PARP inh. (FOne n = 12; CTRL n = 9), PI3K/AKT/mTOR inh. (FOne n = 10; CTRL n = 9) and immunotherapy (ICI) (FOne n = 7; CTRL n = 0). Median PFS following first MTB were 3.2 months (95% CI 2.5-3.8) and 2.6 months (95% CI 2.0-3.8), median OS were 8.7 months (95% CI 6.6-10.8) and 8.4 months (95% CI 6.4-9.7), in the FOne and CTRL arm, respectively. **Conclusions**: Larger NGS panel including Tumor Mutational Burden increased the number of recommended options (TA and ICI), as well as the number of treatment initiation. Clinical trial information: NCT03163732. Research Sponsor: Roche, Other Foundation, Other Government Agency.

3131 **Poster Session**

Primary results from JUPITER, a phase 2 basket trial of combination therapy with trastuzumab and pertuzumab in patients with HER2-amplified solid tumors.

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Background: Human epidermal growth factor receptor 2 (HER2) gene amplification or mutations have emerged as oncogenic drivers and therapeutic targets not limited to breast and gastric cancers, but also in a variety of cancers. Despite its considerable therapeutic potential, the evidence has not been established. To address this unmet need, we conducted an organ-agnostic basket trial targeting HER2-amplified solid tumors. **Methods:** JUPITER is a multicenter, single-arm, phase 2 basket trial for solid tumor patients (pts) with HER2 amplification determined by next-generation sequencing (NGS). Both tissue and liquid NGS results were allowed. HER2 amplification by ISH or HER2 overexpression by IHC were not used for inclusion. Pts had treatment-refractory metastatic tumors, or rare cancers without established standard of care. Breast, gastric, and colorectal cancers were excluded. Pts were treated with intravenous trastuzumab (8 mg/kg loading dose followed by 6 mg/kg) and pertuzumab (840 mg loading dose followed by 420 mg) every 3 weeks until disease progression or any other reason for discontinuation. Tumor response was assessed using RECIST v1.1. Primary endpoint was ORR by blinded independent central review (BICR), and secondary endpoints were ORR assessed by the investigators, progression-free survival (PFS), overall survival (OS), duration of response (DOR), and safety. We set the ORR threshold 5% and expected ORR was 20%. Estimated sample size was 38 patients with one-sided alpha 2.5% and power 80%. **Results:** Between April 2019 and June 2020, 42 pts were consented, and 40 pts were treated. Median age was 62 (range, 21-86) and 60% were females. The most common diagnosis was biliary tract cancer (20%), followed by salivary ductal carcinoma (12.5%) and endometrial cancer (12.5%). At data cutoff (1 Sep 2021), ORR by BICR was 22.5% (95%CI: 10.8%-38.5%). ORR assessed by the investigator was 25% (95%CI: 12.7%-41.2%). PFS, OS and DOR were not reached at data cutoff; 3 responders remained on treatment. Of 40 pts, 32.5% had grade $\geq$ 3 adverse events; 10% were treatment-related, including neutropenia, hypertension, peripheral sensory neuropathy and lymphoedema (all grade 3). No treatment-related death was observed. Exploratory biomarker analysis of response and resistance is in progress. **Conclusions:** Combination therapy with trastuzumab and pertuzumab was well tolerated and showed promising efficacy for the patients with HER2-amplified solid tumors determined by NGS. Clinical trial information: jRCT2031180150. Research Sponsor: AMED (Japan Agency for Medical Research and Development).

3132 **Poster Session**

Reversion mutations in *BRCA1* or *BRCA2* genes: Resistant mechanism(s) in patients treated with platinum-based agents or poly (ADP-ribose) polymerase(PARP) inhibitors.

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Background: Reversion mutations (RM) in homologous recombination pathway genes including *BRCA1/2* have been identified in patients with ovarian, breast, and prostate cancers whose tumors have become refractory to platinum chemotherapy or PARP inhibition. Utilizing a multi-institutional molecular database, we report the prevalence of *BRCA1/2* RM in a large cohort across various tumor types. **Methods:** Primary and/or metastatic tumor samples underwent DNA (underwent NextSeq, 592 genes; NovaSeq, whole-exome) and RNA (NovaSeq, whole transcriptome) sequencing (Caris Life Sciences, Phoenix, AZ). RM were identified by a board-certified molecular geneticist and called only if the patient had been treated with a PARPi or a platinum agent. Baseline clinical and outcomes data were obtained through linked insurance claims data. **Results:** Among 118,000 solid tumors profiled, RM were observed in 54 tumors samples. RMs were seen most commonly in ovarian cancer (OC), 1.5% (23/1500) of tumors with *BRCA1/2* pathogenic mutations (mut), followed by breast cancer (BC) (2.4%, 17/700), endometrial cancer (1.0%, 4/400), pancreatic cancer (1.0%, 2/210), cholangiocarcinoma (2.5%, 2/80), prostate cancer (1.3%, 3/230), cervical cancer (1.4%, 1/70), cancer of unknown primary (1.0%, 1/100), and a neuroendocrine tumor of prostate (1 RM of 9 *BRCA* mut). Among all RM, we detected 17 in *BRCA1* and 6 in *BRCA2* in OC. In BC, we identified 7 RM in *BRCA1* and 10 in *BRCA2*. Frameshift mut that restored the reading frame in *BRCA1/2* were the most common type of RM. Molecular profiles of 14 high-grade serous ovarian cancers (HGSOC) with RM were compared to 87 control HGSOC with pathogenic *BRCA1/2* mut without RM. Tumors with RM had lower ER expression (25% vs. 64%, p = 0.024) and higher *KDM6A* mut rate (15% vs. 0, p = 0.016). Additionally, *TP53* mut rates were similar in RM and control (100% vs. 95%), seen in HGSOC. In patients with RM, 7 of the 14 (50%) *TP53* mut were gain-of-function (GOF) while only 19 of 84 (23%) *TP53* mut in the control group were GOF (p = 0.048). More detailed clinical data were available for 29 patients with RM (17 *BRCA1* & 12 *BRCA2*). Among these patients, 7 had received prior platinum-based chemotherapy (carboplatin or cisplatin), 7 patients were treated with PARP inhibitors (olaparib or rucaparib), or both (n = 7). Notably, 5 patients had been treated with carboplatin (n = 2, ovarian), olaparib (n = 1, breast), or both agents (n = 2, ovarian and prostate) after the detection of RM. **Conclusions**: This dataset is one of the largest reporting on the prevalence of *BRCA1/2* RM across various tumor types. We demonstrate that the rate of RM was low among *BRCA1/2* mutated tumors; this may be because some patients may not have repeat profiling post-treatment. Repeating tumor profiling at times of treatment resistance can help inform therapy selection in the refractory disease setting. Research Sponsor: None.

3133 **Poster Session**

Pan-cancer landscape of *CD274* (PD-L1) and *PDCD1LG2* (PD-L2) structural variations.

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Background: PD-1 receptor and PD-L1 ligand interactions are the target of immunotherapies across multiple tumor types. Established biomarkers that predict response to immunotherapy are microsatellite instability, tumor mutational burden, and PD-L1 immunohistochemistry. Structural variations in *CD274* (PD-L1) and *PDCD1LG2* (PD-L2) have been observed in cancer, but the comprehensive landscape is unknown. Here we describe the genomic landscape of *CD274* and *PDCD1LG2* structural variations, their potential impact on the tumor microenvironment, and evidence that patients with these alterations can benefit from immunotherapy. **Methods:** We analyzed sequencing data from 514 cancer cases with *CD274* and *PDCD1LG2* structural variations across 25 publications and data sources, including large pan-cancer sources: Foundation Medicine, Inc (FMI), The Cancer Genome Atlas (TCGA), and Oncology Research Information Exchange Network. To evaluate immune signature enrichment, we ran the software ImSig on gene expression data. We curated literature reporting clinical outcomes of patients harboring structural variations in *CD274* and *PDCD1LG2*.. **Results:** From 25 studies and datasets, we curated 514 cancer cases with structural variations in *PD-L1* and *PD-L2*, including 158 duplications, 126 deletions, 97 inversions, 178 translocations, and 96 unclassified structural variations, totaling to 655 events. We observed breakpoint 'hotspots' in the 3'-untranslated regions (UTRs) of *PD-L1* and *PD-L2*. Leveraging TCGA data, we observed, in *CD274*-rearranged tumors, significant upregulation in PD-L1 and PD-L2 expression and signatures for interferon signaling, macrophages, monocytes, T cells, and immune cell proliferation (each $p < 0.001$, compared to *CD274* non-rearranged, copy neutral tumors). Furthermore, retrospective review of 12 studies that included patients with structural variations in *CD274* or *PDCD1LG2*, including duplications, inversions and copy number amplifications, revealed a 73% (52/71) response rate to PD-1 immunotherapy with durable responses. **Conclusions:** Our evaluation of *CD274* and *PDCD1LG2* structural variations shows that the 3'-UTR is frequently affected and is associated with increased expression of ligands and immune signatures. Enriched interferon signaling in *CD274*-rearranged tumors is of particular interest, as interferon exposure is known to drive PD-L1 and PD-L2 expression. Retrospective evidence from curated studies suggests that these genomic alterations could identify candidates for PD-1 or PD-L1 immunotherapy. We expect that these findings will better define *CD274* and *PDCD1LG2* structural variations in cancer and support our pan-cancer prospective clinical trial to target these alterations. Research Sponsor: U.S. National Institutes of Health.

3134 **Poster Session**

Defining transcriptomic profiles of early-stage mucinous breast cancers: A FLEX sub study.

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Background: Mucinous breast cancer (MuBC) is a rare subtype of invasive ductal carcinoma (IDC) that accounts for less than 2% of all breast cancers and is associated with a favorable prognosis. Since MuBCs are rare in clinical trials, current treatment guidelines are extrapolated from IDC-no special type (IDC-NST). To provide better understanding of MuBCs and factors contributing to their clinical behavior, we examined the transcriptomic profiles of MuBCs in our FLEX study. **Methods:** The prospective, observational FLEX Study (NCT03053193) includes stage I-III breast cancer patients who receive MammaPrint (MP)/BluePrint (BP) testing and consent to full transcriptome and clinical data collection. For this study, histologically confirmed MuBCs (n = 102) in the FLEX database were included. All patients examined were ER+/HER2- by immunohistochemistry and Luminal by BP. MuBC was compared with IDC matched for Age, MP, and BP index (n = 97). Differential gene expression analyses (DGEA) were performed with R package 'limma' and differentially expressed genes (DEGs) were considered significant if they had an adjusted $p < 0.05$ and fold change ≥ 2. **Results:** DGEA comparing MuBC (n = 102) with IDC (n = 97) revealed 60 DEGs, regardless of the genomic risk, of which 42 genes were upregulated and 18 were downregulated in MuBC relative to IDC. Genes associated with MuBC, such as MUC2, TFF1, CARTPT were among the upregulated genes. Of the 102 MuBC patients, 56 were Luminal A (MP Low Risk-LR) and 46 were Luminal B (MP High Risk-HR) by MammaPrint and BluePrint. Comparison of LR MuBC with LR IDC revealed 111 DEGs. Functional enrichment showed upregulation of pathways involved in estrogen response (early & late) and androgen response and a downregulation of the epithelial to mesenchymal transition (EMT) and E2F pathways in LR MuBC compared to LR IDC. DGEA between HR MuBC and HR IDC revealed only 22 DEGs with immune pathways being downregulated in HR MuBC. DGEA comparing LR MuBC with HR MuBC resulted in 63 DEGs, indicating LR and HR MuBC are biologically distinct types. Interestingly in LR MuBC, the tumor suppressor marker SCUBE2 is upregulated. Over expression of SCUBE2 is associated with better prognosis. **Conclusions:** Although MuBCs are often expected to have low clinical risk, MP revealed that half of the MuBCs examined in this study were MP High Risk (Luminal B). MP low risk MuBC is biologically different from MP low risk IDC, and downregulation of E2F and EMT pathways might lead to favorable prognoses in MP low risk MuBC. MP high risk MuBC showed limited DEGs compared to high-risk IDCs indicating these tumor types are highly genomically similar and likely to benefit from chemotherapy. The downregulation of immune pathways in MP high risk MuBC may lead to immune surveillance escape resulting in metastasis and further investigation is needed. Clinical trial information: NCT03053193. Research Sponsor: None.

3135 **Poster Session**

Clinicopathologic characterization of ERK2 E322K mutation in solid tumors: Implications for treatment and drug development.

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Background: *MAPK1* encodes ERK2, a kinase component of the mitogen activated signaling (MAPK) pathway. *ERK2 E322K* is a known activating mutation that leads to increased phosphorylation and ERK signaling. In vitro studies found this mutation to be associated with resistance to dabrafenib, trametinib, but potential sensitivity to ERK inhibitors. Despite its potential as a drug target, little is known about the clinicopathologic characteristics of this hotspot mutation across solid tumors. **Methods:** Patients with solid tumors underwent tumor next-generation sequencing at Memorial Sloan Kettering Cancer Center between Jan 2015 and Sep 2020 using the MSK-IMPACT assay. Using the cBioPortal database and clinical charts, we analyzed tumors harboring MAPK1/ERK2 E322K mutations, assessed their clinicopathologic characteristics, co-mutational status and overall survival (OS). OS was measured from time of tumor sequencing to date of death or last follow-up. **Results:** A total of 37 tumor samples from 35 patients were identified in 59,822 tumors sequenced (0.06%) to harbor an ERK2 E322K mutation. The distribution across tumor types was as follows: head and neck squamous cell carcinoma (29%), bladder cancer (20%), lymphomas (9%), colorectal cancers (9%), gastric cancers (9%), cholangiocarcinoma (6%), cervical cancers (6%), lung cancers (6%), germ cell tumor (3%), Merkel cell carcinoma (3%), and breast cancers (3%). The OS in patients with metastatic disease and ERK2 E322K was 22.29 months (95%CI: 7.56-NA) months. Other mutations in RAS pathway frequently co-occurred with ERK2 E322K mutation (17/37, 46%). Concurrent mutations are also involved in pathways of cell cycle (71%), PI3K (71%), TP53 (66%), NOTCH (57%), RTK (51%), HIPPO (29%), TGF-beta (29%), WNT (26%), NRF2 (20%), MYC (14%). The median TMB score of samples from solid malignancies was 12.3 (range:0-101, quartiles: 6.9-33.0) mutation/Mb. Two patients (2/35, 6%) had microsatellite-instability high (MSI-H) tumors. The most frequent concurrent activating mutations include ARID1A (29%), FBXW7 (26%), PI3KCA (22%), PI3KR1/2/3 (20%), CDKN2A (11%), PTEN (8%), BRCA1/2(8%), FGFR3 (8%), BRAF (6%), Only one of these 35 patients received treatment targeting BRAF/MEK/ERK pathway and achieved partial response. One patient with NSCLC harboring a concurrent EGFR L858R mutation did not respond to erlotinib. One patient with PI3KCA mutated head and neck cancer did not respond to PI3K inhibitor. Two patients had TMB score of 100.9 and 12.9 mutation/Mb had partial response to pembrolizumab. **Conclusions:** ERK2 E322K mutation is a rare oncogenic mutation across diverse solid tumor types, associated with a high co-occurrence of other activating mutations and a high TMB. The lack of response to other targeted therapies suggests ERK2 E322K is a potential driver mutation. These findings may inform treatment and further development of ERK inhibitors. Research Sponsor: U.S. National Institutes of Health.

3136 **Poster Session**

Using CDKN2A loss in the context of wildtype TP53 to predict sensitivity for the MDM2 inhibitor milademetan.

