3500 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

First-in-human phase I study of ARV-110, an androgen receptor (AR) PROTAC degrader in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC) following enzalutamide (ENZ) and/or abiraterone (ABI). *First Author: Daniel Peter Petrylak, Smilow Cancer Center, Yale University, New Haven, CT*

Background: Proteolysis Targeting Chimera (PROTAC) protein degraders induce selective degradation of targeted proteins by engaging the ubiquitin proteasome system. ARV-110 is an orally bioavailable PROTAC that specifically degrades AR ≥ 95% and achieves anti-tumor activity in ENZ-naïve and -resistant prostate cancer xenograft models. **Methods:** To define the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of ARV-110, pts with ≥ 2 prior therapies for mCRPC, including ENZ and/or ABI, received ARV-110 orally once daily. Dose escalation is per 3+3 design. Endpoints include dose limiting toxicities (DLTs), adverse events (AEs), pharmacokinetics (PK), biomarkers (e.g., AR mutation analysis), RECIST and PSA response. **Results:** By January 2020, 18 pts were dosed: 35 mg (N = 3), 70 mg (N = 4), 140 mg (N = 8), 280 mg (N = 3). 12 pts received both ENZ and ABI; 14 received prior chemotherapy. 1 of 18 pts experienced a DLT (280 mg) of Grade (Gr) 4 elevated AST/ALT followed by acute renal failure while taking rosuvastatin (ROS). A 2nd pt had Gr 3 AST/ALT with ROS that resolved off ROS, permitting ARV-110 retreatment. ROS plasma concentrations demonstrated significant increases concurrent with AST/ALT elevations in both pts. Subsequently, ROS was prohibited without further ≥Gr 2 AST/ALT AEs. No other related Gr 3/4 AEs were reported. ARV-110 PK was generally dose proportional and at 140 mg reached levels associated with preclinical anti-tumor activity. 15 pts were evaluable for PSA response (excludes 1 pt stopped after 1 dose for early progression and 2 pts initiated 2 weeks before cutoff, all at 140 mg). Of these, 8 pts initiated dosing at ≥140 mg. 2 pts achieved confirmed PSA declines of >50%, both at 140 mg. Prior therapy in both pts included ENZ and ABI, chemotherapy, bicalutamide and radium-223 plus other regimens. 1 pt had 2 AR mutations known to confer ENZ resistance. The 2nd pt also achieved an unconfirmed RECIST partial response (confirmatory scan pending). Both responses were ongoing at data cutoff (8+ and 21+ weeks of treatment). **Conclusions:** To date, ARV-110 has an acceptable safety profile. Concurrent ROS is now prohibited. MTD has not yet been established; determination of RP2D continues. ARV-110 demonstrates antitumor activity in mCRPC after ENZ/ABI with 2 ongoing confirmed PSA responses, one of which was associated with tumor reduction. Updated data for this first PROTAC in clinical testing will be presented. Clinical trial information: NCT03888612. Research Sponsor: Arvinas.

3501 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Phase I/II study of avadomide (CC-122) in combination with R-CHOP for newly diagnosed DLBCL. *First Author: Neha Mehta-Shah, Washington University School of Medicine, St. Louis, MO*

Background: In certain subsets of patients (pts) with diffuse large B-cell lymphoma (DLBCL), the failure rate of standard R-CHOP treatment is high. Pts with high-risk disease (International Prognostic score [IPI] 3-5) have a particularly poor prognosis, with 3-y survival rates of ~62% with R-CHOP alone. The cereblon E3 ligase modulator avadomide (CC-122) showed activity in pts with relapsed or refractory DLBCL. We report results of avadomide plus R-CHOP in previously untreated pts with high-risk DLBCL. **Methods:** CC-122-DLBCL-002 (NCT03283202) is a phase 1/2 study of avadomide plus R-CHOP-21 in pts newly diagnosed with DLBCL not otherwise specified with IPI scores 3-5 who were aged ≥18 y. Pts received standard R-CHOP and escalating doses (1-3 mg) of oral avadomide for up to six 21-d cycles (Table). All pts received pegfilgrastim support. Primary objectives were to assess safety, tolerability, and complete response (CR) rate. Secondary objectives include evaluation of additional efficacy parameters (objective response rate [ORR], progression-free survival [PFS], and overall survival) and biomarkers. **Results:** As of July 30, 2019, 35 pts were enrolled in the phase 1 part of the study. Median age was 66 y (range, 20-75), 23 pts (66%) were aged > 60 y, 18 (51%) had an IPI score of 3, and 17 (49%) had an IPI score of 4-5. Thirty-two pts (91%) completed 6 cycles of treatment. Median relative total dose intensity of avadomide was 99% and the average relative dose intensity of R-CHOP was 95%. Six pts had dose-limiting toxicities: 1 pt had neutropenia and bacterial hepatic infection; 1 had pneumonia; 1 had febrile neutropenia (FN); 1 had FN and hypotension; 1 had FN due to skin infections; and 1 had sepsis. The recommended phase 2 dose was 3 mg 2/3 wk. Grade 3/4 adverse events in ≥10% of pts were neutropenia (54%), anemia (20%), leukopenia (20%), lymphopenia (14%), hypophosphatemia (14%), and FN (11%). Among 34 efficacy-evaluable pts, the ORR was 88% (n = 30/34), including a CR rate of 79% (n = 27/34) at the end of treatment. With a median follow-up of 10 mo, the 1-y PFS rate was 80% (95% CI, 58-92). Correlative analyses will be presented at the meeting. **Conclusions:** Avadomide plus R-CHOP was well-tolerated with no significant additive toxicities. The promising efficacy in this high-risk pt population warrants further evaluation of immunomodulatory drugs combined with immunochemotherapy for pts with previously untreated DLBCL. Clinical trial information: NCT03283202.Research Sponsor: Celgene, a wholly owned subsidiary of Bristol-Myers Squibb.