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Background: MDM2 is an E3 ubiquitin ligase that plays a critical role in the degradation of the tumor suppressor p53. Milademetan (RAIN-32) is an orally available, small molecule inhibitor of MDM2 that disrupts the MDM2-p53 complex thereby restoring p53 activity. Approximately 50% of tumors harbor wildtype (WT) *TP53* and thus may be susceptible to strategies that reactivate p53. The *CDKN2A* gene is altered in more than 15% of all tumors (TCGA PanCancer Atlas) and encodes two proteins, $p14^{ARF}$ and p16, which are inhibitors of p53 and cyclin dependent kinases, respectively. Given the role of $p14^{ARF}$ in regulating the MDM2-p53 pathway, we investigated the use of *CDKN2A* loss in the context of WT *TP53* as a strategy for selection of patients who might benefit from milademetan. **Methods:** N/A. **Results:** We evaluated the sensitivity of 215 cancer cell lines to milademetan treatment (Ishizawa et al., 2018) by *CDKN2A* and *TP53* status. The median IC_{50} of *CDKN2A* homozygous (HZ) loss vs. non-HZ loss was 8,620 vs. 10,000 nM. However, when we assessed *CDKN2A* HZ loss with WT *TP53* versus mutant *TP53* the median IC_{50} was 79.5 vs. 10,000 nM demonstrating that the use of both *CDKN2A* and *TP53* was better able to discriminate sensitive vs. resistant cell lines. To validate these *in vitro* findings, we tested milademetan in 5 xenograft models with *CDKN2A* HZ loss and WT *TP53*, all of which demonstrated tumor growth inhibition with milademetan. As suppression of p53 activity by *MDM2* amplification (Kato et al. 2017) or *CDKN2A* loss (Adib et al. 2021) has been associated with resistance to immune checkpoint inhibitors (ICI), we also tested the combination of anti-PD1 with milademetan in the colon-26 syngeneic model (*CDKN2A* HZ loss) and observed a significant enhancement in tumor growth inhibition compared to milademetan or anti-PD1 alone. Based on the differential sensitivity to milademetan using both *CDKN2A* loss and WT *TP53* status we evaluated TCGA Pan-Cancer Atlas data to estimate the frequency of these genetic co-alterations. Among solid tumors types the most frequent percentage of these co-alterations included glioblastoma, mesothelioma, melanoma, bladder, sarcoma, pancreatic and NSCLC. Overall, the percentage of all tumors with co-alteration of *CDKN2A* HZ loss and WT *TP53* was 6.2%. Patients with *CDKN2A* HZ loss had a significantly worse overall survival than those without CDKN2A HZ loss (median OS of 29.7 vs. 97.4 months, $p < 0.0001$), and this was maintained when accounting for tumor type in multivariate analysis ($p < 0.0001$). **Conclusions:** Milademetan showed evidence of preclinical anti-tumor activity across multiple tumor types with *CDKN2A loss* and WT *TP53*. In vivo data supported potential synergy of milademetan with an ICI in this genetic subset. A clinical trial evaluating the safety and efficacy of milademetan plus atezolizumab in advanced solid tumors with *CDKN2A HZ* loss and WT *TP53* (MANTRA-4) is planned. Research Sponsor: Rain Therapeutics.

3137 **Poster Session**

Identification of homologous recombination deficiency (HRD) by RAD51 in a tumor molecular profiling program for precision medicine.

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Background: Tumor molecular profiling by panel sequencing helps to identify candidate patients for precision oncology. Mutations in genes of the homologous recombination repair (HRR) pathway confer DNA repair deficiency and sensitivity to DNA damaging agents, such as PARP inhibitors (PARPi) or platinum-based drugs. RAD51 nuclear foci is a biomarker of functional HRR deficiency (HRD). We aimed to incorporate the RAD51 test in an academic molecular profiling program to identify HRD tumors beyond genetic testing. **Methods:** We included patients with metastatic breast cancer (TNBC, ER+ <60y, 3rd line HER2+ BC), newly diagnosed high-grade epithelial ovarian cancer (HGOC) and metastatic and/or castration-resistant prostate adenocarcinoma (PC) undergoing tumor/germline genetic testing. A customized capture-based targeted sequencing of 450 genes was performed in FFPE tumor samples. RAD51 was manually stained by immunofluorescence and functional HRD was defined as RAD51 score ≤10%. **Results:** Between January 2021 and January 2022, tumor panel sequencing was performed in 279 tumors. Panel sequencing was informative in 264/279 (95%) samples and the RAD51 test was evaluable in 81/90 (90%). In total, 77 samples were evaluable for both tumor/germline sequencing and RAD51, namely 42 BC, 16 HGOC and 19 PC (Table 1). Functional HRD by RAD51 was observed in 15/77 (20%) cases. Panel sequencing identified 17/77 (22%) cases carrying HRR gene alterations, of which nine were confirmed as HRD by RAD51. In BC, 2/6 tumors with HRD by RAD51 did not carry a germline or tumor mutation in HRR genes. HRD tumor profiling triggered the germline analysis of one hereditary *BRCA2* BC patient. Four g*BRCA1/2* BC with HRD by RAD51 became HRR proficient (HRP) at PARPi progression. In addition, the RAD51 test identified 2/5 HGOC and 2/4 PC tumors as HRD despite not carrying a tumor HRR gene mutation. **Conclusions:** RAD51 testing is feasible in an established molecular profiling program and complements gene panel sequencing results by providing evidence of functional HRR status. In particular, the RAD51 test extends the identification of HRD tumors beyond those with HRR gene mutations and captures HRR restoration after PARPi treatment. We aim to expand the analysis of RAD51 to other tumor types. Research Sponsor: Asociación Española Contra el Cáncer (AECC), LaCaixa Foundation (CaixaImpulse grant), Generalitat de Catalunya (AGAUR-Producte and PERIS), Instituto de Salud Carlos III (ISCIII), Fondo Europeo de Desarrollo Regional (FEDER).

Number of samples with both functional HRR status by RAD51 and HRR gene mutation status by panel sequencing in breast, high-grade ovarian and prostate cancers.

Number of cases	Tumor/germline sequencing (HRR genes)	HRD by RAD51	HRP by RAD51
BC (n = 42)	mutated	4	6
	non-mutated	2	30
HGOC (n = 16)	mutated	3	1
	non-mutated	2	10
PC (n = 19)	mutated	2	1
	non-mutated	2	14
All tumor types(n = 77)	*mutated*	***9 (12%)***	***8 (10%)***
	non-mutated	***6 (8%)***	***54 (70%)***

3138 **Poster Session**

Paired tumor/normal sequencing to overcome racial differences in tumor mutational burden (TMB).

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Background: TMB is routinely reported in cancer patients tested with broad-panel next generation sequencing and has become a predictive biomarker associated with response to checkpoint inhibitor (CPI) therapy. Sequencing of paired tumor and normal specimens allows correction of TMB estimates with patient-specific germline variants. When a paired normal specimen is unavailable, TMB estimates are corrected using germline variant annotations derived from population-scale germline variant surveys. Germline variants do not generate neoantigens, which is the putative target of the immune response in CPI treated patients. To evaluate TMB differences in paired sequencing (PS) and tumor-only sequencing (TOS), we compared TMB assessments—stratified by race—in two common malignancies.. **Methods:** Using de identified records from the Tempus clinico-genomic database, cohorts of patients with non-small cell lung cancer (NSCLC) and breast cancer sequenced using the Tempus xT NGS platform (DNA-seq of 595-648 genes at 500x coverage, whole exome capture RNA-seq) and noted to not have microsatellite instability, were identified for analyses. The Kruskall-Wallis test was used to compare TMB distributions. **Results:** Among 4,817 NSCLC patients with race information (13% Black (B), 5% Asian (A), 82% White (W), 3,052 had PS, and 1,765 had TOS performed. Median TMB for B, A, and W patients was 5.8, 2.6, and 4.7 (within group $p < 0.0001$), respectively in patients with PS, and 9.5, 6, and 7.4 (within group $p < 0.0001$), in patients with TOS. Comparisons across PS and TOS were highly significant ($p < 0.0001$). The absolute difference in median TMB was 3.7, 3.4, and 2.5, respectively. Among 3,191 patients with breast cancer (17% B, 4% A, 78% W), 2,220 had PS, and 971 had TOS. Median TMB for B, A, and W patients was 2.6, 2.1, and 2.6 (within group $p = 0.11$), respectively, in patients with PS, and 6.3, 5.8, and 4.7 (within group $p < 0.0001$) in patients with TOS. Comparisons across PS and TOS were highly significant ($p < 0.0001$). The absolute difference in median TMB was 3.7, 3.7, and 2.1, respectively. **Conclusions:** PS reduces estimated TMB compared to TOS across all racial groups with a pronounced difference in Black and Asian racial groups. This is expected as population databases of germline variation are based on cohorts predominantly from individuals of European ancestry, leading to artifactually high TMB in minorities tested with TOS. As a result, artifactually elevated TMB estimates from TOS may promote treatment with CPI in patients with a low probability of response which could exacerbate known race-based outcome disparities. PS provides a more accurate estimate of TMB regardless of race and could reduce the use of CPI in patients with a low likelihood of response. Research Sponsor: Tempus Labs, Inc.

3139 **Poster Session**

Next-generation sequencing (NGS) for identifying actionable molecular alterations in patients with newly diagnosed and recurrent IDHwt-glioblastoma (GBM): A large mono-institutional experience.

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Background: NGS panels allow the identification of alterations within hundreds of cancer-related genes and can guide a personalized strategy in glioma treatment. **Methods:** From Nov 2019 to Jan 2022 at Veneto Institute of Oncology, Padua, Italy, a large cohort of IDHwt-GBM tissues was analyzed by NGS (FoundationOneCDx). We identified all potential actionable molecular alterations at diagnosis and/or at recurrence. High tumor mutational burden (TMB) was defined as ≥10 mutations/megabase. **Results:** We analyzed 429 IDHwt-GBM samples: NGS profile was available for 419 samples (97.7%); sample failures in 10 cases (2.3%). 351 (84%) and 68 (16%) GBM samples derived from surgery at diagnosis and recurrence, respectively. All patients received radiotherapy and/or temozolomide as first line therapy. Among all the analyzed samples, the most frequent actionable molecular alterations were: CDKN2A (57%), CDKN2B (53%), EGFR amplification (39%), EGFR mutation (24%), PTEN loss (27%), RB1 (23%), NF1 (18%), PIK3CA (18%), CDK4 (15%), MDM2 (10%), PDGFRA (8%), BRCA1-2 (7%), FGFR1-3 (7%), Myc (6%), JAK (6%), ROS1 (5%), METmut (2%), METampl (2%), BRAF V600E (2%). No NTRK1/2/3 druggable alterations were observed. High TMB was found in 18 samples. Incidence of actionable molecular alterations in newly diagnosed and relapsed GBM samples is described in the Table. The incidence of alteration of EGFR (ampl/mut), RB1, PIK3CA was statistically different between the two subgroups of samples (Fisher test). To date, 10% of patients received a personalized treatment as compassionate use, off-label use or in clinical trials (9 Dabrafenib/Trametinib, 8 Alpelisib, 3 Erdafitinib, 2 Ipatasertib, 1 Alectinib, 1 Capmatinib, 1 Palbociclib, 1 Entrectinib, 1 Pamiparib). Activity analysis is still ongoing. **Conclusions:** NGS is feasible in GBM samples. Potentially, a high rate of patients could receive a personalized treatment. The activity analysis is ongoing. However, the incidence of actionable molecular alterations may differ between diagnosis and recurrent GBM samples. Research Sponsor: None.

Gene alteration	All cases (out of 419 cases)	%	At Diagnosis (out of 351 cases)	%	At Recurrent (out of 68 cases)	%	p
CDKN2A	240	57,3	195	55,6	45	66,2	0,1
CDKN2B	221	52,7	180	51,3	41	60,3	0,1
EGFR ampl	163	38,9	129	36,8	34	50,0	**0,04**
PTEN loss	113	27,0	99	28,2	14	20,6	0,2
EGFR mut	102	24,3	78	22,2	24	35,3	**0,02**
RB1	98	23,4	47	13,4	51	75,0	**0,0001**
NF1	76	18,1	64	18,2	12	17,6	0,9
PIK3CA	75	17,9	55	15,7	20	29,4	**0,009**
CDK4	64	15,3	58	16,5	6	8,8	0,1
MDM2	45	10,7	42	12,0	3	4,4	0,08
BRCA1-2	44	10,5	33	9,4	11	16,2	0,1
POLE	34	8,1	29	8,3	5	7,4	0,9
PDGFRA	33	7,9	29	8,3	4	5,9	0,6
FGFR1-3	28	6,7	22	6,3	6	8,8	0,4
MYC	27	6,4	22	6,3	5	7,4	0,7
JAK	24	5,7	18	5,1	6	8,8	0,2
ROS1	21	5,0	19	5,4	2	2,9	0,5
MET mut	10	2,4	8	2,3	2	2,9	0,6
MET ampl	9	2,1	7	2,0	2	2,9	0,6
BRAF V600E	9	2,1	6	1,7	3	4,4	0,1
NTRK1-3	0	0,0	0	0,0	0	0,0	NA
H-TMB	18	4,3	12	3,4	6	8,8	0,09

3140 **Poster Session**

Combining autophagy and immune characterizations to predict prognosis and therapeutic response in lung adenocarcinoma.

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Background: As a key regulator of programmed cell death, autophagy is critical for maintaining the stability of the intracellular environment. Increasing evidences have found that the clinical importance of the interaction between autophagy and immune status in LUAD. Reliable prognostic signatures based on combination of autophagy and immune status have not been well-established. We aimed to explore the potential autophagy-immune-derived biomarkers to predict prognosis and therapeutic response in lung adenocarcinoma. **Methods:** Patients from GSE72094 dataset were randomized 7:3 to a training set or an internal validation set. Three independent cohorts, TCGA, GSE31210 and GSE37745, were used as the external verification. Unsupervised hierarchical clustering was used to identify the autophagy-associated and immune-associated molecular patterns for LUAD based on autophagy-genes and immune-genes. The LASSO analysis, univariate and multivariate cox regression analysis were performed to filtrate significant prognostic autophagy-immune-based genes, followed with model construction and patient stratification. Tumor immune microenvironment and functional pathways were investigated. The potential therapeutic responses were explored by GDSC database, TIDE algorithm, and immunotherapy clinical cohorts. **Results:** We found that autophagy cluster A had the better survival prognosis ($p < 0.001$) and high immune status ($p < 0.001$) was identified as favorable factors for patients' overall survival. We merged autophagy and immune subtype into a two-dimensional index to characterize the combined prognostic classifier 535 genes were defined as autophagy-immune-related DEGs. Four genes (C4BPA, CD300LG, CD96, and S100P) were identified to construct the autophagy-immune-related prognostic risk model. Survival analysis and receiver operating characteristic curve showed significant prognostic efficacy. Through ssGSEA and CIBERSORT analysis, the majority of immune infiltrating cells were shown to be enriched in the low-risk group. What's more, the expression of crucial immune checkpoint molecules, such as PD-1, PD-L1 and CTLA-4, was observed highest in low-risk group ($p < 0.001$). TIDE and immunotherapy clinical cohorts' analysis showed that low-risk group was predicted with more potential responders to immunotherapy. In addition, there are different patterns of autophagy between low- and high- risk patients. GO, KEGG and GSEA function analysis focus on cell cycle, MAPK, apoptosis, MTORC1 and selective autophagy pathway. Docetaxel, rapamycin and sorafenib may be the potential drugs candidate in high-risk group ($p < 0.01$). **Conclusions:** In summary, the autophagy-immune-based gene signature represents a promising tool for risk stratification tool in lung adenocarcinoma, which can regard individualized treatment and follow-up scheduling for patients. Research Sponsor: Natural Science Foundation of Guangdong Province, China.

3141 **Poster Session**

The distribution of genetic mutations correlated with resistance to KRAS^{G12C} inhibitors in Chinese patients with lung cancer.

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Background: In lung cancer, p.G12C is the most frequent variant in Kirsten rat sarcoma viral oncogene homologue (KRAS) gene. KRAS^{G12C} inhibitors have shown promising efficacy in lung cancer in recent clinical trials, acquired resistance, however, eventually occurred in most patients. Preliminary studies revealed that a number of genetic mutations were correlated with resistance to this type of drugs, including *KRAS* secondary mutations, *KRAS* activating mutations, mutations in RTK-RAS-MAPK signaling pathways members, oncogene rearrangements and copy number gain. To clarify the potential clinical application of KRAS^{G12C} inhibitors, herein we analyzed the distribution of reported resistance gene alterations in a large and natural group of Chinese lung cancer, as well as the gene mutation landscape of the subset of patients with suspected resistant mutations. **Methods:** A total of 32878 Chinese lung cancer including early-stage, late-stage without treatment or late-stage with previously treated were analyzed in this study. Wide NGS panel testing was used to detected single nucleotide variants (SNV), copy number variants (CNV) and oncogenic gene rearrangements. **Results:** *KRAS* mutations were detected in 2767 (8.4%) cases, of which *KRAS* G12C was the most common variant (30.86%). Among 854 patients (2.6%) harbored *KRAS* G12C, 75 (10%) carried the above resistance mutations, such as G12D/R/V (n = 7). Fusions (20%) which previously observed only in coloretal cancer were unexpectedly detected in this corhort, including *EML4-ALK* (n = 1), *FGFR1-MECOM* (n = 1), *EWSR1-CHEK2* (n = 2), *SPEN-KAZN* (n = 2), *MET-KCNB2* (n = 1), *NOTCH2-NOTCH2NLA* (n = 5), *SMARCA4-DNAH8* (n = 1), and *LIPM-FAS* (n = 1). Furthermore, *KRAS* (46.7%), *MYC* (25.3%) and *MET* (10.7%) were amplified. Among this subset of patients with resistant mutations, *TP53* (66%), *LRP1B* (25%), and *STK11* (22%) were the most frequently mutated genes. It is noteworthy that *STK11/KEAP1 /NFE2L2* gene mutation was detected in nearly 30% in this group of patients. **Conclusions:** The results of our analysis suggested that about 10% *KRAS* G12C-mutated Chinese lung cancer patients would be resistant to *KRAS* G12C inhibitors. Moreover, a small number patients have co-mutated genes which were negatively related to immunotherapy in NSCLC, indicating they were also inappropriate for immunotherapy. Research Sponsor: None.

3142 **Poster Session**

A digital imaging analysis (DIA) platform for identifying tertiary lymphoid structures (TLS) in lung adenocarcinoma (LUAD).

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Background: Previous studies of non-small cell lung cancer (NSCLC) have shown that TLS can be predictive of therapy response and a positive prognostic factor for survival. Currently, TLS identification is manually performed by pathologists with limited morphological criteria. Standardizing TLS detection with an automated DIA workflow could guide clinical trials in precision medicine by improving patient stratification. Here, we investigate the reproducibility and sensitivity of our DIA platform for evaluating TLS in LUAD using digital histopathology and machine learning. **Methods:** TLS were assessed by 3 pathologists on whole slide images (WSI) in a validation cohort of 22 LUAD samples using current TLS characterization criteria of dense lymphoid structures, the presence/absence of a germinal center, and high endothelial venules (HEVs). The intraclass correlation coefficient (ICC) was used to measure reproducibility between pathologists. The BostonGene DIA platform was used to train models for automated TLS detection. Quantitative measurements of area, lymphocyte number, and density of each TLS were obtained. A prospective cohort of 8 samples was used to compare pathologist and DIA identification of TLS. Normalized numbers of TLS in the tumor area were used for cohort stratification for overall survival (OS) analysis using the Kaplan-Meier method in an independent clinical cohort of 104 TCGA-LUAD patients. **Results:** A panel of 3 pathologists identified 326 unique TLS from 22 samples. Between-pathologist detection of TLS, independent of germinal center or HEV criteria, resulted in good reproducibility with an ICC of 0.77. Our DIA platform exhibited excellent reproducibility with an ICC of 0.94 when compared to validated prospective cohort annotation. In total, 155 and 189 TLS were identified by pathologists and our DIA platform, respectively. The DIA platform demonstrated a markedly improved sensitivity of 0.91 for TLS identification. Furthermore, OS analysis revealed that a TLS density greater than 0.94 TLS per mm^2 of tumor assessed by DIA is a statistically significant independent biomarker of better OS in the LUAD cohort from TCGA. **Conclusions:** These results demonstrate the BostonGene DIA platform detects TLS in LUAD, with improved reproducibility and sensitivity over previous methods. Additionally, the DIA platform showed a TLS density greater than 0.94 TLS per mm^2 of tumor is a positive prognostic marker for OS in LUAD. Standardized TLS DIA identification can be exploited in digital pathology applications for future clinical trials, informing clinicians of predictive and prognostic information during the decision-making process. Research Sponsor: BostonGene Corporation.

3143 **Poster Session**

Rapid access to biomarker data in a community setting: Integration of next-generation sequencing into routine pathologic workflow.

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Background: Biomarker data in the form of next generation sequencing (NGS) are critical to the delivery of precision cancer care. Onsite testing is often limited to large academic centers, requiring smaller community centers to rely on samples send outs. Turnaround time for biomarkers can be lengthy and can adversely affect the delivery of optimal therapy in many tumor types. This study aims to evaluate the feasibility of rapidly delivered comprehensive NGS in a community center using a novel workflow in the laboratory by integrating NGS into the routine immunohistochemistry (IHC) service. **Methods:** An automated NGS workflow utilizing the Genexus integrated sequencer with the Oncomine precision assay GX (OPA, Thermofisher Scientific), was validated for clinical use and integrated into the routine diagnostic IHC service. During the study period (Oct 2020 – Oct 2021), NGS biomarker data was generated and reported alongside IHC biomarkers where applicable. A retrospective chart review was performed to assess the early experience and performance characteristics of this novel approach to biomarker testing. **Results:** A total of 578 solid tumor samples underwent genomic profiling. Median turnaround time for biomarker results was 3 business days (IQR 2-5). The majority (n = 481, 83%) of cases were resulted in fewer than 5 business days. Tumor types included lung cancer (n = 310, 54%), melanoma (n = 97, 17%), and colorectal cancer (n = 68, 12%). Specimen types included surgical resections (n = 104, 18%), core biopsies (n = 411, 71%), and cytology specimens (n = 63, 11%). NGS testing detected key driver alterations at expected prevalence rates in respective tumor types; lung *EGFR* (16%), *ALK* (3%), *RET* (1%), melanoma *BRAF* (43%), colorectal *RAS/RAF*wild-type (33%), among others. **Conclusions:** This is the first study demonstrating the clinical feasibility and turnaround time statistics of automated comprehensive NGS performed and interpreted in parallel with diagnostic histopathology and immunohistochemistry in a community setting. This novel approach of integrating biomarkers, IHC, and morphology offers rapid turnaround by removing the need for outsourcing biomarker data. This model could be adopted by other community centers to improve rapid access to biomarker data and therapeutic decision making. Research Sponsor: Pfizer Canada, Pharmaceutical/Biotech Company.

3145 **Poster Session**

Impact of clonal hematopoiesis on tumor control following radiation therapy.

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Background: Clonal hematopoiesis (CH) has well established associations with adverse clinical outcomes including all-cause mortality, cardiovascular disease, and progression to hematologic malignancy. The presence of CH has also been demonstrated to adversely impact survival from non-hematologic cancers, however whether CH may modulate response to radiation therapy (RT) in solid tumors is not known. Here we investigate the potential impact of CH mutations on radiation outcomes. **Methods:** We analyzed data from two previously well annotated cohorts of patients with tumors harboring somatic *ATM* mutations (n = 358) and *FAT1* mutations (n = 365) who received RT and underwent prospective tumor and matched WBC sequencing utilizing the MSK-IMPACT assay. CH variants were detected in the blood samples utilizing a well-validated variant detection and filtration pipeline. Given that pathogenic mutations in ATM have been shown to be strongly associated with improved response to RT, these patients were excluded to avoid confounding. Additionally, patients with blood sampling for CH assessment that occurred more than 6 months after RT were excluded to address the possibility of therapy-related CH. We compared outcomes including irradiated tumor progression in patients with and without CH. **Results:** The final analysis consisted of 412 patients who underwent 811 total courses of radiation. A wide spectrum of solid tumor types were represented, most commonly non-small cell lung cancer (32.5%) and breast cancer (11.9%). A total of 161 patients (39.0%) had CH, with the most commonly mutated genes being *DNMT3A* (25.6%), *PPM1D* (6.2%), *TET2* (5.8%), and *TP53* (5.0%), consistent with prior studies of CH. Patients with CH were older at blood sample collection (67.6 vs 60.2 years, $p < 0.001$), reflecting an expected increase in CH burden with age. Fine Gray competing risks analysis, with death treated as a competing event and with clustering around patient identifier, showed no difference in irradiated tumor progression between patients with and without CH (HR 1.03, 95% CI 0.69 – 1.53, $p = 0.896$). Similarly, subanalyses by CH variant allele frequency and putative CH-driver mutations did not reveal an association between CH and response to RT. A hypothesis generating subgroup analysis by common cancer types, however, suggested that CH was associated with increased risk of progression post-radiation in prostate (HR 4.68, 1.14 – 19.1) and thyroid (HR 3.13, 1.55 – 6.34) cancer cohorts, warranting further investigation. **Conclusions:** We found no difference in irradiated tumor progression among patients who did and did not have CH. There may be an association between CH and poor radiation outcomes in certain cancer types, and further studies are needed to clarify the specific clinical and genomic factors that may influence radiation response. Research Sponsor: None.

3146 **Poster Session**

De novo EGFR T790M mutations in a community-based oncology practice.

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Background: With the 2018 FDA approval of osimertinib for first-line treatment in EGFR-mutated lung cancers, the prevalence of acquired EGFR T790M mutations is expected to decrease, heightening the significance of de novo T790M mutations. Previous studies have reported a wide range of de novo T790M prevalence, and smaller retrospective studies have indicated that germline T790M may comprise the majority of de novo T790M mutations. Here, we assess the frequency of de novo T790M mutations in a community-based setting and report on germline T790M mutations occurring within this population. **Methods:** Patients with T790M-positive lung cancer were identified using Sarah Cannon's clinicogenomics database containing information for patients treated within the Sarah Cannon research network. All T790M mutations were detected on tissue- and plasma-based NGS tests delivered as part of routine care. De novo and germline EGFR T790M status was determined via manual electronic health record chart review. When available, allele fraction and %cfDNA values were extracted from the structured NGS report and analyzed separately. **Results:** Of T790M-positive lung cancers with available pretreatment testing results, 36% (16/44) were confirmed to be T790M+ prior to EGFR TKI exposure; five of these patients received germline testing, and all five were confirmed to have originated in the germline. Two patients with germline T790M mutations detected on testing ordered by external providers were added to our de novo T790M+ patient analysis after chart review. Co-occurring EGFR mutations, including L858R, were detected in pre-TKI samples for 78% (14/18) of de novo T790M+ patients (Table). Co-occurring mutations in TP53, KRAS, PTEN, or RB1 were detected in pre-TKI samples of all patients without co-occurring EGFR mutations. EGFR C797S was observed after osimertinib treatment in one of four patients with post-TKI testing results. Of confirmed germline T790M+ cases with available allele frequencies, 100% (4/4) had allele fractions >0.5 (tissue) and/or %cfDNA values >50% (plasma). Average allele fraction and %cfDNA values were higher for de novo T790M mutations (allele fraction: 0.5 ± 0.2; %cfDNA: 40% ± 20%) than for acquired T790M mutations (allele fraction: 0.3 ± 0.2; %cfDNA: 2% ± 2%). **Conclusions:** Roughly one-third of T790M mutations detected in real-world settings occur before EGFR TKI exposure and may be associated with germline inheritance. Allele frequency may be a potential indicator of de novo T790M mutations in scenarios where pre-treatment data is not available. Future studies will investigate the impact of de novo T790M mutations on treatment response and evolution of resistance mechanisms in osimertinib-treated patients. Research Sponsor: None.

Co-occurring EGFR mutations in pre-TKI samples.

EGFR Variant	N (%)
L858R	6 (33)
Exon 19 Deletion	2 (11)
G719S	3 (17)
L861Q	2 (11)
H835L	1 (6)
None	4 (22)

N: number of de novo T790M+ patients.

3147 **Poster Session**

Construction of a near-term predictive model for irAEs induced by PD-1 inhibitors.

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Background: Immune checkpoint inhibitors have opened a new chapter in cancer therapy, but the incidence of irAEs caused by them is high, and severe irAEs can be fatal. The current research on irAEs is almost focused on early predictions, and there is a lack of near-term predictions (the cycle before the occurrence of irAEs). Absolute eosinophil count (EO#) has been reported to be associated with immune-related pneumonia, but its association with other systemic irAEs requires further exploration. The aim of this study was to explore the near-term predictive value of neutrophil/lymphocyte (NLR), platelet/lymphocyte (PLR), and EO# for PD-1 inhibitor-induced irAEs. **Methods:** The data are from tumor patients who received PD-1 inhibitor therapy in our department from July 2019 to May 2021. A total of 146 cases were included, of which 56 had irAEs. The data of NLR, PLR and EO# in the cycle before the occurrence of irAEs (the median number of cycles was the second cycle) were collected, and the data of the second cycle was used as the control for patients without irAEs group. Logistic method was used to analyze the correlation between NLR, PLR and EO# and irAEs, and a predictive model was constructed. The sensitivity and specificity of the model were evaluated by ROC curve. This study was registered on Chinese Clinical Trail Registry (ChiCTR2100049849). **Results:** A total of 146 tumor patients were included, of which 56 developed at least one irAEs. Grade 1-2 irAEs occurred in 39 cases, grade 3-4 in 12 cases (including cardiac, liver, lung and skin toxicity), grade 5 in 2 cases(including cardiac and lung toxicity), and ungraded in 3 cases. The data of the cycle before the occurrence of irAEs were analyzed. Univariate analysis showed that NLR (odds ratio [OR], 1.4, $p< 0.05$) and EO# (OR, 12.6, $p< 0.05$) were associated with irAEs, and multivariate analysis suggested NLR (OR, 1.7, $p< 0.001$) and EO# (OR, 20.4, $p< 0.05$) were independent risk factors for irAEs. The prediction model composed of NLR, PLR and EO# had a correct rate of 76.7% (AUC = 0.752) in predicting the occurrence of irAEs in the near-term cycle, with a sensitivity of 51.8% and a specificity of 92.2%; the correct rate of predicting irAEs of grade 3 and above was as high as 91.9% (AUC = 0.778), the sensitivity was 14.3% and the specificity was 99.2%. **Conclusions:** The model composed of NLR, PLR and EO# may predict the occurrence of irAEs in the near-term cycle, especially the prediction of irAEs above grade 3, which can provide early warning for the occurrence of irAEs. Clinical trial information: ChiCTR2100049849. Research Sponsor: None.

3148 **Poster Session**

Landscape of endocytosis pathway in colorectal cancer (CRC).

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Background: Recent proteogenomic analyses of CRC revealed that driver gene alterations are enriched in the endocytosis pathway (Vasaikar S, et al. Cell 2019;177:1035-49). Endocytosis is a cellular system involving post-translational modification of plasma membrane proteins through internalization, intracellular trafficking, degradation, and recycling. Clathrin-mediated endocytosis (CME) is the main endocytic portal, and endosomal sorting complexes required for transport (ESCRT) play a critical role in the lysosomal degradation pathway. Besides the well-known function of endocytosis attenuating signaling pathways through receptor clearance from the cell surface, the opposite function contributing to signal maintenance has also been reported. However, the clinical implications of the endocytosis pathway alterations in CRC are largely unclear. **Methods:** We retrospectively reviewed CRC patient samples (n = 15025) submitted to a commercial CLIA-certified laboratory (Caris Life Sciences, Phoenix AZ). Next-generation sequencing of DNA and RNA (whole-transcriptome sequencing) and immunohistochemistry (IHC) were performed. CME-related (47 genes) and ESCRT-related (35 genes) expression signatures were calculated as composite z-scores and compared between subgroups stratified by *RAS*/*BRAF* mutation status, MSS/MSI status, tumor sidedness, and consensus molecular subtype (CMS). *VPS4A*/*VPS4B* expression correlation with major oncogenic pathway signatures (composite z-scores) and *CMTM6*/*CMTM4*/*HIP1R* expression association with PD-L1+ IHC were also assessed. **Results:** Among 17 endocytosis-related genes, no pathogenic/likely pathogenic mutations were identified. The CME-related signature was increased in *RAS*/*BRAF* wild type vs. mutant (0.93 z-score difference, $p=0.04$) and MSS vs. MSI-high (6.0 z-score difference, $p<0.01$), while the ESCRT-related signature was higher in MSS compared to MSI-high (2.7 z-score difference; $p<0.01$). No differences between tumor sidedness were observed in both CME- and ESCRT-related signatures (0.81 and 1.17 z-score differences, respectively). CMS4 had the highest expression of both signatures, while CMS3 had the lowest, of both CME- and ESCRT-related genes (each > 20 z-score difference, $p<0.01$). *VPS4A* and *VPS4B* expression had a strong positive correlation with WNT, EGFR/MAPK, TGF-beta, and Notch pathway signatures (0.65-0.83 Spearman, all $p<0.01$). *CMTM6* expression was positively associated with PD-L1+ IHC (1.2-fold increase vs PD-L1-negative, $p<0.01$), while *CMTM4* and *HIP1R* expression showed a negative association (0.7- and 0.9-fold decrease, respectively, $p<0.01$). **Conclusions:** This large study indicates endocytosis pathway expression is positively associated with oncogenic pathway signaling in CRC. Further analysis of *RAS*/*BRAF* wild type, MSS, and CMS4 patient subgroups are warranted to determine the efficacy of targeting endocytosis pathways in CRC. Research Sponsor: This work was supported by the National Cancer Institute [P30CA 014089 to HJL], Gloria Borges WunderGlo Foundation, Dhont Family Foundation, Daniel Butler Memorial Fund, Victoria and Philip Wilson Research Fund, and San Pedro Peninsula Cancer Guild.

3149 **Poster Session**

BRAF-targeted therapy for locally advanced ameloblastoma of the mandible: A potential neoadjuvant strategy.