Dose Level	Avadomide Dose	Schedule
1	1 mg	D1-5 & D8-12 (5/7 d; 2/3 wk)
2	2 mg	D1-5 & D8-12 (5/7 d; 2/3 wk)
3	3 mg	D1-5 & D8-12 (5/7 d; 2/3 wk)
4	3 mg	D1-5, D8-12, & D15-19 (5/7 d; 3/3 wk)

3502 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

CX-2029, a PROBODY drug conjugate targeting CD71 (transferrin receptor): Results from a first-in-human study (PROCLAIM-CX-2029) in patients (Pts) with advanced cancer. *First Author: Melissa Lynne Johnson, Sarah Cannon Research Institute, Nashville, TN*

Background: CX-2029 is a PROBODY drug conjugate (PDC) of MMAE, a potent microtubule inhibitor, directed against CD71 (transferrin receptor 1). In addition to being an abundant tumor antigen, CD71 is highly expressed on normal cells, precluding targeting by a traditional antibody drug conjugate (ADC). PDCs are masked ADCs, unmasked predominantly by tumor-associated proteases, thereby restricting target engagement to tumors. Both a CD71 PDC and ADC displayed broad activity in multiple xenograft tumor models; in toxicology studies, the PDC was tolerable at doses consistent with efficacy in non-clinical tumor models while the ADC was not. **Methods:** In a phase 1/2 first-in-human study of PDC CX-2029 in advanced solid tumors (NCT03543813), pts with ECOG 0–1 and ≥1 prior systemic therapy were enrolled into escalating dose cohorts of the PDC CX-2029 given IV every 21 days. Endpoints included evaluation of MTD, safety, antitumor activity, and potential biomarkers; plasma and tissue samples were collected for PK/PD analyses. Preliminary results are reported. **Results:** As of 30 November 2019, 34 pts were enrolled (median age 59 y; 59% male; 71% ECOG 1; median [range] of 3 [1–16] prior therapies). Pts received a median of 3 (1–12) CX-2029 doses. Starting dose for escalation was 0.1 mg/kg. Following a single CX-2029 dose, median molar ratio of masked CX-2029 to total CX-2029 for AUC_{tau} was 0.938 (0.864–0.942); the ratio of free MMAE to total CX-2029 was <0.03. Infusion-related reactions were the most common treatment-related AE (TRAE) of any grade (88%; primarily low grade and with first infusion), followed by anemia (56%), fatigue and nausea (24% each), neutropenia (21%), and leukopenia (12%). Grade 3+ TRAEs in ≥10% pts were anemia (35%) and neutropenia (18%). In 32 response-evaluable pts, 1 pt had a confirmed partial response (squamous NSCLC); 9 had stable disease including 1 pt with ocular melanoma treated for 36 weeks. **Conclusions:** The observed safety profile for CX-2029 effectively reduces on-target toxicity for this previously undruggable target, supporting the PROBODY platform. Evidence of anti-tumor activity was observed. Dose escalation continues. Clinical trial information: NCT03543813. Research Sponsor: CytomX Therapeutics, Inc.

3503 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Results from a phase I, open-label study of ceralasertib (AZD6738), a novel DNA damage repair agent, in combination with weekly paclitaxel in refractory cancer (NCT02630199). *First Author: Jeeyun Lee, Samsung Medical Center, Seoul, South Korea*

Background: Ataxia Telangiectasia and Rad3 Related (ATR) is an apical kinase with a critical role in the DNA-damage response. During normal DNA replication, ATR is recruited at stalled replication forks which can progress to double strand breaks if left unrepaired. AZD6738 is an oral inhibitor of the serine/threonine protein kinase ATR, a member of the phosphoinositide 3-kinase related kinase (PIKK) family. **Methods:** Eligible patients (pts) with advanced solid tumours were administered AZD6738 in combination with fixed dose paclitaxel 80 mg/m2 D1, D8, D15 in 28-day cycles. The dose of AZD6738 was escalated to reach a maximum tolerated dose (MTD) in a rolling 6 design. The trial evaluated safety, MTD, pharmacokinetics (PK) and pharmacodynamics (PD). Translational studies on plasma samples included cytokine analysis, panel sequencing of ctDNA, as well as IHC and immunofluorescence of immune cell markers. **Results:** 58 pts (34 melanoma, 15 gastric cancer (GC), 4 sarcoma, 3 colon cancer, 1 neuroendocrine and 1 hepatocellular cancer) were enrolled in 7 dose cohorts ranging 40mg OD to 240 mg BID. One dose-limiting toxicity (DLT) of neutropenic fever occurred in each cohort of n = 6 evaluable pts at AZD6738 160 mg BD and 240 mg BD days 1-14. Per protocol, the maximum tolerated dose of AZD6738 is 240 mg BID days 1-14. The most common toxicities (all causality, all grade) were: anorexia/nausea (n = 15, 26%), leukopenia (n = 11, 19%) and anemia (n = 11, 19%). 51 pts are evaluable for efficacy; we observed 1 complete response (1.9 %, melanoma), 12 confirmed partial responses (23.5%; 2 gastric, 10 melanoma all of which were post-immunotherapy), 18 stable disease (35.3%) and 20 disease progression (39.2%). The overall confirmed response rate from the dose escalation is 25.5%. Genomic analysis of baseline plasma (27 pts) revealed enrichment of NF1 somatic mutations and activating NRAS mutations amongst melanoma pts (6/18 and 4/18, respectively). Cyclical changes in interleukin-12 levels were observed in three pts with disease control which could reflect an immunological component to the mechanism of response. We will present a comprehensive case report of a patient with dramatic and durable response. **Conclusions:** We conclude that AZD6738 can be safely combined with weekly paclitaxel and propose a recommended phase II dose and schedule. The combination of AZD6738 and paclitaxel demonstrated promising anti-tumor activity with durable responses, especially in melanoma pts after failing anti-PD1 therapy. Clinical trial information: NCT02630199. Research Sponsor: None.