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Background: Ameloblastoma is a rare benign but locally aggressive odontogenic neoplasm, with 2% of cases representing ameloblastic carcinoma or metastatic ameloblastoma. It affects young adults with high recurrence rates after surgery. The standard therapy is radical bone resection with subsequent functional, aesthetic & psychological impairments. Therefore, other therapeutic options, including neoadjuvant approach, should be considered. Sixty to 70% of mandible Ameloblastoma carry a BRAF mutation, usually V600E, and previous case reports have shown durable responses to treatment with BRAF inhibitors in these patients. We sought to explore the possibility of neoadjuvant BRAF or BRAF+-MEK inhibition as neoadjuvant treatment in mandible Ameloblastoma. Here we present results of 12 patients with locally advanced disease who were treated with BRAF with or without MEK inhibitors. **Methods:** Patients who were unable to undergo jaw preservation surgery for locally advanced Ameloblastoma with a BRAF V600E mutation were treated with Dabrafenib or Dabrafenib-Tratmetinib in an EAP form. Patient records were analyzed for baseline parameters, treatment regimen, toxicity, response to therapy and the ability to convert to a mandible preservation surgery. Data were collected and analyzed in accordance with Sheba Medical Center IRB approval. Statistical analyses were done with STATA v.17. **Results:** Twelve patients were treated with Dabrafenib/ Dabrafenib-Tratmetinib between 2017-2021. Five patients received BRAF-MEK inhibitors and 7 BRAF inhibitor alone. Median age was 21. Ten patients(83%) showed excellent response to therapy and have successfully converted from planned radical bone resection to mandible preservation surgery. The other 2 patients are still on therapy and have also showed deep responses that enable conversion to mandible preservation. Median time to surgery was 10 months. With median follow up of 18 months, no cases of recurrence were documented. Rate of adverse events was as expected with only 1 case of G3-4 (hepatitis). **Conclusions:** Targeted therapy with BRAF with or without MEK inhibition may serve as an important therapeutic tool for locally advanced Ameloblastoma with the potential of organ preservation treatment, and is an important example of oncological therapy assisting in non-cancerous tumors. Research Sponsor: None.

3150 **Poster Session**

Updated survival follow-up for phase I study of abexinostat with pazopanib in patients with solid tumor malignancies.

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Background: Histone deacetylase (HDAC) inhibition downregulates HIF-1a, which may be effective in overcoming resistance to VEGF-targeting tyrosine kinase inhibitors. We report the updated survival follow-up for patients treated with abexinostat and pazopanib in a phase Ib trial. **Methods:** Patients with solid tumor malignancies were enrolled in this phase Ib, open-label trial (NCT01543763) of abexinostat in combination with pazopanib (3+3 design), with a dose expansion restricted to renal cell carcinoma (RCC). Patients received a 1-week run-in period with abexinostat alone, and then combination abexinostat with pazopanib during a 28-day treatment cycle until disease progression, unacceptable toxicity or study withdrawal. Plasma samples from 29 patients were sent for metabolomics analysis. **Results:** 51 patients were enrolled: N = 36 patients in dose escalation, N = 15 in dose expansion. At the time of last report in 2017, 5 patients remained on study treatment: N = 4 with RCC, and N = 1 with thymic neuroendocrine carcinoma. 4 of these patients have now had disease progression. Median duration of therapy measured 44.9 months (range 39.8-102.2). One patient with metastatic RCC (patient 1) remains on study treatment, after progression on 5 prior lines of systemic therapy. With updated survival follow-up, median OS measured 12.4 months in the dose escalation arm and 27.65 months in the RCC dose expansion cohort. Overall median duration of therapy in all 51 patients measured 5.6 months (range 1-103 months). Progression-free survival among patients with high PBMC HDAC2 expression (> 0.4) remains longer compared to those with low expression (median 6.3 vs. 3.7 months, p = 0.0041). Metabolomics analysis demonstrated a negative correlation between HDAC2 and N6-acetyllysine, suggesting that baseline HDAC2 may impact efficacy of HDAC inhibition. **Conclusions:** The combination of abexinostat with pazopanib appears promising, with the potential for long-term responses particularly in patients with metastatic RCC. This has led to an ongoing phase III trial examining this combination in RCC. Clinical trial information: NCT01543763. Research Sponsor: GlaxoSmithKline, Pharmacyclics.

Patient	Pazopanib dose (mg/ daily)	Abexinostat Dose (mg/m^2 twice daily)	Histology	Age at Study Entry	Number of Prior Systemic Therapies	Duration of Therapy (months)	Best Response
1	400	30	RCC	71.1	5	102.2	Partial response
2	800	45	Thymic neuroendocrine carcinoma	66.5	1	57.7	Stable disease
3	800	45	RCC	52	2	43.4	Partial response
4	800	45	RCC	60	None	39.8	Partial response
5	800	45	RCC	73	None	44.9	Partial Response

3151 **Poster Session**

Combination treatment of radiofrequency ablation and peptide neoantigen vaccination: Promising modality for future cancer immunotherapy.

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Background: We previously reported the safety and immunogenicity of a personalized neoantigen-based peptide vaccine, iNeo-Vac-P01, in patients with a variety of cancer types. The current study investigated the synergistic effects between radiofrequency ablation (RFA) and neoantigen vaccination in cancer patients and tumor-bearing mice. **Methods:** 28 cancer patients were enrolled in this study, including 10 patients who had received RFA treatment within 6 months before scheduled for vaccination, and 18 patients who had not. Individualized neoantigen peptide vaccines were designed, manufactured, and delivered for all patients, followed by subcutaneous administration of GM-CSF as an adjuvant. Mouse models were used to validate the synergistic efficacy of combination treatment of RFA and neoantigen vaccination. **Results:** Longer median progression free survival (mPFS) and median overall survival (mOS) were observed in patients receiving RFA prior to vaccines compared to patients only receiving vaccines (4.42 and 20.18 months vs. 2.82 and 10.94 months). *Ex vivo* ELISpot assay showed that patients who received both had stronger IFN-γ responses against patient-specific neoantigens at baseline and post vaccination. Mice receiving RFA together with vaccine displayed higher antitumor immune responses than mice receiving single modality; addition of anti-PD-1 further enhanced the antitumor response. **Conclusions:** Neoantigen vaccination after RFA treatment led to an overall increase in clinical response and immune response among patients of different cancer types. Combination treatment of both modalities in mice further validated their synergistic antitumor potentials, which could be further enhanced by the addition of anti-PD-1. The mechanisms of their synergies require further investigation. Clinical trial information: NCT03662815. Research Sponsor: National Natural Science Foundation of China; Medical Science and Technology Project of Zhejiang Province; National Natural Science Foundation of China; Natural Science Foundation of Zhejiang Province; Health Commission of Zhejiang Province.

3152 **Poster Session**

Do early phase trials predict clinical efficacy in subsequent phase III biomarker-enriched randomized trials?

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Background: Efficacy endpoints of randomized controlled trials (RCT) are commonly used as the basis of regulatory drug approvals. Recently, promising results in early phase trials have resulted in approval of biomarker-targeted therapies. We examined if early phase trial results were associated with efficacy in subsequent biomarker-enriched RCTs. **Methods:** All cancer drug RCTs conducted between January 2006 and March 2021 were identified through Clinicaltrials.gov. Trials were eligible if a biomarker was used to select a patient population for treatment with a targeted agent. Associated early phase trials were included if they matched the RCT in treatment setting and patient population. Trials pairs were compared using objective response rate (ORR) and progression-free survival (PFS). We assessed difference in endpoints using summary measures (e.g., average, range). We examined whether early phase trials results were associated with RCT results using logistic regression. **Results:** The search yielded 2,157 unique phase III RCTs and 27 RCTs met eligibility criteria pairing with associated early phase trials, where 17 RCTs met their primary endpoint. The most common biomarkers were EGFR+ (n = 8), HER2+ (n = 5) and PD-L1 (n = 5). Based on average difference of trial pairs, ORR was similar between trials (1.59%, 95% CI = -2.5-5.6, p = 0.50) and median PFS was slightly higher in early phase trials (1.95 months, 95% CI = 0.91-2.99, $p < 0.05$). On an individual pair basis, there was large range of variability in the difference between early phase trials and RCTs for ORR (range = -23.9-20.2%) and median PFS (range = -0.8-7.4 months). The probability of the RCT meeting its primary endpoint is 50% or 95%, when the early phase trial ORR is 41.2% (95% CI = 35.2-47.1%) or 77.7% (95% CI = 71.7-83.6%), respectively. **Conclusions:** Through comparison of early phase trials and subsequent phase III RCT, we found that, overall, ORR has minimal bias in early phase trials, and median PFS appears to be slightly overestimated. Substantial variability in results for trial pairs suggests that, on an individual basis, results in early phase trial can be inconsistent with results in subsequent RCT. Early phase trial results may be associated with RCTs meeting their primary endpoint when ORR is very high; however, caution must be exercised when using early phase trials as representative of RCTs for decision-making as the predictive ability of early phase trials is limited. Research Sponsor: None.

TPS3153 **Poster Session**

First-in-human study of the B7-H4 antibody-drug conjugate (ADC) AZD8205 in patients with advanced/metastatic solid tumors.

Funda Meric-Bernstam, Do-Youn Oh, Yoichi Naito, Toshio Shimizu, Vincent Chung, Haeseong Park, Stephanie Gaillard, Fujun Wang, Zachary A. Cooper, Krista Kinneer, Marlon Rebelatto, Lyndon Kirby, Nadia Luheshi, Neil Miller, Andreea Varga, Linda R. Mileshkin; University of Texas MD Anderson Cancer Center, Houston, TX; Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Integrated Major in Innovative Medical Science, Seoul National University Graduate School, Seoul, South Korea; National Cancer Center Hospital, Tokyo, Japan; City of Hope, Duarte, CA; Washington University School of Medicine, St. Louis, MO; Johns Hopkins University, Baltimore, MD; AstraZeneca, Gaithersburg, MD; AstraZeneca, Cambridge, United Kingdom; Peter MacCallum Cancer Centre, Melbourne, Australia

Background: ADCs are a class of anti-cancer agents that leverage the selectivity of monoclonal antibodies to preferentially target and deliver chemotherapeutic agents to cancer cells. AZD8205 is an ADC, administered by IV infusion, that consists of a human anti-B7-H4 antibody conjugated via a cleavable linker to a topoisomerase I inhibitor (TOP1i) warhead. B7-H4 is a transmembrane protein that binds to an unknown receptor on activated T cells, inhibiting their function. It is highly expressed by a wide variety of tumors including cholangiocarcinoma (CCA) and breast, ovarian and endometrial cancers, and is associated with poor prognosis. AZD8205 specifically binds to B7-H4 expressing tumor cells and is internalized. The TOP1i warhead is released, interfering with TOP1 during DNA replication leading to transcription-mediated DNA damage and cell death. TOP1i ADCs have shown clinical activity in several tumor types including breast cancer. In preclinical studies, AZD8205 has shown promising antitumor activity in various patient-derived xenograft models and an acceptable toxicity profile. This first-in-human study (NCT05123482) is evaluating AZD8205 for the treatment of selected advanced/metastatic tumors. **Methods:** This phase I/IIa, open-label, dose-escalation and dose-expansion study is currently investigating AZD8205 monotherapy in patients ≥18 years old (≥20 years for Japan) with CCA, breast, ovarian or endometrial cancers. Eligibility criteria include relapsed/metastatic disease following standard of care treatment, measurable disease per RECIST v1.1, and ECOG PS 0–1. Key exclusion criteria include spinal cord compression or leptomeningeal carcinomatosis, symptomatic brain metastases, and history of interstitial lung disease/pneumonitis. Expression of B7-H4 will be evaluated using a validated central laboratory immunohistochemistry assay on tumor samples collected before, during, and when feasible, after AZD8205 treatment. In the escalation phase, patients will receive AZD8205 followed by 21 days of observation for dose-limiting toxicities. Patients will be enrolled in escalating dose cohorts using the modified toxicity probability interval-2 model with at least 3 evaluable patients per dose level. Patients will continue on study treatment until disease progression, initiation of alternate anticancer therapy, unacceptable toxicity, or withdrawal of consent. Primary objectives are to determine the safety and tolerability of AZD8205 and identify the maximum tolerated dose and/or recommended phase 2 dose. Secondary objectives include assessing initial activity (objective response and progression-free survival by RECIST v1.1, and overall survival), pharmacodynamics, pharmacokinetics, and immunogenicity. The trial is currently recruiting and will enroll patients globally. Clinical trial information: NCT05123482. Research Sponsor: AstraZeneca.

TPS3154 **Poster Session**

Phase 1 study of SGN-PDL1V, a novel, investigational vedotin antibody–drug conjugate directed to PD-L1, in patients with advanced solid tumors (SGNPDL1V-001, trial in progress).

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Background: Programmed cell death ligand 1 (PD-L1) is a cell-surface protein involved in the programmed cell death protein 1 (PD-1)/PD-L1 immune checkpoint, which inhibits T-cell activation. Elevated PD-L1 expression is observed across a broad spectrum of solid tumor types. Expression of PD-L1 in tumors can signal through PD-1 on T cells to inhibit T-cell effector function. Blockade of the PD-1/PD-L1 signaling axis may restore antitumor immunity by reactivating T-cell effector function in the tumor microenvironment. SGN-PDL1V is a novel, investigational vedotin antibody–drug conjugate directed to PD-L1 with multiple proposed mechanisms of action including monomethyl auristatin E (MMAE)-directed cytotoxicity, bystander effect, and immunogenic cell death (ICD). Even in xenograft models with low, heterogeneous PD-L1 expression, SGN-PDL1V demonstrated antitumor activity via direct cytotoxicity and the bystander effect. Cytotoxicity mediated by SGN-PDL1V also led to immune activation due to MMAE-induced ICD (Kwan et al 2021). These preclinical findings provide a rationale for evaluating SGN-PDL1V in patients (pts) with advanced solid tumors. **Methods:** SGNPDL1V-001 (NCT05208762) is a phase 1, first-in-human, multicenter, open-label trial designed to evaluate the safety, tolerability, pharmacokinetics (PK), and antitumor activity of SGN-PDL1V in pts with advanced solid tumors. This study includes 3 parts: dose escalation (Part A), dose and schedule optimization cohorts (Part B), and dose expansion in disease-specific cohorts and a biology cohort (Part C). Adult pts (≥18 years) with histologically/cytologically confirmed metastatic/unresectable solid tumors, including non-small cell lung cancer, head and neck squamous cell carcinoma, esophageal squamous cell carcinoma, melanoma, or ovarian cancer, will be eligible. Pts must have ECOG PS 0–1 and have failed or are unable to tolerate standard therapies. Pts must have PD-L1 expression ≥1 by tumor proportion score or combined positive score based on historical testing. Prior treatment with an MMAE-containing agent or an anti–PD-L1 agent (within 6 months) is not permitted. Primary endpoints include adverse events, laboratory abnormalities, dose-limiting toxicities, and cumulative dose-level safety. Secondary endpoints include rate and duration of objective response, progression-free survival, overall survival, PK, and incidence of antidrug antibodies. Exploratory endpoints include pharmacodynamics (PD), PK/PD relationships, and patient-reported outcomes. Safety and antitumor activity endpoints will be assessed using descriptive statistics. Objective response rate will be analyzed by tumor type, dose levels, and schedules. Enrollment for Part A is ongoing at sites in North America and is planned in Europe. Clinical trial information: NCT05208762. Research Sponsor: Seagen Inc.

TPS3155 **Poster Session**

Phase 1 study of SGN-B7H4V, a novel, investigational vedotin antibody–drug conjugate directed to B7-H4, in patients with advanced solid tumors (SGNB7H4V-001, trial in progress).

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Background: B7-H4, a B7 immune checkpoint ligand, is expressed at low levels in normal tissue and negatively regulates T-cell function by inhibiting T-cell proliferation and cytokine production. B7-H4 expression is elevated in solid tumors, including breast, ovarian, and endometrial cancers. Targeting B7-H4–expressing tumor cells may relieve B7-H4–mediated T-cell inhibition. SGN-B7H4V is a novel, investigational vedotin antibody–drug conjugate directed to B7-H4 with proposed mechanisms of action including monomethyl auristatin E (MMAE)-directed cytotoxicity, bystander effect, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis. SGN-B7H4V elicited antitumor activity in cell line-derived xenograft models of triple-negative breast cancer (TNBC) and patient-derived xenograft models of TNBC and ovarian cancer (Gray et al 2021), providing a rationale to evaluate SGN-B7H4V in patients (pts) with advanced solid tumors. **Methods:** SGNB7H4V-001 (NCT05194072) is a phase 1, first-in-human, multicenter, open-label trial evaluating the safety, tolerability, pharmacokinetics (PK), and antitumor activity of SGN-B7H4V in pts with advanced solid tumors. This study includes 3 parts: dose escalation (Part A), dose and schedule optimization (Part B), and dose expansion in disease-specific cohorts and a biology cohort (Part C). Adult pts (≥18 years) with histologically/cytologically confirmed locally advanced unresectable or metastatic solid tumors including high-grade serous epithelial ovarian cancer, primary peritoneal cancer, fallopian tube cancer, human epidermal growth factor receptor 2-negative and hormone receptor-positive breast cancer, TNBC, endometrial carcinoma, squamous non-small cell lung cancer, cholangiocarcinoma, or gallbladder carcinoma, are eligible. Pts must have ECOG PS 0–1 and relapsed/refractory disease or be intolerant to standard-of-care therapies. Prior treatment with an MMAE-containing agent or a B7-H4–targeted agent is not permitted. Primary endpoints include the rate of adverse events, laboratory abnormalities, dose-limiting toxicities, and cumulative dose-level safety. Secondary endpoints are objective response rate (ORR), complete response rate, duration of objective response (DOR), progression-free survival (PFS), overall survival (OS), PK, and incidence of antidrug antibodies. Exploratory endpoints include pharmacodynamic (PD) analyses, PD and PK exposure measurements, B7-H4 characterization on malignant cells, and biomarker analyses. Safety and antitumor activity endpoints will be assessed using descriptive statistics. ORR will be analyzed by tumor type and dose. DOR, PFS, and OS will be estimated using the Kaplan–Meier method. Enrollment for Part A is ongoing in North America and is planned in Europe. Clinical trial information: NCT05194072. Research Sponsor: Seagen Inc.

TPS3156 **Poster Session**

TIP: A phase I/II study of MGTA-117, an anti-CD117 antibody-drug conjugate, in patients with adult acute myeloid leukemia (AML) and myelodysplasia with excess blasts (MDS-EB).

Andrew S. Artz, Onyee Chan, Sherif Farag, Mark Juckett, Partow Kebriaei, Philip L. McCarthy, Anurag K Singh, Peter Westervelt, Jeff Humphrey, William L. Baeder, Alison Occhiuti, Jeanie Tang, Kirk Bertelsen, Kevin A. Goncalves, Yasuhiro Tabata; City of Hope, Duarte, CA; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; IU Simon Cancer Ctr, Indianapolis, IN; University of Minnesota, Minneapolis, MN; The University of Texas MD Anderson Cancer Center, Department of Stem Cell Transplantation & Cellular Therapy, Houston, TX; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Division of Hematologic Malignancies and Cellular Therapeutics, University of Kansas Medical Center, Kansas City, KS; Washington University, St. Louis, MO; Magenta Therapeutics, Cambridge, MA; Magenta Therapeutics, Burlington, NJ

Background: Hematopoietic stem cell transplantation (HSCT) is used with curative intent for AML and MDS-EB. MGTA-117 is a novel Ab-drug conjugate (ADC) in development for conditioning prior to HSCT. MGTA-117 selectively targets CD117 (c-Kit) with a human monoclonal Ab to CD117 conjugated to an amanitin payload that depletes CD117-expressing cells by inhibiting RNA polymerase II. Human hematopoietic stem cells and AML tumor cells express high levels of CD117, and MGTA-117 potently depletes these target cells, with an IC50 of <10pM in vitro. MGTA-117 has demonstrated in vitro and in vivo stability, confirming its characterization as a highly potent and selective agent. In a primate GLP toxicology study, MGTA-117 maximally depleted bone marrow stem cells at a dose not associated with evidence of toxicity in other tissues. Dose-dependent reduction of peripheral reticulocytes, produced from CD117+ erythroid precursors in the bone marrow, was an early and time sensitive biomarker of bone marrow CD117+ cell depletion. Higher doses were associated with the elevation of transaminases and histopathology that were asymptomatic and transient. Highest Non- Severely Toxic Dose (HNSTD) was used to establish the starting dose in this First-in-Human study. Based upon dose exposure and allometric scaling, it is expected that the clinical exposures after a 0.02 mg/kg dose in the first human cohort will provide an optimal > 100-fold safety margin over exposures observed after the 0.3 mg/kg dose that was the HNSTD in the primate GLP toxicology study. **Methods:** This phase I/II, multicenter, open-label, dose-escalation study will investigate the safety, tolerability, PK profile, PD activity, and blast depletion activity of MGTA 117 given intravenously as a single dose in adults with R/R AML or MDS-EB. Patients must be 18-75 yrs, have a WHO-defined diagnosis of CD117+ R/R AML or MDS-EB with ≥5% marrow myeloblasts. Patients must have ECOG PS ≤2, and adequate hepatic, renal, and cardiac function. The primary objective is to establish a minimum safe and biologically effective (MSBE) dose of MGTA-117 in R/R AML and MDS-EB patients based on safety and CD117 receptor occupancy (RO) in circulating leukemic blasts after dosing. The observation period for dose limiting toxicities is 21 days. Patients will be followed for changes in reticulocyte, neutrophil, and platelet counts in PB and percent change from baseline in leukemic blasts or stem/progenitor cells in PB and/or BM. CD117 receptor occupancy by MGTA-117 will be measured and MSBE dose will be based on safety and receptor occupancy. The study is designed with the possibility that subjects would proceed to HSCT >28 days after MGTA-117 administration, if eligible per the local transplant practices. Clinical trial information: NCT05223699. Research Sponsor: Magenta Therapeutics.

TPS3157 **Poster Session**

First-in-human, phase 1, open-label, dose-escalation, dose-expansion study of ADCT-901 as monotherapy in patients with select advanced solid tumors.

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Background: Kidney associated antigen 1 (KAAG1) is highly and selectively expressed on tumor cell surface, such as ovarian, prostate, and triple negative breast cancers (TNBC), and is rapidly internalized and co-localized with a lysosomal marker, making an ideal candidate for an antibody-drug conjugate (ADC) target. ADCT-901 is an ADC composed of a humanized monoclonal antibody IgG1 against KAAG1, conjugated through a cathepsin-cleavable linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin. In mouse xenograft models of human-derived TNBC, ovarian, and renal cancers significant tumor reduction was observed after a single dose of ADCT-901, providing the rationale for clinical development of a PBD-based ADC to treat KAAG1 expressing tumors (Zammarchi et al, AACR 2019). This study aims to identify the recommended dose and schedule for expansion and to characterize safety and tolerability of ADCT-901 in patients (pts) with selected advanced solid tumors that generally express KAAG1. **Methods:** ADCT-901-101 is a phase 1, multicenter, 2-part, open-label study that will enroll ~70 pts (NCT04972981). Part 1: pts will receive escalating doses of ADCT-901 guided by a 3+3 design (1st dose: 15 μg/kg every 3 weeks [Q3W]; highest dose: 290 μg/kg Q3W). Dose escalation will be evaluated by administering the lowest dose to first 3 pts, then increasing/decreasing the dose based on dose-limiting toxicity (DLT) experienced by pts. The dose and schedule of ADCT-901 identified in part 1 will be tested in part 2 to characterize safety, tolerability, and preliminary efficacy of ADCT-901. Primary endpoints include incidence of DLTs (part 1 only), frequency/severity of adverse events (AE) and serious AE, clinically significant changes in vitals, laboratory values, overall tolerability, and frequency of dose interruptions and reductions. Secondary endpoints include overall response rate, duration of response, progression-free and overall survival, pharmacokinetic parameters of ADCT-901 total antibody, PBD-conjugated antibody, unconjugated SG3199 in serum, and frequency of confirmed positive antidrug antibody responses. Exploratory endpoints include tumor modulation and potential pharmacodynamic changes. Key inclusion criteria: pathologic diagnosis of selected solid tumor (cholangiocarcinoma, renal cell carcinoma, ovarian/fallopian tube and prostate cancers, TNBC) locally advanced or metastatic at time of screening, pts refractory or intolerant to existing therapy, tissue biopsy or available tissue sample, ECOG of 0-2, and adequate organ function based on predefined laboratory parameters. Pts with symptomatic CNS metastases and clinically significant third space fluid accumulation will be excluded. The study opened for recruitment in September 2021; enrollment is ongoing. Funding: ADC Therapeutics; medical writing: CiTRUS Health Group. Clinical trial information: NCT04972981. Research Sponsor: ADC Therapeutics.

TPS3158 **Poster Session**

ELU-FRα-1: A study to evaluate ELU001 in patients with solid tumors that overexpress folate receptor alpha (FRα).

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Background: ELU001 is a novel, first-in-class, new molecular entity described as a C'Dot Drug Conjugate (CDC). ELU001 consists of ~12 folic acid targeting moieties and ~22 exatecan topoisomerase-1 inhibitor payloads on Cathepsin-B cleavable linkers covalently bound to the surface of each silicon core/polyethylene glycol C'Dot nanoparticle. CDCs are small in size (~6 nm), have a greater ability to penetrate into and through tumors as compared to ADCs, and are rapidly eliminated by the kidneys. The rapid systemic elimination is expected to lead to less toxicity than is observed with targeting platforms like ADCs that have a longer half-life in circulation. ELU001's high avidity is believed to promote internalization into FRα overexpressing cancer cells, selectively delivering it's ~22 molecules of payload. The first-in-human clinical trial, ELU-FRα-1, is currently recruiting patients that have advanced, recurrent or refractory FRα overexpressing tumors considered to be topoisomerase 1 inhibitor-sensitive based on the literature, and, in the opinion of the Investigator, have no satisfactory therapeutic options available. **Methods:** This is a Phase 1 / 2 multicenter, open label clinical trial with two parts: Part 1 Dose Escalation and Part 2 Tumor Group Expansion Cohort(s). In Part 1, patients with cancer types with a high likelihood of having FRα overexpressing tumors based on historical data, (specifically, ovarian, endometrial, colorectal, gastric, gastroesophageal junction, triple negative breast, or non-small cell lung cancers, or cholangiocarcinoma), will be enrolled to the study. Patients will receive ELU001 on a weekly dose regimen (QW) (once a week for 3 weeks, 1 week rest) or every other week dose regimen (Q2W, with no rest between cycles). Retrospective analysis of FRα expression will be determined. Part 2 uses a Simon's Two-Stage design to evaluate 4-6 tumor group expansion cohorts, each consisting of patients with specific tumor types (to be identified based on emerging data) that overexpress FRα (prospectively determined prior to enrollment). The primary objective for Part 1 is to identify the MTD/RP2D and for Part 2 is ORR. Dose Escalation will recruit about 25 patients per dose regimen (QW or Q2W). Dose Expansion will recruit about 15 patients per tumor group expansion cohort. Secondary objectives are anti-tumor activity (DOR, PFS, TFST, PFS2, OS), frequency, severity and tolerability of adverse events, PK, ADA, and FRα expression assessments. The study is actively enrolling in the US – Cohorts 1-2 have been completed without DLT. Enrollment to Cohort 3 began in December 2021. Clinical trial information: NCT05001282. Research Sponsor: Elucida Oncology.

TPS3159 **Poster Session**

Phase 1 study of SGN-ALPV, a novel, investigational vedotin antibody–drug conjugate directed to ALPP/ALPPL2 in advanced solid tumors (SGNALPV-001, trial in progress).

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Background: Alkaline phosphatase placental (ALPP) and ALPP-like 2 (ALPPL2) are proteins with 98% sequence similarity that are highly expressed in ovarian, endometrial, gastric, and testicular cancers. Restricted normal tissue expression and efficient lysosomal trafficking of ALPP and ALPPL2 highlight their potential as anticancer targets. SGN-ALPV is a novel investigational vedotin antibody–drug conjugate composed of a humanized anti-ALPP/ALPPL2 monoclonal antibody, a protease-cleavable linker, and the microtubule disrupting agent monomethyl auristatin E (MMAE). The proposed mechanism of action of SGN-ALPV is binding to ALPP/ALPPL2 on the cell surface, where it is internalized and trafficked to the lysosome. Lysosomal proteases cleave the linker to release MMAE into the cytoplasm, where it binds and disrupts the microtubule network, causing cell cycle arrest and apoptosis. Additional mechanisms of action of SGN-ALPV include immunogenic cell death and apoptosis of neighboring cells via the bystander effect. Promising preclinical data support the evaluation of SGN-ALPV in a clinical trial. **Methods:** SGNALPV-001 (NCT05229900) is a phase 1, open-label, multicenter study designed to evaluate the safety, tolerability, pharmacokinetics (PK), and antitumor activity of SGN-ALPV in patients (pts) with select advanced solid tumors. This study consists of 3 parts: dose escalation (Part A), dose and schedule optimization (Part B), and dose-expansion in disease-specific cohorts and a biology cohort (Part C). Adult pts (≥18 years) with confirmed ovarian, endometrial, non-small cell lung, gastric, cervical cancer, or testicular germ-cell tumors, relapsed or refractory to approved therapies, with measurable disease per RECIST v1.1 and an ECOG PS 0–1 are eligible. Primary endpoints include incidence of adverse events, laboratory abnormalities, dose-limiting toxicities, and cumulative safety. Secondary endpoints include estimates of antidrug antibodies, PK parameters, objective response rate, duration of response, progression-free survival, and overall survival. Exploratory endpoints are pharmacodynamic and biomarker measurements. Safety and antitumor activity endpoints will be summarized using descriptive statistics. Enrollment for Part A is ongoing in sites in North America and Europe. Enrollment for Parts B and C will be opened upon completion of Part A. Clinical trial information: NCT05229900. Research Sponsor: Seagen.

TPS3161 **Poster Session**

Phase 1 study of patritumab deruxtecan (HER3-DXd; U3-1402) in combination with osimertinib in patients with advanced *EGFR*-mutated NSCLC.

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Background: Although first-line treatment with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor osimertinib improved survival in patients (pts) with advanced/metastatic *EGFR*-mutated (*EGFRm*) non-small cell lung cancer (NSCLC), therapy after acquired resistance to osimertinib remains an unmet need. HER3 is expressed in the majority of *EGFRm* NSCLCs. HER3-DXd is a novel, investigational, HER3-directed antibody-drug conjugate that demonstrated preliminary single-agent clinical activity in *EGFRm* NSCLC. In preclinical models of *EGFRm* NSCLC, osimertinib increased membrane HER3 expression, improved the internalization rate of HER3-DXd, and enhanced tumor growth inhibition by HER3-DXd. Therefore, HER3-DXd with osimertinib might improve outcomes in pts with disease that progressed with osimertinib therapy. This phase 1 study (NCT04676477; U31402-A-U103) evaluates HER3-DXd in combination with osimertinib in pts with advanced *EGFRm* NSCLC that has progressed with first-line osimertinib therapy. **Methods:** This is an open-label, 2-part study of HER3-DXd in combination with osimertinib. Pts are enrolling in North America, Europe, and Asia. Dose escalation enrolls pts with locally advanced/metastatic NSCLC with an *EGFR*-activating mutation (exon 19 del or L858R) and progression during or after osimertinib therapy. Pts receive HER3-DXd 1.6, 3.2, 4.8, or 5.6 mg/kg intravenously (IV) every 3 weeks (Q3W) in combination with osimertinib 40 or 80 mg orally (PO) once daily (QD). Pts are enrolled in each cohort guided by safety (dose-limiting toxicities) using a Bayesian logistic regression model. Primary objectives of dose escalation are to assess safety and tolerability of the combination and identify a recommended combination dose (RCD). In dose expansion, pts will be randomized 1:1 to receive either HER3-DXd and osimertinib at the RCD (arm 1, [≈60 pts]) or HER3-DXd 5.6 mg/kg IV Q3W (arm 2, [≈60 pts]). A third arm (arm 1b, [≈60 pts]) may be added to evaluate 2 provisional RCDs of HER3-DXd + osimertinib. The primary objective of dose expansion (arms 1, 2, and 1b) is to evaluate efficacy of the combination vs that of monotherapy. The primary endpoint is objective response rate (ORR) as assessed by blinded independent central review. Other efficacy endpoints include ORR by investigator and duration of response, disease control rate, time to response, progression-free survival, and overall survival. If the RCD includes an osimertinib dose of 80 mg PO QD, ≈30 pts with advanced *EGFRm* NSCLC without prior treatment will be enrolled and treated at the RCD in a separate cohort; the primary objective is to assess safety and tolerability. A tumor sample after progression with osimertinib (or prior to entry) is required for pts enrolled in dose expansion for retrospective evaluation of HER3 and biomarker analyses. Clinical trial information: NCT04676477. Research Sponsor: Daiichi Sankyo Inc.

TPS3162 **Poster Session**

Datopotamab deruxtecan (Dato-DXd) plus pembrolizumab in treatment-naive advanced/metastatic (adv/met) non–small cell lung cancer (NSCLC) with PD-L1 ≥ 50% and without actionable genomic alterations.