3504 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Phase I monotherapy dose escalation of RGX-202, a first-in-class oral inhibitor of the SLC6a8/CKB pathway, in patients with advanced gastrointestinal (GI) solid tumors. *First Author: Johanna C. Bendell, Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN*

Background: About 65% of advanced colorectal cancer (CRC) patients (pts) have creatine kinase B (CKB) expressing tumors. CKB expressing (CKB+) GI cancer cells import creatine via the creatine transporter SLC6a8 and utilize it to generate intracellular ATP. RGX-202, a small molecule inhibitor of SLC6a8, reduces intracellular creatine and ATP levels, leading to apoptosis. RGX-202 treatment triggers complete tumor regressions in multiple CKB+ preclinical models, including KRAS mutant CRC. **Methods:** RGX-202-001 is a phase I escalation/expansion study of RGX-202 +/- FOLFIRI in pts with advanced GI tumors. The primary safety objective during dose escalation is to identify the maximum tolerated dose (MTD), or the maximum tested dose at which multiple dose-limiting toxicities (DLTs) are not observed. The primary efficacy objective is to estimate the antitumor activity of RGX-202 by RECIST. **Results:** As of January 31, 2020, 17 pts have been treated in 4 single agent dose escalation cohorts: 600 mg BID (3 pts), 1200 mg BID (4 pts), 2400mg BID (5 pts) and 3600mg BID (5pts) given continuously. No DLTs were observed and an MTD was not reached. Treatment-related adverse events (TRAEs) occurring in $>$ 2 pts are shown in the Table. There were no Grade 4 TRAEs. At the highest dose, 2 of 3 CRC pts had prolonged disease control: a patient with a KRAS G13D mutant cancer had SD for 14 weeks; and a patient with KRAS G12V mutant (MSS) cancer had a confirmed PR ongoing at 30 weeks. Exposure to RGX-202 was greater than dose-proportional and the average $AUC_{0\text{-}24}$ ranged from ~15,700 ng-hr/mL in cohort 1 to 241,097 ng-hr/mL in in Cohort 4. Serum and urine creatine levels, pharmacodynamic markers of SLC6a8 inhibition, correlated with systemic exposure to RGX-202. **Conclusions:** Among 17 patients treated with single agent therapy, no DLTs occurred; notably, exposures predicted to be sufficient to inhibit human tumor growth from preclinical models were achieved along with concomitant pharmacodynamic effects. These data, along with a durable PR observed in the highest dose cohort, support further development of RGX-202. Consequently, dose escalation in combination with FOLFIRI in patients with advanced GI cancers is underway with plans for expansion in CKB+ CRC pts. Clinical trial information: NCT03597581.Research Sponsor: Rgenix.

	All Patients (N=17) n (%)	
TRAE Term	**Any Grade**	**Grade 3**
Nausea	8 (47)	1 (6)
Vomiting	7 (41)	1 (6)
Diarrhoea	5 (29)	0
Decreased appetite	4 (24)	0
Fatigue	4 (24)	0
Blood alkaline phosphatase increased	2 (12)	0
Muscle spasms	2 (12)	0
Weight decreased	2 (12)	0

3505 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Tolerability and preliminary efficacy of BXQ-350 for refractory solid tumors and high-grade gliomas: First-in-human, first-in-class phase I trial. *First Author: Olivier Rixe, GRU Cancer Center, Augusta, GA*

Background: BXQ-350 is a first-in-class agent comprised of Saposin C (SapC) and dioleoyl phosphatidylserine (DOPS). SapC, a multifunctional lysosomal-activator glycoprotein that preferentially interacts with tumor cell phospholipids, has demonstrated anti-tumor effects in both *in vitro* and *in vivo* preclinical models. The tolerability and preliminary efficacy of BXQ-350 in the first-in-human study are summarized here. **Methods:** Eighty-six refractory solid tumor (ST) or high-grade glioma (HGG) patients age $\geq$18 (36F: 50M, age 24-81) were enrolled in a 3-part first-in-human trial (NCT02859857) from 2016-2019 and received at least one dose of BXQ-350. Doses were administered via intravenous infusion during 28-day cycles until disease progression occurred. The previously reported part 1 dose escalation portion of the study (9 HGG, 9 ST patients) established the highest planned dose of 2.4mg/kg as safe but did not identify a maximum tolerated dose. The part 2 expansion cohort treated 37 patients (18 HGG and 19 ST) and an additional part 3 cohort treated 31 ST gastrointestinal (GI) patients, both at the 2.4 mg/kg dose level. Preliminary antitumor activity was evaluated (RECISTv1.1 or RANO). **Results:** There were no BXQ-350-related serious adverse events, dose limiting toxicities or withdrawals with the exception of 1 allergic type reaction. Three patients (Glioblastoma, Ependymoma, Appendiceal) demonstrated a partial response per RECIST/RANO. Two HGG patients with progressive radiologic enhancement were seen to have treatment effect at surgery, and hence considered to have stable disease. Seven patients (2 HGG, 3 GI, 2 other ST) remain on study and have received treatment for 9+ to 41+ months, with 5 patients treated for $>$ 1 year. A continuing treatment protocol is planned in order to allow these patients to remain on BXQ-350 treatment. **Conclusions:** BXQ-350 was well tolerated with no significant dose-limiting toxicities at the highest planed dose level. Preliminary results indicate this novel agent demonstrated possible anti-tumor activity in refractory solid tumors and HGG. Clinical trial information: NCT03967093). Research Sponsor: Bexion Pharmaceuticals.