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Background: First-line treatment with immunotherapy has significantly improved survival in patients with adv/met NSCLC. Pembrolizumab (pembro) as monotherapy has shown superior efficacy compared with chemotherapy in treatment-naive patients with advanced NSCLC and PD-L1 expression ≥50%, but most patients will ultimately experience progression. Dato-DXd is an antibody-drug conjugate (ADC) consisting of a humanized anti-TROP2 IgG1 monoclonal antibody attached to a topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker. In the ongoing phase 1 TROPION-PanTumor01 study (NCT03401385; DS1062-A-J101), Dato-DXd 6 mg/kg monotherapy demonstrated an objective response rate (ORR) of 28% and a manageable safety profile in pretreated patients with NSCLC. In addition, preclinical studies showed that DXd ADCs combined with an anti–PD-1 antibody was more effective than monotherapy with either agent alone. The tolerability of Dato-DXd 6 mg/kg in combination with pembrolizumab was confirmed in the phase 1b TROPION-Lung02 trial (NCT04526691; DS1062-A-U102). Here we describe the phase 3 TROPION-Lung08 trial evaluating Dato-DXd combined with pembro in treatment-naive patients with adv/met NSCLC. **Methods:** TROPION-Lung08 (NCT05215340; DS1062-A-U304) is a global, randomized, open-label, phase 3 trial of Dato-DXd plus pembro vs pembro alone in treatment-naive patients with adv/met non-actionable oncogenic driven NSCLC with PD-L1 ≥50% (as determined by PD-L1 IHC 22C3 pharmDx assay). Approximately 740 patients will be randomized to receive pembro 200 mg plus Dato-DXd 6 mg/kg or pembro 200 mg alone every 21 days until discontinuation or 35 cycles of pembro. Randomization will be stratified by Eastern Cooperative Oncology Group performance status (0 vs 1), histology (squamous vs nonsquamous), geographic region (East Asia vs rest of world), and smoking status (former/current vs never). Patients must have stage IIIB/IIIC NSCLC ineligible for curative treatment or stage IV disease. Patients must not have received prior systemic therapy; if patients received neoadjuvant/adjuvant systemic therapy without immune checkpoint inhibitors, it must have been given ≥6 months before the diagnosis of adv/met disease. The primary endpoints are progression-free survival (assessed by blinded independent central review per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) and overall survival, with target hazard ratios of 0.65 and 0.75, respectively. Secondary endpoints include ORR, duration of response, time to response, disease control rate, safety, and antidrug antibody prevalence. Pharmacokinetic parameters, biomarkers, and patient-reported outcomes will also be explored. Clinical trial information: NCT05215340. Research Sponsor: Daiichi Sankyo Inc.

TPS3163 **Poster Session**

TARGET National: A U.K.-wide liquid-based molecular profiling program to enhance recruitment to early-phase trials.

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Background: Precision medicine programs have largely focused on tissue-based assays to screen patients for genomic variants amenable to experimental targeted therapies. Challenges faced in such studies include time taken to acquire archival biopsies and limitation in capturing tumor heterogeneity and clonal evolution. The TARGET study (Rothwell, Nature Medicine 2019) previously demonstrated feasibility of using ctDNA to match patients to early phase trials with the benefit of rapid turnaround of results. With an ever-increasing number of novel therapies in development targeting rare genomic alterations across different tumor types, ctDNA holds great promise in enhancing recruitment to studies with rapid and efficient comprehensive genomic profiling assays covering a broad range of variants. There is need to perform profiling at scale to identify rare alterations and to utilise networks for identification of suitable clinical trials across the country. ctDNA is not detectable in all patients (owing to differences across disease types/ burden), thus tissue analysis still plays an important role. **Methods:** TARGET National is an investigator-initiated multi-centre molecular profiling study. The primary endpoints are to establish a national framework to offer profiling from blood samples (or tissue if appropriate) for patients being considered for early phase clinical trials across the UK Experimental Cancer Medicine Centre (ECMC) Network, and to measure the number of patients receiving matched therapy (MT). Secondary endpoints include curating the genomic landscape of the early phase population in the UK, and outcomes for patients receiving MT versus unmatched. Enrolment began in July 2021 and >250 patients have been recruited across 9 ECMCs with plans to expand to 20 centres by Q3 2022. Planned enrolment is 6000 patients over 5 years. Patients must be ≥ 16 years old, provide written consent, have histologically confirmed advanced solid cancer, progressing disease and be considered fit enough to receive an experimental therapy. ctDNA is analysed with Foundation Medicine Liquid CDx with option for other providers. A multi-disciplinary national Molecular Tumor Board enables interpretation of genomic reports and identifies suitable clinical trials, supported by eTARGET; a bespoke clinical-genomic data capture solution including trial finding software. The study provides broad access to genomic profiling throughout the UK, increasing experience with ctDNA assays, and will improve opportunities for patients to participate in early phase research. The UK database will provide means for identification of rare genomic patient groups for new first-in-human studies, and the program provides a national infrastructure to collect additional samples for translational research and pre-clinical models to progress understanding of biological predictors of response and resistance. Clinical trial information: NCT04723316. Research Sponsor: The Christie Charity, Other Foundation, Pharmaceutical/Biotech Company.

TPS3164 **Poster Session**

DELFI-L101: Development of a blood-based assay that evaluates cell-free DNA fragmentation patterns to detect lung cancer.

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Background: Despite longstanding national recommendations, uptake of lung cancer screening in the US remains low. Barriers include access to lung cancer screening, costs, and concerns over potential harms like false-positives and radiation exposure. The DELFI technology evaluates fragmentation patterns of cfDNA using supervised machine learning to distinguish cancer from non-cancer [PMID30943338; 34417454; 31142840]. **Methods:** The DELFI-L101 is a case-control observational study (NCT04825834) prospectively enrolling at academic and community sites. Eligible participants (≥50 years of age) are individuals who currently smoke or previously smoked, with smoking histories of ≥20 pack-years. Individuals are ineligible if they had cancer treatment in the prior year or a history of hematologic malignancies or myelodysplasia. Cases are individuals with pathologically confirmed cancers (group A – lung, group C – non-lung). Controls are those without cancer (group B) as determined by low-dose computed tomography screening completed within 6 weeks of enrollment. Cases and controls are identified among enrollees from all participating sites. Total enrollment is estimated to be ~2500 participants across all groups. Blood samples are collected at enrollment for DELFI analyses, which involves cfDNA isolation from plasma, low-coverage, whole-genome, next-generation sequencing, and machine learning methods. Clinical data (medical history, demographics, and diagnostic, surgery, imaging, and pathology reports, and/or other diagnostic information) are collected at enrollment and at 12 months post-enrollment. The primary objective is to train and test a classifier for the detection of lung cancer using the DELFI technology with other biomarkers and clinical features. Secondary objectives include the evaluation of classifiers to distinguish lung cancer from other cancers, modeling benefits and harms using performance estimates of these classifiers, and description of the analytical performance (eg, repeatability and reproducibility) of the DELFI technology and classifiers. The primary endpoint is the accuracy of lung cancer detection as measured by sensitivity, specificity, and the area under the receiver operating characteristic curve. Secondary endpoints include accuracy of tissue of origin classification, and adverse events associated with blood sample collection. The training and performance characterization of a DELFI classifier will further the development of an affordable, accessible, blood-based cancer detection tool with potential to overcome barriers to lung cancer screening. Clinical trial information: NCT04825834. Research Sponsor: Delfi Diagnostics, Inc.

TPS3165 **Poster Session**

A phase 2 study of the MDM2 inhibitor milademetan in patients with *TP53*-wild type and *MDM2*-amplified advanced or metastatic solid tumors (MANTRA-2).

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Background: Murine double minute 2 (MDM2) is a potent negative regulator of the tumor suppressor p53. MDM2 induces degradation of p53 and promotes tumorigenesis in solid tumors, and preclinical models have shown that inhibition of MDM2 can restore p53 tumor suppressor activity in *TP53*-wild type (WT), *MDM2*-amplified tumors. We performed a mutual exclusivity analysis of patients with solid tumors (n = 42,125; AACR Project GENIE) and found that the frequency of co-occurring *TP53* mutations decreased with increasing *MDM2* copy number. An *MDM2* copy number of 12 was chosen as the threshold. An estimated 1.1% of solid tumors meet this molecular criteria, excluding glioblastomas, dedifferentiated liposarcomas, and intimal sarcomas where this signature is enriched. Milademetan (RAIN-32), an oral, selective MDM2 inhibitor, inhibits growth of *TP53*-WT/*MDM2*-amplified cell lines and patient-derived xenograft models from varying tumor types. Furthermore, tumor regression was observed in 3/3 non-liposarcoma patients with *MDM2* copy number > 12 in a phase 1 trial of milademetan. MANTRA-2 (RAIN-3202) is a phase 2, multicenter, single-arm, open-label, basket trial designed to evaluate the efficacy or clinical benefit of milademetan in *TP53*-WT solid tumors with *MDM2* amplification (copy number ≥ 12). **Methods:** Eligible patients must be ≥ 18 years of age with histologically and/or cytologically confirmed locally advanced, incurable or metastatic solid tumors refractory to standard therapy. Local testing demonstrating *TP53* WT and *MDM2* amplification is required, defined as a *MDM2* copy number ≥ 12 or 6-fold increase. Patients with well-differentiated/de-differentiated liposarcomas, intimal sarcomas, or primary central nervous system tumors are excluded. Prior treatment with an MDM2 inhibitor is not permitted. Patients receive milademetan 260 mg orally once daily on Days 1–3 and 15–17 of a 28-day cycle. Tumor response is evaluated by RECIST v1.1 at Weeks 8, 16, 24, and 32, and then every 12 weeks. Primary endpoint: objective response rate. Secondary endpoints include: duration of response; progression-free survival; growth modulation index; disease control rate; overall survival; safety; health-related quality of life scores. Exploratory endpoints include: biomarkers in blood and/or tumor tissue; pharmacodynamics; pharmacokinetics. Enrollment of 65 patients is planned to ensure that 57 patients have centrally confirmed *TP53* WT and *MDM2* copy number ≥ 12. The trial opened in November 2021 and is actively enrolling patients. Clinical trial information: NCT05012397. Research Sponsor: Rain Therapeutics, Inc.

TPS3166 **Poster Session**

Rationale and design of phase 1 FTIH study of FOXP3 antisense oligonucleotide AZD8701 in patients with selected advanced solid tumors.

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Background: The forkhead box family transcription factor FOXP3 is essential for T regulatory cells (Tregs) development and immune suppressive function. Tregs are an integral component of the adaptive immune system and contribute to maintaining tolerance to self-antigens and preventing autoimmune diseases. In the context of cancer, however, Tregs contribute to tumor progression by suppressing antitumor immunity. To date inhibition of Treg-mediated immunosuppression tested in the clinic has lacked specificity. Targeting FOXP3 provides a selective approach to impair the immunosuppressive function of Tregs but targeting transcription factors has been a challenge using conventional drug modalities. AZD8701 employs next-generation antisense oligonucleotide (ASO) technology (Ionis Pharmaceuticals) to bind mRNA with high affinity and selectively reduce human Foxp3 mRNA expression levels. Foxp3-specific ASOs promote potent dose-dependent reductions in Foxp3 mRNA and protein in vitro. In preclinical models, AZD8701 induced Foxp3 knockdown results in Tregs with a reduced immunosuppressive capacity, loss of immunosuppressive markers, and increased markers of activation on $CD8^+$ T-cells. AZD8701 reduces tumor growth as monotherapy in preclinical models and increased tumor inhibition is obtained by combining AZD8701 with a PD-L1 inhibitor. **Methods:** This is a Phase I multicenter study of AZD8701 alone or in combination with durvalumab in participants with selected advanced solid tumors. Eligible patients must have ECOG performance status 0 or 1, measurable target lesion per RECIST v1.1 and be diagnosed with selected tumor types as described below. Monotherapy and combination dose escalation phase is open for participants with head and neck squamous cell carcinoma (HNSCC), triple-negative breast cancer (TNBC), non-small-cell lung cancer (NSCLC), clear cell renal cell carcinoma (ccRCC), gastroesophageal cancer, melanoma, cervical cancer, small-cell lung cancer (SCLC), and/or solid tumors that have demonstrated a response to prior programmed death-ligand-1 (PD-[L]1) treatment (as defined by duration of response > 18 weeks). Participants with NSCLC, HNSCC, TNBC, and ccRCC will be included in the pharmacodynamic cohort at the selected monotherapy dose and/or disease expansion cohorts. The primary objectives are to assess safety and tolerability and to determine the preliminary antitumor activity of AZD8701 (objective response rate) when administered as monotherapy or in combination with durvalumab. Secondary endpoints include, disease control rate, duration of response, progression free survival and overall survival, pharmacokinetics and pharmacodynamics (including changes in Foxp3 mRNA in paired tumor samples). The trial is currently recruiting. Clinical trial information: NCT04504669. Research Sponsor: AstraZeneca.

TPS3167 **Poster Session**

Design and rationale of a phase 1 dose-escalation study of AMG 193, a methylthioadenosine (MTA)-cooperative PRMT5 inhibitor, in patients with advanced methylthioadenosine phosphorylase (MTAP)-null solid tumors.

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Background: Protein arginine methyltransferase 5 (PRMT5) is an emerging target for cancer treatment. MTAP homozygous deletion occurs in 15% of cancers and often coincides with deletion of the tumor suppressor gene CDKN2A, leading to buildup of its substrate MTA. MTA shares close structural similarity to S-adenosyl methionine (SAM), the substrate methyl donor for PRMT5. By competing with SAM, MTA partially inhibits PRMT5. Thus, MTAP-null cancers are susceptible to further PRMT5 inhibition (Kryukov *Science* 2016). Current direct/indirect PRMT5 inhibitors (PRMT5i) showed preliminary anticancer activity, albeit with considerable toxicities due to their indiscriminate activities. AMG 193 is an MTA-cooperative PRMT5i that preferentially targets the MTA-bound state of PRMT5 that is enriched in MTAP-null tumors and represents a novel strategy to increase the therapeutic margin of this class of inhibitors. AMG 193 potently inhibits MTAP-null cancer cell lines and patient-derived xenografts. **Methods:** NCT05094336 is a first-in-human (FIH), multicenter, open-label, phase 1/1b/2 trial evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and efficacy of AMG 193 in patients with advanced MTAP-null solid tumors. Eligible patients ($\geq$ 18 years) with histologically confirmed locally advanced/metastatic solid tumors not amenable to curative treatment with surgery and/or radiation, homozygous MTAP and/or CDKN2A deletion (by local next generation sequencing), or MTAP protein loss in tumors (by central immunohistochemistry), measurable disease, ECOG PS 0–1, adequate hematopoietic, renal, liver, pulmonary, cardiac, coagulation function and glucose control will be included. The study will be conducted in 3 parts, each with subparts. Here, we describe Part 1a/b (dose exploration). Five dose levels are planned. Treatment continues until progression or withdrawal. The primary objectives are to evaluate the safety and tolerability of AMG 193 monotherapy; endpoints include dose-limiting toxicities, treatment-emergent adverse events, serious adverse events, electrocardiograms, laboratory abnormalities, and vital signs. Secondary objectives include the characterization of the PK parameters of AMG 193 including C_{max}, T_{max}, and AUC after single or multiple doses. This study is expected to enroll approximately 30 patients in Part 1a/b. This is the first FIH trial open for enrollment for this new class of PRMT5i and enrollment is ongoing. Clinical trial information: NCT05094336. Research Sponsor: Amgen Inc.

TPS3168 **Poster Session**

A phase 1, first-in-human study of IK-930, an oral TEAD inhibitor targeting the Hippo pathway in subjects with advanced solid tumors.

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Background: The transcriptional enhanced associate domain (TEAD) family of proteins are key transcription factors in the Hippo signaling pathway and play a critical role in cell proliferation, migration, angiogenesis, and apoptosis. Published literature demonstrates that approximately 10% of all solid tumors present with a dysregulated Hippo pathway and subsequent constitutive activation of TEAD, which drives gene expression involved in cell growth and pro-survival signaling. Deficiencies in neurofibromin 2 (NF2), a key regulator of the Hippo pathway, can be found in over 40% of cases of malignant pleural mesothelioma (MPM). *NF2* deficiency also occurs at high incidence in meningiomas, cholangiocarcinomas, thymoma, and schwannoma. Gene fusions in in Yes1 associated transcriptional regulator (YAP1) or WW domain containing transcription regulator 1 (TAZ/WWTR1) are also indicative of high TEAD activation and can be seen in solid tumors including epithelioid hemangioendothelioma (EHE) where >90% of cases are associated with TAZ-CAMTA1 gene fusion and the other 10% of cases have YAP1/TFE3 gene fusion. IK-930 is a novel, selective, small molecule inhibitor of TEAD that prevents palmitate binding and thereby disrupts aberrant TEAD-dependent transcription. In preclinical models, IK-930 demonstrates antitumor activity in mouse xenograft models with Hippo pathway genetic alterations. IK-930 is under clinical investigation as an oral agent in patients with advanced solid tumors. **Methods:** This is a phase 1, first-in-human, open-label, multicenter dose escalation and dose expansion study to evaluate the safety and tolerability of IK-930 as monotherapy, and to determine the recommended phase 2 dose (RP2D) and/or maximum tolerated dose (MTD) using the Bayesian Optimal Interval Design (BOIN). Eligible participants in dose escalation include adult patients with advanced or metastatic solid tumors for whom there is no available therapy known to confer clinical benefit. Patients will receive escalating doses of IK-930 starting at 25mg daily. IK-930 will be administered initially in a 28-day cycle and will progress to a 21-day cycle when evaluated as safe and well-tolerated. A dose expansion phase will follow with four genetically defined cohorts of solid tumors, including: *NF2*-deficient MPM (Cohort 1), other *NF2*-deficient solid tumors agnostic to tumor type (Cohort 2), EHE with *TAZ-CAMTA1* or *YAP1-TFE3* gene fusions (Cohort3), and solid tumors with *YAP1/TAZ* gene fusions agnostic to tumor type (Cohort 4). Primary endpoints include evaluation of dose-limiting toxicities and treatment-emergent adverse events and determination of RP2D and/or MTD. Secondary objectives include evaluation of preliminary antitumor activity by RECIST 1.1 and pharmacokinetic (PK) parameters. The study began in January 2022 and is currently enrolling. Clinical trial information: NCT05228015. Research Sponsor: Ikena Oncology.