3506 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Phase II study of copanlisib in patients with tumors with *PIK3CA* mutations (*PTEN* loss allowed): NCI MATCH EAY131-Z1F. *First Author: Senthil Damodaran, Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The NCI-MATCH (EAY131) is a platform trial that enrolls patients (pts) with solid tumors, lymphomas, or multiple myeloma to targeted therapies based on matching genomic alterations of interest (NCT02465060). Arm Z1F evaluated copanlisib, a highly selective, pan-Class 1 PI3K inhibitor with predominant activity against both the δ and α isoforms in pts with *PIK3CA* mutations. **Methods:** Pts received copanlisib (60 mg IV) on days 1, 8, and 15 in 28-day cycles until progression/toxicity. Tumor assessment was every 2 cycles. The primary endpoint was objective response rate (ORR); secondary endpoints were PFS, 6-month PFS, and predictive biomarkers. Pts with *KRAS* mutations, HER2+ve breast cancers, lymphomas were excluded. **Results:** 35 pts were enrolled (from 8/2/18 to 12/27/18), of which, 28 pts were available for analysis (7 patients, not eligible or did not start therapy). Multiple histologies were enrolled with gynecologic (n = 7), gastrointestinal (n = 6), and genitourinary (n = 5) the most common tumors. Median age 61 (range 42-78). 75% of pts had $\geq$ 3 lines of prior therapy. 54% of *PIK3CA* mutations were located in the helical domain, 32% in kinase domain and 14% in other domains. Twenty-six pts had co-occurring gene alterations (median 3; range 1-9), with 9 patients having 4 or more gene alterations. The ORR was 11% (3/28, 90% CI: 3%-25%). Partial responses were seen in uterine cancer, clear cell carcinoma of anterior abdominal wall, and liposarcoma. 6 pts had $>$ 6 months of stable disease and clinical benefit rate was 32% (9/28). Two pts are still on treatment. The most common reason for protocol discontinuation was disease progression (n = 18, 69%). Thirty pts were included for toxicity analysis. Ten pts (33%) had grade 1 or 2 toxicities, 16 pts (53%) had grade 3 toxicities, and one patient (3%) had grade 4 toxicity (CTCAE v5.0). Most common toxicities include hyperglycemia (n = 19), fatigue (n = 11), hypertension (n = 10), diarrhea (n = 10), and nausea (n = 9). Total of 5 deaths were reported, none related to treatment. **Conclusions:** Copanlisib showed meaningful clinical activity across various tumors with *PIK3CA* mutation in the late-line refractory setting. Further study either alone or in combinations in select tumors is warranted. G3/4 toxicities observed were consistent with reported toxicities for PI3K pathway inhibition. Clinical trial information: NCT02465060. Research Sponsor: U.S. National Institutes of Health.

3507 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Phase I study of 9-ing-41, a small molecule selective glycogen synthase kinase-3 beta (GSK-3β) inhibitor, as a single agent and combined with chemotherapy, in patients with refractory tumors. *First Author: Benedito A. Carneiro, Brown University, Lifespan Cancer Institute, Providence, RI*

Background: Overexpression of GSK-3β, a serine/threonine kinase, is associated with advanced stage malignancies, aggressive tumor growth, and chemotherapy resistance. 9-ING-41 is a GSK-3β inhibitor with significant broad spectrum preclinical antitumor activity, including chemotherapy-resistant models. This first-in-human study (NCT03678883) is evaluating the safety, pharmacokinetics (PK), and efficacy of 9-ING-41 monotherapy and in combination with chemotherapy in patients (pts) with refractory malignancies. **Methods:** 9-ING-41 is given intravenously (IV) twice-weekly as a single-agent (21-day cycle) or combined with gemcitabine, gemcitabine/nab-paclitaxel, carboplatin, carboplatin/paclitaxel, doxorubicin, lomustine or irinotecan in patients previously treated with the same chemotherapy. **Results:** As of Jan 2020, 101 pts were enrolled. Tumor types: 25 pancreatic (PDAC), 14 colorectal (CRC), 10 non-small cell lung cancer (NSCLC), 8 GBM and other gliomas, 7 melanoma, 5 appendiceal, 4 breast (BC), 30 others. Seven single agent dose levels (DL) completed (1, 2, 3.3, 5, 7, 9.3, 12.4 mg/kg) without any 9-ING-41-attributable SAEs. 9-ING-41 attributable AEs include: transient visual change (color perception; n = 29), starting at DL 3 (3.3mg/kg), all G1/2; infusion reactions (n = 14), all G1/2, starting at DL 5 (7mg/kg). 9-ING-41's mean terminal half-life is 12-20 hrs. C_{max} and $AUC_{0\text{-}72}$, are dose proportional with no accumulation. One BRAFV600K-mutated melanoma with $>$ 20 brain metastases, post checkpoint/BRAF/MEK failure has an ongoing CR starting at cycle 2 and sustained after 9 months on treatment. 32 (31%) pts had SD as best response (6 PDAC, 6 CRC, 3 appendiceal, 2 BC, 2 salivary gland, 2 melanoma, 1 Merkel cell, 2 GBM/glioma, 1 RCC, 1 HCC, 1 NSCLC, 1 esophageal, 1 parotid gland, 1 nasopharyngeal, 1 peritoneal, 1 T cell-ALL). 8 pts remained on study treatment $>$ 5 months (1 melanoma, 3 PDAC, 1 appendiceal, 1 GBM, 1 peritoneal, 1 salivary gland) with median treatment duration of 198 days (range 163-261). 32 pts continue to receive 9-ING-41. **Conclusions:** 9-ING-41 has dose-proportional PK, is well tolerated with significant antitumor activity as monotherapy and in combination with chemotherapy in pts with refractory tumors. 1 ongoing CR was observed in a refractory BRAF-mutated melanoma. A biologically active dose has been reached, although MTD has not been determined. Enrollment is ongoing. Clinical trial information: NCT03678883. Research Sponsor: Actuate Therapeutics.

3508 Poster Discussion Session; Displayed in Poster Session (Board #238), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Phase Ib study of a novel bivalent IAP antagonist APG-1387 in combination of pembrolizumab for patients with advanced solid tumors. *First Author: Drew W. Rasco, South Texas Accelerated Research Therapeutics, San Antonio, TX*

Background: APG-1387 is an IAP (inhibitor of apoptosis proteins) antagonist that has strong antitumor activity in multiple xenograft cancer models and acts as a host immune modulator, supporting its exploration for use in combination with checkpoint inhibitors for cancer therapy. **Methods:** This "3+3" dose escalation and dose expansion study evaluated APG-1387 combined with pembrolizumab in patients with refractory or intolerant advanced solid tumors (NCT03386526). APG-1387 was administered IV once weekly with pembrolizumab 200 mg on day 1 of a 21-day cycle. Study aims were to assess safety/tolerability, recommended phase 2 dose (RP2D), pharmacokinetics (PK), pharmacodynamics (PD), and efficacy. **Results:** As of December 25, 2019, total 28 patients had been treated in 3 dose cohorts of APG-1387: 20 mg (n = 4), 30 mg (n = 3), and 45 mg (n = 21, 18 in dose expansion). The median line of prior systemic cancer therapies was 3.0 (1-12). No dose-limiting toxicity was observed. The most common treatment-related adverse events (TRAEs; ≥10%) were fatigue (28.6%), arthralgia (14.3%), headache (14.3%), and tumor pain (10.7%). One patient in the 45-mg cohort had grade 2 Bell's Palsy. G3^{+} TRAEs were autoimmune colitis, hypoxia, increased lipase, mucosal inflammation, pneumonitis, and tumor pain in 1 patient each (3.6%). Treatment-related SAEs were 1 G3 autoimmune colitis, 1 G2 myocarditis, and 1 G3 pneumonitis. The maximum tolerated dose (MTD)/RP2D for APG-1387 was 45 mg. Among 25 efficacy-evaluable patients, 1 with ER^{+}, HER2^{-} breast cancer receiving APG-1387 30 mg after failing 5 lines of therapy (PD-1 treatment-naïve, microsatellite stable) achieved confirmed PR (-79.2%) for 6 cycles but discontinued due to pneumonitis; another patient with PD-L1^{-} non–small-cell lung cancer treated at 45 mg had confirmed PR (-65.0%) for 6 cycles (ongoing). Other 11 patients had SD for 2-11 cycles. The disease control rate was 52%. Preliminary PK data showed a dose-proportional increase in APG-1387 exposure from 20 mg to 45 mg. Preliminary PD data showed that APG-1387 induced rapid degradation of cellular IAP1 and X-linked IAP in peripheral blood mononuclear cell samples; Increased serum release of interleukins (IL-12, IL-10) and monocyte chemotactic protein 4 was dose and time dependent. **Conclusions:** APG-1387 combined with pembrolizumab is well tolerated. Encouraging antitumor effects were observed in patients with several tumor types. The ongoing study will further evaluate the efficacy of this combination. Clinical trial information: NCT03386526. Research Sponsor: Ascentage Pharma Group Inc., Rockville, MD.

3509 Poster Discussion Session; Displayed in Poster Session (Board #239), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

First-in-human study of palcitoclax (APG-1252), a novel dual Bcl-2/Bcl-xL inhibitor, demonstrated advantages in platelet safety while maintaining anticancer effect in U.S. patients with metastatic solid tumors. *First Author: Nehal J. Lakhani, START-Midwest, Grand Rapids, MI*