TPS3169 **Poster Session**

Phase 1a/b open-label study of IK-175, an oral AHR inhibitor, alone and in combination with nivolumab in patients with locally advanced or metastatic solid tumors and urothelial carcinoma.

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Background: Aryl Hydrocarbon Receptor (AHR) is a ligand-activated transcription factor that regulates the activity of multiple innate and adaptive immune cells. Kynurenine, generated from tryptophan by IDO1 and TDO2, is a ligand that binds AHR and leads to a net immunosuppressive tumor microenvironment, making AHR an attractive therapeutic target in multiple cancer types. IK-175 is a selective, small molecule inhibitor of AHR being developed as an oral agent. In preclinical mouse tumor models, IK-175 demonstrates antitumor activity as a single agent or in combination with checkpoint inhibitors. AHR immunohistochemistry (IHC) tumor microarray analysis across 15 different tumor types revealed that bladder cancer has the highest level of AHR protein expression and nuclear localization indicative of ligand-bound and active AHR signaling. Therefore, nuclear AHR in urothelial carcinoma tumors is being investigated for potential predictive clinical benefit with IK-175. **Methods:** This is a first-in-human, phase 1a/b, open-label, multicenter, dose-escalation and expansion study of IK-175 as a single agent and in combination with nivolumab. The primary objectives are to determine the maximum tolerated dose (MTD) and/or maximum administered dose (MAD), identify the recommended phase 2 dose (RP2D), and evaluate the safety and tolerability of IK-175 alone and in combination with nivolumab. Secondary objectives are to evaluate the pharmacokinetics (PK) of IK-175, evaluate pharmacodynamic (PD) immune effects, and assess preliminary antitumor activity. Key exploratory objectives are to evaluate the PD effects on peripheral immune cells and target gene expression, to assess candidate baseline biomarkers, and correlative analyses of tumor AHR nuclear localization with clinical response. The study is exploring tumor AHR nuclear localization by IHC as a predictive biomarker in patients with urothelial carcinoma. A minimum of 10 patients with a positive AHR nuclear localization test (cutoff for positive AHR is 65% tumor cells positive for 2+/3+ nuclear AHR by a validated IHC assay) will be enrolled in the combination arm. IK-175 is administered daily in 21 or 28 day-cycles as a single agent, and in combination with nivolumab (480 mg q4w on Day 1 of every cycle), in adult patients with advanced solid tumors (dose escalation) and urothelial carcinoma (dose expansion). Key eligibility criteria include patients with histologically confirmed solid tumors (including urothelial carcinoma) who have locally recurrent or metastatic disease that have progressed on or following all standard of care therapies deemed appropriate by the treating physician including prior checkpoint inhibitors. Estimated enrollment is 93 patients; the study began in January 2020 and is ongoing. Clinical trial information: NCT04200963. Research Sponsor: Ikena Oncology.

TPS3170 **Poster Session**

Phase 1 study of KT-413, a targeted protein degrader, in adult patients with relapsed or refractory B-cell non-Hodgkin lymphoma.

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Background: Oncogenic mutations in myeloid differentiation primary response 88 (MYD88) occur in approximately 25% of diffuse large B-cell lymphoma (DLBCL) cases, including approximately 30% of activated B-cell DLBCL and up to 70% of primary extranodal DLBCL, and are associated with poor survival following 1st line therapy. MYD88 mutations result in activation of the NF-κB pathway which drive a range of pro-tumor activities including upregulation of proinflammatory cytokines and genes involved in tumor cell proliferation and survival. Activation of this pathway results in upregulation of IRF4 through the transcription factors Ikaros and Aiolos, which in turn further augments NF-kB activation while simultaneously downregulating Type I IFN signaling, thereby preventing oncogene-induced cell death. Constitutive NF-kB pathway activation resulting from MYD88 mutations is dependent on the interleukin-1 receptor associated kinase 4 (IRAK4), a key component of the myddosome complex which normally stimulates NF-kB signaling following TLR or IL-1R engagement and MYD88 activation. KT-413 is a potent and selective heterobifunctional small molecule protein degrader mediating the degradation of both IRAK4 and the IMiD substrates Ikaros and Aiolos via the ubiquitin-proteasome system. The therapeutic hypothesis is that degradation of IRAK4 and IMiD substrates will maximize NF-κB inhibition while simultaneously upregulating the Type I Interferon response, thus restoring the apoptotic response and enabling oncogene-mediated cell death, resulting in robust antitumor response in MYD88-mutant DLBCL. KT-413 induced strong antitumor activity, including complete or partial regressions, in cell line- and patient-derived xenograft models of MYD88^{MT} DLBCL (Mayo 2021). **Methods:** KT-413 is being evaluated in an open label, dose escalation (Phase 1a) study in patients with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (NHL), followed by dose expansion (Phase 1b) in patients with R/R DLBCL with documented tumor MYD88 mutation status. All patients must be ineligible or refused auto-SCT or CAR-T therapy. The Phase 1a (n = 40) utilizes an accelerated titration followed by a 3+3 design in ascending doses of IV administered KT-413 in once every 21-day cycles to identify the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) (primary endpoint). Secondary endpoints include pharmacokinetics (PK) and preliminary pharmacodynamic effects (PD) using blood and tumor tissue. Once MTD/RP2D is determined in 3-6 patients, it will be confirmed by enrolling additional patients with B-cell NHL, for a total of nine. In Phase 1b, up to 40 R/R DLBCL patients will be enrolled into one of two cohorts (n = 20): MYD88^{MT} or MYD88^{WT} to further characterize tolerability, PK, PD and evaluate the clinical activity of KT-413. KT413-DL-101 began enrollment in February 2022. Clinical trial information: NCT05233033. Research Sponsor: Kymera Therapeutics.

TPS3171 **Poster Session**

Phase 1 study of KT-333, a targeted protein degrader, in patients with relapsed or refractory lymphomas, large granular lymphocytic leukemia, and solid tumors.

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Background: The signal transducer and activator of transcription 3 (STAT3) protein is activated by cytokines and growth factors resulting in tumor growth and promotion and hindering antitumor immunity. Approximately 70% of human cancers including both hematological malignancies and solid tumors exhibit increased levels of phosphorylated STAT3 (pSTAT3). There is evidence of constitutive activation of STAT3 through genetic mutations or aberrant cellular signaling pathways in tumors such as large granular lymphocytic leukemia (LGL-L), peripheral T-cell lymphoma (PTCL), and cutaneous T-cell lymphomas (CTCL). Hyperactivation of STAT3 has been reported in a variety of solid tumors. In several of these cancers, the levels of pSTAT3 and/or activated STAT3 have been shown to correlate with poor clinical prognosis. As with other transcription factors, selective inhibition of STAT3 has been proven to be difficult with conventional therapeutic approaches. KT-333 is a potent highly selective, heterobifunctional small molecule degrader of STAT3. In preclinical studies, durable tumor regressions were seen with weekly KT-333 administration in STAT3-dependent T cell lymphomas, and antitumor activity was seen in solid tumors in combination with anti-PD1 (ASH 2021, SITC 2021). **Methods**: KT-333 is being evaluated in an open-label, dose escalation (Phase 1a, n = 40) study in patients with lymphomas relapsed or refractory (R/R) to at least two prior systemic treatments or for whom standard therapies are unavailable. Dose escalation will be conducted by accelerated titration followed by a 3+3 design in ascending doses of intravenous KT-333 administered once weekly in 28-day cycles to evaluate safety and define the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) (primary endpoint). Secondary endpoints include pharmacokinetics (PK) in plasma and urine and preliminary pharmacodynamic effects (PD) of KT-333 using blood (peripheral blood mononuclear cells [PBMCs], plasma/serum) and tumor tissue. After confirming the MTD/RP2D in patients with lymphoma, patients with advanced solid tumors will be enrolled in a separate Phase 1a cohort at the MTD/RP2D. In Phase 1b (n = 80), patients with PTCL, CTCL, LGL-L (T-cell LGL-L or chronic lymphoproliferative disorder of natural killer-cells), or solid tumors R/R to at least one prior systemic standard of care treatment or for whom standard therapies are not available, will be enrolled in separate 20 patient cohorts. This will further characterize safety, PK, PD and evaluate the clinical activity of KT-333. Treatment with KT-333 will continue until disease progression, unacceptable toxicity, or patient refusal. KT333-TL-101 began enrolling in January 2022. Clinical trial information: NCT05225584. Research Sponsor: Kymera Therapeutics.

TPS3172 **Poster Session**

A two-part, phase II, multi-center study of the ERK inhibitor ulixertinib (BVD-523) for patients with advanced malignancies harboring MEK or atypical BRAF alterations (BVD-523-ABC).

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Background: Ulixertinib (BVD-523) is a small molecule inhibitor of extracellular signal-regulated kinases 1/2 (ERK1/2) in development as a novel anti-cancer drug. Early clinical data demonstrated antitumor activity, especially for patients with tumors harboring atypical BRAF or MEK1/2 alterations (Sullivan et al., Cancer Discov. 2018;8(2):184-195). Atypical BRAF (non-V600) alterations can be categorized according to characteristics of molecular signaling (Class II or III), are seen in approximately 3% of all human cancers, and there are currently no approved therapies for this indication. Similar to atypical BRAF alterations, the incidence of MEK1/2 alterations are rare in human tumors (< 1 %). Preclinical data have demonstrated activity of ulixertinib in MEK mutant models. Ulixertinib has FDA fasttrack designation for patients with solid tumors, other than CRC, with specific BRAF mutations (G469A, L485W, or L597Q). Designed with intent to register, the BVD-523-ABC clinical trial will continue evaluation of ulixertinib in patients with tumors harboring any atypical BRAF or MEK1/2 alteration (NCT04488003). **Methods:** This multi-center, phase II study, will be conducted in two parts and assess the clinical benefit, safety, pharmacokinetics, and pharmacodynamics of ulixertinib in patients with advanced malignancies. Ulixertinib will be administered at the RP2D of 600 mg BID for 28-day treatment cycles. Eligible patients will have locally advanced or metastatic cancer which progressed following standard systemic therapies, or for which the patient is not a candidate or refused systemic therapy. Planned correlative analyses include reverse phase protein array and transcriptomics of tumor tissue. Part A is open-label and tumor agnostic, except for group 4 and 6 (CRC patients only). Patients will enroll into one of six groups based on BRAF (groups 1-4) or MEK1/2 (groups 5-6) tumor alteration (38 patients per group). Overall response rate (ORR) is the primary endpoint for Part A, with secondary endpoints including duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Part B is tumor histology specific. Patients will be randomized to receive either ulixertinib or physician's choice of treatment in a 2:1 ratio. Up to three specified tumor histologies will be defined, guided by available Part A data (n = 80-100 per histology). The primary endpoint of Part B is PFS, and secondary endpoints include OS, ORR, and DOR. This study has enrolled 43 patients of the planned 228 in Part A at the time of abstract submission. Clinical trial information: NCT04488003. Research Sponsor: BioMed Valley Discoveries.

TPS3173 **Poster Session**

Phase 1/2 dose escalation study of NUV-422, a potent inhibitor of cyclin-dependent kinases 2, 4, and 6, in recurrent or refractory (r/r) high-grade gliomas (HGG) and solid tumors.

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Background: CDKs that govern the G1-S transition of the cell cycle (CDK2, CDK4 and CDK6) are deregulated in many cancers. CDK2 expression, in particular, is associated with worse overall survival in glioblastoma (GB), disease-free recurrence in prostate cancer, and resistance to approved CDK4/6 inhibitors (CDK4/6i) in breast cancer. These provide rationale for inhibition of CDK2/4/6 as a potential novel therapeutic strategy in these cancers. NUV-422 is a potent (low nM) small molecule CDK2/4/6i with limited activity against CDK1, a target potentially associated with toxicities in other CDKi. Preclinical studies have shown that NUV-422 has favorable blood-brain barrier penetration, inhibited growth of multiple glioma cell lines in vitro, and exhibited antitumor activity in GB xenograft models. NUV-422 also exhibited antitumor activity in multiple patient-derived xenograft (PDX) models of HR+ HER2- mBC resistant to CDK4/6i, and PDX models of prostate cancer resistant to anti-androgens. **Methods:** NUV-422-02 (NCT04541225) is a phase 1/2, first in human, open label, multicenter study to evaluate single-agent NUV-422 (given orally) in patients with advanced solid tumors (r/r HGG, r/r HR+ HER2- mBC, or r/r mCRPC). The Ph 1 dose escalation will use a 3+3 design to evaluate safety, tolerability, and PK of NUV-422 and establish the recommended phase 2 dose (RP2D). Ph 1 also includes a randomized surgical substudy to characterize PK and pharmacodynamics (PD) of preoperative NUV-422 in resected GB tumor tissue. After the RP2D is identified, parallel enrollment into phase 2 expansion cohorts will begin. Cohort 1 will evaluate isocitrate dehydrogenase wild type (IDH-WT) GB. Cohort 2 will evaluate HR+ HER2- mBC (without active brain metastases); Cohort 3 will evaluate mCRPC; and Cohort 4 will evaluate HR+ HER2- mBC with active brain metastases. The Ph 2 primary endpoint is objective response rate. Secondary efficacy endpoints include clinical benefit rate, duration of response, progression-free survival, and overall survival. Response assessments will be based on response criteria appropriate to the tumor type (HGG [RANO]; HR+HER2- mBC [RECIST 1.1 or RANO-Brain Metastases]; mCRPC [RECIST 1.1, PCWG3, prostate-specific antigen decrease]). Blood, urine, or tumor tissue will be obtained to assess safety, PK, PD, and for additional exploratory analyses to characterize NUV-422 mechanism of action. Enrollment was initiated in December 2020, and dose escalation is ongoing. The NUV-422 program will also be expanded in 2022 to include additional studies in mBC and mCRPC in combination with standard of care treatments. Clinical trial information: NCT04541225. Research Sponsor: Nuvation Bio.

TPS3174 **Poster Session**

A phase I trial of elimusertib in combination with cisplatin or with cisplatin plus gemcitabine in advanced solid tumors with an emphasis on urothelial carcinoma.

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Background: Cisplatin, a well-established backbone of combination therapy of various advanced solid tumors, inhibits DNA synthesis by forming DNA cross-links and adducts. Despite the activity of cisplatin, tumor cells can either be refractory or develop resistance to treatment. Cisplatin has been demonstrated to cause cell cycle G2/M arrest, which may allow for DNA damage response (DDR) and repair. Ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad 3-related (ATR) protein kinases are key regulators of DDR, and contribute to maintaining genomic integrity in response to various exogenous and endogenous genotoxic insults like cytotoxic chemotherapy. In fact, cisplatin has been shown to transiently increase ATR expression. Inhibitors of ATR have been studied in combination with cisplatin both *in vitro* and *in vivo*, demonstrating enhanced activity. The oral small molecule ATR inhibitor elimusertib, which has been studied as a single agent in a Phase I study, has also demonstrated enhanced activity with cisplatin *in vitro* in lung cancer and bladder cancer cell lines. We sought to conduct a Phase I study evaluating the combination of elimusertib with cisplatin or with cisplatin and gemcitabine. **Methods:** In the first cohort, patients with histologically confirmed advanced solid tumors for which cisplatin-based therapy would be considered appropriate, who exhibit adequate organ function, and have received < 300 mg/m^2 of cisplatin previously are treated with cisplatin on Day (D) 1 and with elimusertib on D2 & 9 of each 21-day cycle. The study follows a phase I queue (IQ) 3+3 dose escalation design, following standard practices for dose-limiting toxicity (DLT) impact on escalation, and when the maximum tolerated dose (MTD) is established with cisplatin alone, this will inform the first dose level of the next cohort, in which patients will be treated with cisplatin on D1, gemcitabine on D1 & 8, and elimusertib on D2 & 9 of each 21-day cycle. An expansion cohort will enroll urothelial carcinoma patients when the second MTD is established. The primary objective of the study is to evaluate the safety and MTD of elimusertib in combination with cisplatin, as well as in combination with cisplatin and gemcitabine. Secondary study objectives include evaluation of pharmacokinetics of elimusertib in these combinations, preliminary efficacy, and evaluating the association between ATM expression and responses to therapy. Currently, 6 patients have been enrolled to the first cohort of the study. Clinical trial information: NCT04491942. Research Sponsor: U.S. National Institutes of Health.