Background: Targeting Bcl-2/Bcl-xL proteins is considered as an important approach for anticancer drug development. Palcitoclax (APG-1252) was being developed to reduce on-target platelet toxicity without diminishing antitumor potency. **Methods:** The phase 1 study was to evaluate the safety/tolerability, pharmacokinetics (PK), and preliminary efficacy (assessed per RECIST 1.1) of palcitoclax in US patients with metastatic small-cell lung cancer (SCLC) or other solid tumors (NCT03080311). A standard "3+3" design was applied to the dose-escalation stage. Palcitoclax was administered IV infusion for 30 minutes, twice a week (BIW) or once a week (QW) for 3 weeks in a 28-day cycle. Once the maximum tolerated dose / recommended phase 2 dose (MTD/RP2D) was determined, additional patients were treated in a dose-expansion stage. **Results:** The dose-escalation phase has been completed with 42 patients (31 on BIW and 11 on QW) who received palcitoclax at 8 dose cohorts ranging 10 mg - 400 mg. Most adverse events (AEs) were grade 1 or 2 (G1 or G2), and 26.2% patients had ≥ G3 TRAEs. The most common TRAEs were platelet count decreased (14.3%), aspartate aminotransferase increased (9.5%), and alanine aminotransferase increased (7.1%). Rapid platelet drop was observed in patients treated at 320 mg and 400 mg, which was transient and resolved rapidly within 2-6 days. Palcitoclax at 240 mg once weekly was determined to be MTD/RP2D. Of 36 efficacy-evaluable patients, 3 patients with SCLC, neuroendocrine prostate cancer, and ovarian cancer respectively achieved partial response (PR) and 8 patients had stable disease (SD) as their best overall response. One patient with SCLC had a PR that lasted over 21 cycles. Preliminary PK analyses showed that C_{max} and AUC were approximately dose proportional over the range of 10 mg to 320 mg following the IV infusion on Day 1, with a mean $T_{1/2}$ of 3.0-13.0 hours. **Conclusions:** Palcitoclax is safe and well tolerated, with a favorable platelet toxicity profile. Its promising antitumor effect supports its further development in combination therapies for treatment of patients with SCLC and other solid tumors. Clinical trial information: NCT03080311. Research Sponsor: Ascentage Pharma Group Inc., Rockville, MD.

3510 Poster Discussion Session; Displayed in Poster Session (Board #240), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Safety and efficacy of pyrotinib in patients with NSCLC and other advanced solid tumors with activating *HER2* alterations: A phase I basket trial. *First Author: Bob T. Li, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Pyrotinib is a potent, irreversible tyrosine kinase inhibitor (TKI) that blocks signal transduction through the erythroblastic leukemia viral oncogene homolog (erbB) receptors, which has previously demonstrated promising antitumor activity in patients (pts) with breast cancers. We studied the safety and efficacy of pyrotinib in pts with non-small cell lung cancer (NSCLC) and other solid tumors with activating human epidermal growth factor receptor 2 (*HER2, ERBB2)* alterations. **Methods:** This is an open-label, multicenter phase 1 dose expansion basket trial of pyrotinib given 400mg oral daily at 28-day cycles. Expansion cohorts included pts with *HER2*-mutant NSCLC and advanced solid tumors with *HER2* mutation or amplification. *HER2* testing was conducted using next generation sequencing or fluorescence *in situ* hybridization. Primary endpoints included toxicities as evaluated by NCI CTCAE v5.0, and overall response rate (ORR) as evaluated by RECIST v1.1. Secondary objectives included progression-free survival (PFS). **Results:** A total of 62 pts were enrolled. The median age was 67 (range 40 – 86 years), 61% were female and the median lines of prior systemic therapy was 3 (range 1-11). There were no treatment related deaths. The most common adverse events were diarrhea (96.8%), nausea (82.3%) and vomiting (41.9%). The only ≥ grade 3 treatment related toxicity was diarrhea (24.2%). Prophylactic anti-diarrhea treatment was introduced to facilitate continuation of pyrotinib. At the Jan 13, 2020 cut-off, 24 pts with *HER2*-mutant NSCLC (20, i.e. 65% of which were the A775_G776insYVMA mutation) and 18 pts with *HER2*-mutant or amplified solid tumors completed end of Cycle 2 imaging scan and were evaluable for tumor responses. The ORR was 19% (8/42, 95% CI 7-31%); confirmed responses include a complete response (CR) and 3 partial responses (PRs) in *HER2*-mutant NSCLC, and 4 PRs in *HER2*-amplified cholangiocarcinoma, ovarian, endometrial and salivary gland carcinomas. There were 7 stable disease ≥ 6 months. Median progression-free survival was 5.4 months (95% CI 4.4-7.3). **Conclusions:** Pyrotinib demonstrated a manageable safety profile and encouraging efficacy in pts with heavily pre-treated *HER2*-mutant NSCLC. Furthermore, it is the first TKI to produce durable responses in pts with *HER2*-amplified biliary tract, ovarian, endometrial and salivary gland cancers. These results warrant further clinical development of pyrotinib. Clinical trial information: NCT02500199. Research Sponsor: Hengrui Therapeutics Inc.

3511 Poster Discussion Session; Displayed in Poster Session (Board #241), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

CodeBreak 100: Phase I study of AMG 510, a novel KRAS^{G12C} inhibitor, in patients (pts) with advanced solid tumors other than non-small cell lung cancer (NSCLC) and colorectal cancer (CRC). *First Author: David S. Hong, MD Anderson Cancer Center, Houston, TX*

Background: Kirsten rat sarcoma viral oncogene homolog (*KRAS*) p.G12C mutation occurs in approximately 13% of NSCLC and 1%–3% of CRC and other solid tumors. AMG 510 is a first-in-class small molecule that specifically and irreversibly inhibits KRAS^{G12C}. Previously, AMG 510 showed preliminary antitumor activity and favorable tolerability in pts with *KRAS* p.G12C mutant NSCLC or CRC in the phase 1, first-in-human trial. Here, we report results in pts with other tumor types from the same trial. **Methods:** This study evaluates AMG 510 in pts with locally-advanced or metastatic *KRAS* p.G12C mutant solid tumors. Key inclusion criteria: *KRAS* p.G12C mutation via local testing and prior systemic anticancer treatment (tx). Oral daily doses of 180, 360, 720, and 960 mg were tested in the dose escalation, and 960 mg was selected for expansion. Primary endpoint is safety; key secondary endpoints include pharmacokinetics and objective response rate as assessed per RECIST 1.1. Response is assessed every 6 weeks (wks) for 24 wks then every 12 wks thereafter. **Results:** As of January 8, 2020, 25 pts (9 female, median age 60 years [range: 40–75]) with tumor types categorized by investigators as histology other than NSCLC and CRC were enrolled and dosed (10 pancreatic cancer, 4 appendiceal cancer, 2 endometrial cancer, 2 unknown primary cancer, 1 bile duct cancer, 1 sinonasal cancer, 1 ampullary cancer, 1 small bowel cancer, 1 melanoma, 1 small cell lung cancer, and 1 esophageal cancer). 23 pts received 960 mg dose. 20 pts (80.0%) had ≥2 prior lines of tx. At data cutoff, 13 pts (52.0%) remained on tx; 9 (36.0%) and 3 (12.0%) pts remained on tx for ≥3 and ≥6 months, respectively. Median follow up was 4.3 months (range: 0.1–12.6). Tx-related adverse events (TRAEs) occurred in 9 pts (36.0%). 2 pts (8.0%) had grade 3 TRAEs, including diarrhea (1/25) and pneumonia (1/25, serious AE). No dose-limiting toxicities, grade ≥4, or fatal TRAEs were reported. No TRAEs led to tx discontinuation. 3 pts had not been followed up for ≥7 wks by the data cutoff. 22 pts were followed up for ≥7 wks, and their best overall responses were: 3 confirmed partial response (1 appendiceal, 1 melanoma, and 1 endometrial), 13 stable disease (6 pancreatic, 2 appendiceal, 1 ampullary, 1 bile duct, 1 endometrial, 1 sinonasal, and 1 unknown primary), and 6 progressive disease. **Conclusions:** AMG 510 was well tolerated and demonstrated clinical activity in pts with advanced *KRAS* p.G12C mutant solid tumors other than NSCLC and CRC. Clinical trial information: NCT03600883. Research Sponsor: Amgen Inc.

3512 Poster Discussion Session; Displayed in Poster Session (Board #242), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Phase Ib study of a novel, small-molecule MDM2 inhibitor APG-115 combined with pembrolizumab in U.S. patients with metastatic solid tumors. *First Author: Anthony W. Tolcher, NEXT Oncology, San Antonio, TX*

Background: APG-115 activates p53-mediated apoptosis in tumor cells retaining wild-type *TP53*. It also functions as a host immune modulator and enhances antitumor activities when combined with PD-1 blockade preclinically. MDM2 amplification is associated with hyperprogression in patients treated with checkpoint inhibitors. **Methods:** The Phase Ib / II study was designed to evaluate APG-115 combined with pembrolizumab in patients with metastatic solid tumors (NCT03611868). APG-115 was administered orally every other day for 2 weeks, at dose ranging from 50 mg – 200 mg, with pembrolizumab at 200 mg IV on Day 1 of a 21-day cycle. Study objectives were to assess safety including dose-limiting toxicity (DLT), serious adverse events (SAEs), treatment-related AEs (TRAEs), pharmacokinetics (PK), pharmacodynamics (PD), and efficacy (assessed by RECIST v1.1), to determine recommended phase 2 dose (RP2D). **Results:** As of December 25, 2019, the enrollment of phase 1b study was completed. Total 19 patients had been treated in four APG-115 cohorts: 50 mg (n = 3), 100 mg (n = 3), 150 mg (n = 6), and 200 mg (n = 7). No DLT was observed, The TRAEs (≥15%) were nausea (47.4%), fatigue (36.8%), decreased platelet count (26.3%), and decreased appetite (21.1%), as well as diarrhea, vomiting, decreased neutrophil or white blood cell count, and hypothyroidism in 15.8% each. Grade > 3 TRAEs included decreased neutrophil and thrombocytopenia in 15.8% each. Two SAEs were treatment related: G3 febrile neutropenia and G3 adrenal insufficiency. No new safety finding from combination with Pembrolizumab. The RP2D of APG-115 was 150 mg. One patient with ovarian cancer has a CR lasting for 15 months, 2 patients had PR for 8-9 months: one NSCLC failed IO therapy, another with appendix cancer, and 7 had SD for 1.5-7 months. The objective response rate was 15.8%, and the disease control rate (DCR) was 52.6%. PK data indicated an approximately dose-proportional increase in APG-115 exposure over the range of 50-200 mg on Day 1. PD-PK analyses showed that serum macrophage inhibitory cytokine-1 (MIC-1) increase was time and dose dependent, the MIC-1 elevation correlated with APG-115 exposure, indicating p53 activation in these patients. **Conclusions:** APG-115 in combination with pembrolizumab is well tolerated. Encouraging antitumor effects were observed in several tumor types. The phase II study is ongoing in the cancer patients with specific bio-marker profiling. Clinical trial information: NCT03611868. Research Sponsor: Ascentage Pharma Group Inc., Rockville, MD.