TPS3175 **Poster Session**

A first-in-human phase I dose-escalation trial of the B7-H6/CD3 T-cell engager BI 765049 ± ezabenlimab (BI 754091) in patients with advanced solid tumors expressing B7-H6.

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Background: B7-H6 is a member of the B7 family of immune receptors, which is expressed in several solid tumors, but with little to no expression detected in normal tissues[Brandt et al. J Exp Med 2009;206.1495–503; Boehringer Ingelheim. Data on file]. BI 765049 is a novel IgG-like bispecific T-cell engager (TcE) designed to bind simultaneously to B7-H6 on tumor cells and CD3 on T cells, resulting in cytolytic synapse formation and tumor lysis. Preclinical studies have demonstrated that BI 765049 monotherapy induced dose-dependent antitumor activity in humanized *in vivo* CRC tumor models. Consistent with the mode of action, treatment with BI 765049 led to profound infiltration of T cells into the tumor tissue, which correlated with apoptosis and tumor shrinkage. The inflammatory tumor microenvironment created by treatment with the B7-H6/CD3 TcE also led to an increase of PD-1 on T cells and PD-L1 on the tumor cells [Hipp et al. AACR Annual Meeting 2021]. This upregulation of PD-(L)1 provides the rationale for combining BI 765049 with a PD1 inhibitor. **Methods:** NCT04752215 is a first-in-human, open-label, dose-escalation trial of BI 765049 ± the PD-1 inhibitor, ezabenlimab. Adults with advanced, unresectable and/or metastatic CRC, NSCLC, HNSCC, hepatocellular, gastric or pancreatic carcinoma are eligible. Patients must have progressed on, or be ineligible for, standard therapies. B7-H6 positivity must be confirmed at screening by central review (immunohistochemistry assay) in archived tissues/fresh biopsies (except CRC). Patients must have ≥1 evaluable lesion (modified RECIST 1.1) outside of the central nervous system and adequate organ function. The primary objective is to determine the maximum tolerated dose (MTD) or recommended dose for expansion of BI 765049 ± ezabenlimab, based on dose-limiting toxicities during the MTD evaluation period. Further objectives are to evaluate safety, tolerability, PK/PD, and preliminary efficacy of BI 765049 ± ezabenlimab. The trial will assess up to four intravenous dosing regimens: A (BI 765049 once every 3 weeks [q3w]); B1 (BI 765049 qw); B2 (BI 765049 qw with step-in dosing); C (BI 765049 + ezabenlimab q3w). Dose escalation will be guided by a Bayesian Logistic Regression Model with overdose control that will be fitted to binary toxicity outcomes using a hierarchical modelling approach to jointly model all dosing regimens. Treatment will be allowed to continue until confirmed progressive disease, unacceptable toxicity, other withdrawal criteria, or for a maximum duration of 36 months, whichever occurs first. Approximately 150–175 patients will be screened and ~120 patients enrolled. As of January 2022, eight patients have been recruited in early dose-escalation cohorts. Clinical trial information: NCT04752215. Research Sponsor: Boehringer Ingelheim.

TPS3176 **Poster Session**

A phase 1 dose-escalation and expansion-cohort study of the oral CDK7 inhibitor XL102 as a single-agent and in combination therapy in patients (pts) with advanced solid tumors.

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Background: XL102 is an orally bioavailable, selective, and covalent small-molecule inhibitor of cyclin-dependent kinase 7 (CDK7). CDK7 is a serine/threonine kinase that is overexpressed in multiple tumor types. CDK7 controls cell cycle progression via the phosphorylation of CDKs (1, 2, 4, and 6) and regulates transcription through phosphorylation of RNA polymerase II. XL102 induced cell death in various cancer cell lines and caused tumor regression in multiple human tumor cell line to mouse xenograft tumor models. Here, we present the study design of an ongoing phase 1 trial in pts with advanced solid tumors, including hormone receptor-positive breast cancer (HR+BC), triple-negative breast cancer (TNBC), epithelial ovarian cancer (EOC), and metastatic castration-resistant prostate cancer (mCRPC).
Methods: This first-in-human, open-label, phase 1 trial (NCT04726332) consists of a dose-escalation stage and a disease-specific cohort expansion stage. In the dose-escalation stage (modified interval 3+3 design), a maximum tolerated dose and/or recommended dose (MTD/RD) of XL102 will be established (primary endpoint) for use alone (solid tumors) and then for use in combination with standard dose fulvestrant (HR+BC) or abiraterone/prednisone (mCRPC); dose escalation will require ~36 pts for the single-agent cohort and ~15 pts for each combination cohort. Pts enrolled in the dose-escalation stage must have an unresectable or metastatic tumor for which available therapies are intolerable, ineffective, or do not exist. Upon determining the MTD/RD for each regimen, the cohort-expansion stage will enroll according to Simon's Two-Stage Minimax design, assuming a power of 80% and one-sided α of 15%, for single-agent XL102 (HR+BC, TNBC, EOC, and mCRPC) and XL102 in combination therapy (HR+BC and mCRPC); the expansions will enroll ~36 pts for each single-agent cohort and ~44 pts for each combination cohort. Pts enrolled in the expansion stage must have measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), adequate organ function, and exposure to prior therapy, with specific therapy requirements based on the disease cohort. The primary endpoint of the expansion stage is objective response rate (ORR) of XL102 alone and in combination therapy as assessed by investigator per RECIST v1.1. Secondary endpoints are safety, tolerability, and pharmacokinetics. Exploratory endpoints include duration of response (DOR) and progression-free survival (PFS) as assessed by the investigator per RECIST v1.1, overall survival, and correlation of tumor and blood biomarkers with response. ORR, DOR, and PFS may also be assessed by blinded independent radiology committee in selected expansion cohorts. The study began enrolling pts in February 2021 and is ongoing. Total enrollment is estimated to be up to 298 pts. Clinical trial information: NCT04726332. Research Sponsor: Exelixis, Inc.

TPS3177 **Poster Session**

Phase 1 study of C019199, an oral CSF-1R/DDRs/VEGFR2 multiple kinase inhibitor, to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with advanced solid tumors, including tenosynovial giant cell tumor.

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Background: C019199 was designed to be a tumor immune microenvironment (TME) modulator in order to improve the efficacy against tumor growth when combined with immune checkpoint inhibitors, like anti-PD1 or anti-PD-L1. It was shown to have a specific inhibition profile against CSF-1R, DDR1 and VEGFR2 with IC_{50} of 14nM, 40nM and 79nM, respectively. CSF-1R's inhibition may deplete Tumor-associated macrophages (TAMs) in TME, help the infiltration of T cells and enhance T cell responses. But a single modulating mechanism may not be strong enough or may be vulnerable and easily overcome by tumors. C019199 can reshape the TME by additionally inhibiting DDRs and VEGFR2, which may remove the "physical barrier" of tumor extracellular matrix and further increase T cell infiltration on top of inducing tumor blood vessels normalization. As a single agent with the appropriate combination of multiple modulation effects, it will potentially turn "cold" tumors into "hot" tumors. Preclinical studies have shown that C019199 inhibits tumor growth in multiple animal tumor models and has better antitumor efficacy when combined with immune checkpoint blockades. **Methods:** A first-in-human, open label, multicenter, dose-escalation/expansion study of C019199 is currently enrolling. Eligible subjects (age $\geq$ 18 years and <76 years) with histologically or cytologically confirmed relapsed, refractory, or progressive metastatic solid tumors will be enrolled in. In Part A, the safety and tolerability of C019199 will be assessed in about 25 subjects to identify the maximum tolerated dose and recommended phase II dose (PR2D). In Part B, the safety and antitumor activity of the RP2D will be assessed in about 60 subjects in disease-specific expansion cohorts. Primary endpoints are adverse events, laboratory abnormalities, dose-limiting toxicities. Secondary endpoints will include pharmacokinetics, objective response rate, progression-free survival, and disease control rate. Exploratory biomarker analyses include CSF-1 and VEGF. Clinical trial information: CTR20202045. Research Sponsor: Fujian Haixi Pharmaceuticals Co., Ltd.

TPS3178 **Poster Session**

A phase 1/2 study of DCC-3116 as a single agent and in combination with trametinib in patients with advanced or metastatic solid tumors with RAS or RAF mutations.

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Background: Autophagy, a catabolic process to resupply nutrients and recycle damaged organelles, is activated by cancer cells to survive hypoxia, limited nutrients, or chemotherapy. The RAS family of oncoproteins are the most commonly mutated oncoproteins in human cancer and require autophagy for tumor growth and survival. RAS activates signaling through the mitogen-activated protein kinase (MAPK) pathway that is responsible for regulating cell survival. ULK1/2 are kinases that receive and process input from nutrient and stress sensors to initiate autophagy. Inhibition of the MAPK pathway releases tonic inhibition of ULK1/2 and triggers autophagy as a survival mechanism, suggesting that ULK1/2 may provide a promising therapeutic target. DCC-3116 is a potent and selective ULK inhibitor that showed preclinical antitumor activity in combination with the MAPK kinase inhibitor trametinib (Smith et al. 2019 AACR-NCI-EORTC Poster). Here, we describe the Phase 1 study of DCC-3116 monotherapy and combination therapy with trametinib in patients with RAS or RAF mutant advanced or metastatic solid tumors. **Methods:** This is a Phase 1/2, multicenter, open-label, first-in-human study evaluating safety, tolerability, clinical activity, pharmacokinetics, and pharmacodynamics of DCC-3116 as a single agent and in combination with trametinib (NCT04892017). The study consists of single agent and combination dose escalation cohorts and expansion of combinations with demonstrated safety. Single-agent oral DCC-3116 will be administered twice daily (BID) in escalating cohorts in 28-day cycles until the recommended Phase 2 dose (RP2D) is determined. Subsequently, the single-agent RP2D or one level below the maximum tolerated dose (MTD) will be administered in combination with trametinib. Participants in the dose escalation phase must be ≥18 years with a histologically confirmed diagnosis of advanced or metastatic solid tumor with a documented RAS or RAF mutation, have progressed despite standard therapies, and have received ≥1 prior anticancer therapy. In the dose expansion phase, DCC-3116 will be given BID with trametinib in 28-day cycles to participants with pancreatic ductal adenocarcinoma, non-small cell lung cancer, colorectal cancer, or melanoma (Cohorts 1–4, respectively). Primary outcomes are incidence of adverse events, identification of MTD, and objective response rate per RECIST v1.1. Secondary outcomes include duration of response, clinical benefit rate, time to response, progression-free survival, and pharmacokinetic/pharmacodynamic attributes. Participants in dose expansion cohorts must be ≥18 years and meet cohort-specific criteria including histologically confirmed diagnoses, documented mutation status, and number of prior lines of systemic therapy. This study is recruiting and plans to enroll up to 130 participants. Clinical trial information: NCT04892017. Research Sponsor: Deciphera Pharmaceuticals, LLC.

TPS3179 **Poster Session**

A multicenter, open-label, phase 1a/b study of HC-7366, a modulator of integrated stress response (ISR) kinase GCN2 in subjects with advanced solid tumors.

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Background: To survive harsh tumor microenvironments, cancer cells actively utilize ISR as an adaptive stress response and survival mechanism. General control nonderepressible 2 (GCN2), a serine-threonine kinase is essential for maintaining cellular homeostasis in amino acid stress conditions. HC-7366 is a novel, highly selective, and potent GCN2 kinase modulator. Single agent HC-7366 has demonstrated potent anti-tumor activity resulting in regression and complete responses in several pre-clinical tumor models. **Methods:** This is a first in human, multicenter, open label, Phase 1a/b dose escalation and expansion study to establish the maximum tolerated dose, evaluate safety and tolerability, and determine the recommended Phase 2 dose of daily oral dosing of HC-7366 in patients (pts) with advanced solid tumors. Up to 36 pts with squamous cell carcinoma of the head and neck (SCCHN), colorectal cancer (CRC), non-small cell lung cancer (NSCLC), or transitional cell carcinoma of the bladder (TCC) will be enrolled into Phase 1a; other solid tumors are eligible if selection criteria are met (capped at 50%). A 3+3 design will be employed and dose escalation determined by occurrence of dose limiting toxicities (DLT) within Cycle 1 (21 days). A Safety Monitoring Committee will review each cohort when the planned number of pts complete the DLT period. Six dose levels (10, 20, 40, 75, 125, 150 mg) of HC-7366 will be evaluated. Phase 1b will be an expansion of up to two Phase 1a dose levels and enroll 15 pts per cohort. Secondary endpoints include ORR, DOR, TTF, PFS, and OS. Pharmacokinetic data will be profiled. Exploratory objectives include evaluation of pharmacodynamic markers in tumor biopsies and immunophenotyping in blood samples. Main inclusion criteria include: SCCHN, CRC, NSCLC, TCC or other solid tumors; >1 radiologically measurable lesion per RECISTv1.1; >1 biopsiable lesion at baseline; no immune checkpoint inhibitor within 4 weeks (wks) of 1st dose; ECOG 0 or 1; <10% body weight loss in 4 wks before 1st dose & serum albumin >3 g/dL; and normal/adequately controlled pan-endocrine function. Main exclusion criteria include: autoimmune disease, organ transplant, retinitis or photosensitive skin disorders; history of interstitial lung disease or pneumonitis within 1yr; and overt or latent disorders of the exocrine pancreas. Formal hypothesis testing will not be performed. Descriptive statistics of parameters of interest will be presented by dose level and safety parameters will be summarized. The trial is sponsored by HiberCell, Inc. Approximately 9 US sites will participate. Clinical trial information: NCT05121948. Research Sponsor: HiberCell, Inc.

TPS3180 **Poster Session**

Efficacy of afatinib in patients with advanced/metastatic solid tumors harboring *NRG1* gene fusions: A novel, prospective real-world outcomes study based on single-patient protocol data.

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Background: Oncogenic neuregulin 1 (*NRG1)* gene fusions occur in ~0.2% of solid tumors overall and in up to 31% of cases of invasive mucinous lung adenocarcinoma [Laskin et al. *Ann Oncol*. 2020;31(12):1693–1703; Cadranel et al. *Oncologist.* 2021;26(1):7–16]. NRG1 fusion proteins provide an extracellular anchor for the epidermal growth factor (EGF) domain of NRG1 to bind to ErbB3 (HER3), leading to HER3 heterodimerization and activation of downstream signaling pathways, resulting in oncogenesis. Afatinib, an irreversible pan-ErbB tyrosine kinase inhibitor, represents a potential treatment for *NRG1*-fusion positive (*NRG1+*) tumors. This study aims to examine the safety and efficacy of afatinib in patients with *NRG1+* solid tumors, for which no authorized targeted therapy exists. **Methods:** This prospective, decentralized, US study (NCT05107193) will include 40 evaluable patients aged ≥18 years. Participating molecular test providers across the USA will identify eligible fusions in the course of routine diagnostic assays. When a patient with an *NRG1* fusion is identified, participating test providers will notify the treating physician of the study as a treatment option for the patient. Patients' primary oncologists will then contact the trial sponsor to confirm patient eligibility. Once approved by the central Institutional Review Board, patients will receive afatinib on a single-patient protocol basis, until disease progression or treatment is no longer tolerated. The recommended dosage per SmPC is 40 mg orally QD. Patients will be screened and enrolled into the study at their existing point-of-care setting. Inclusion criteria include a histologically or cytologically confirmed diagnosis of an advanced, unresectable/metastatic, non-hematologic malignancy with an *NRG1* fusion, evaluable per RECIST 1.1. Any coding gene as the *NRG1* fusion partner is permitted. Fusion status will be confirmed prospectively by a contracted molecular test provider. Exclusion criteria include prior systemic anti-cancer therapy or investigational drug within 14 days or 5 half-lives (whichever is shorter) of the start of afatinib treatment; an actionable driver mutation other than *NRG1* fusion for which FDA-approved targeted therapy is available; and prior treatment with an ErbB-targeted therapy. The primary endpoint of the study is confirmed objective response (OR) by independent central review per RECIST 1.1, defined as best overall response of either complete response or partial response and analysed as the proportion of patients with an OR. The key secondary endpoint is duration of response, defined as the time from the first documented OR to progression or death. Secondary endpoints include time to OR and disease control per investigator assessment. Safety will also be assessed. The study is open for recruitment. Clinical trial information: NCT05107193. Research Sponsor: Boehringer Ingelheim.