3513 Poster Discussion Session; Displayed in Poster Session (Board #243), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Phase I study of rucaparib and irinotecan in advanced solid tumors with homologous recombination deficiency (HRD) mutations. *First Author: Mallika Sachdev Dhawan, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA*

Background: Poly (ADP-ribose) polymerase inhibitors (PARPi) are approved for multiple tumor types with HRD mutations. In efforts to prolong durations of response, combination treatments of PARPi and chemotherapy are being explored. However, expected overlapping toxicities have previously limited the tolerability of PARPi-chemotherapy combinations. Preclinical studies suggest that the inhibition of PARP will prevent the repair of topoisomerase induced DNA strand breaks. In this Phase I trial, we test whether pulse dosing and alternate treatment schedules of rucaparib and irinotecan are safe and tolerable. **Methods:** Rucaparib and irinotecan were dose escalated in a 3+3 design. Patients with advanced solid tumors and somatic or germline known or suspected pathogenic mutations in HRD were accepted on trial. 15 patients have been enrolled in 3 cohorts and treated with rucaparib 400 mg BID (days 1-7) and irinotecan 65 mg/m2 (cohort 1) or 100 mg/m2 (cohort 2) every 2 weeks or 100 mg/m2 every 3 weeks (cohort 2i). **Results:** Tumor types on trial are heterogeneous and include pancreatic ductal adenocarcinoma (PDAC: 3), cholangiocarcinoma, neuroendocrine carcinoma of the pancreas, ovarian cancer/primary peritoneal carcinoma (3), prostate cancer, small bowel carcinoma, squamous cell carcinoma of the tonsil, testicular cancer, triple negative breast cancer, and urothelial carcinoma. 14/15 patients had 3+ prior lines of therapy. Mutation types include: 7 ATM, 3 BRCA1, 3 BRCA2, 1 CHEK2, and 1 PALB2. All patients were previously exposed to platinum chemotherapies; 8/15 had progressive disease while on platinum. 5/15 patients had prior PARPi with progression. There were 3 DLT events, all of which were related to grade 3 or 4 neutropenia. Of the 13 patients evaluable for response, there was one confirmed partial response (PR). 5 patients have remained on study for longer than 6 months and 3 patients with ATM mutations have remained on study for longer than one year (primary peritoneal cancer, small bowel carcinoma, PNET). 4/5 patients with clinical benefit had prior platinum progression and 1/5 had previously progressed on a PARPi. Our current recommended phase 2 dose is rucaparib 400 mg BID days 1-7 and irinotecan 100 mg/m2 every 3 weeks. **Conclusions:** The pulse dosing schedule of rucaparib and irinotecan has allowed for long term tolerability and exposure to both agents with encouraging efficacy in patients with ATM mutations. Further testing of PARPi and topoisomerase inhibitors at this schedule in patients with ATM mutations is planned. Clinical trial information: NCT03318445. Research Sponsor: Clovis.

3514 Poster Discussion Session; Displayed in Poster Session (Board #244), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Lurbinectedin (LUR) in combination with Irinotecan (IRI) in patients (pts) with advanced solid tumors: Updated results from a phase Ib-II trial. *First Author: Santiago Ponce Aix, Hospital Universitario 12 De Octubre, Madrid, Spain*

Background: LUR is a novel agent that exerts antitumor activity through inhibition of trans-activated transcription and modulation of tumor microenvironment. Preclinical synergism/additivity in combination with IRI has been reported, thus prompting the conduct of this clinical trial. **Methods:** Phase Ib-II trial to evaluate escalating doses of LUR on Day (D) 1 plus a fixed dose of IRI 75 mg/m^2 on D1 and D8 every 3 weeks (q3w) in pts with advanced solid tumors (+/- G-CSF, if dose-limiting toxicities [DLTs] were neutropenia). Starting dose was LUR 1.0 m/m^2 + IRI 75 mg/m^2. **Results:** 77 pts have been treated to date at 5 dose levels, 51 of them at the recommended dose (RD). Baseline characteristics of all 77 pts were: 48% females, 68% ECOG PS=1; median age 57 years (range, 19-75 years); median of 2 prior lines (range, 0−4 lines). The maximum tolerated dose (MTD) was LUR 2.4 mg/m^2 + IRI 75 mg/m^2 with G-CSF, and the RD was LUR 2.0 mg/m^2 + IRI 75 mg/m^2 with G-CSF. DLTs in Cycle 1 occurred in 2/3 evaluable pts at the MTD and 3/13 evaluable pts at the RD, and comprised omission of IRI D8 infusion due to grade (G) 3/4 neutropenia (n=3 pts) or G2-4 thrombocytopenia (n=2). At the RD (n=51), common G1/2 non-hematological toxicities were nausea, vomiting, fatigue, diarrhea, anorexia and neuropathy. G3 non-hematological toxicities (diarrhea 10%, fatigue 10%) and G3/4 hematological abnormalities (neutropenia 49%, thrombocytopenia 10%) were transient. **Conclusions:** The combination of LUR and IRI had acceptable tolerance, with no unexpected toxicities. Transient myelosuppression was dose-limiting. The RD is LUR 2.0 mg/m^2 on D1 + IRI 75 mg/m^2 on D1 and D8 q3w with G-CSF. Antitumor activity was observed at the RD in SCLC pts, as well as in endometrial carcinoma pts. Hints of activity were also observed in STS pts. Updated results will be presented. Clinical trial information: NCT02611024. Research Sponsor: PharmaMar SA.

Main efficacy data for selected tumors at the RD are shown below.

Tumor type evaluable	SCLC (n=13)	Endometrial Ca. (n=10)	STS (n=9)	Glioblastoma (n=13)
ORR (PR)	8 (61.5%)	3 (30%)	0%	0%
DCR (PR+SD)	84.6%	100%	88.9%	38.5%
PFS at 6 months (95% CI)	36.3% (4.1-68.4%)	66.7% (36.0-97.5%)	50.8% (16.2-85.4%)	0%

Ca, carcinoma; CI, confidence interval; DCR, disease control rate; n, number of evaluable patients; ORR, overall response rate as per RECIST v.1.1; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SCLC, small cell lung cancer; SD, stable disease; STS, soft tissue sarcoma.

3515 Poster Discussion Session; Displayed in Poster Session (Board #245), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Pen-866, a miniature drug conjugate of a heat shock protein 90 (HSP90) ligand linked to SN38 for patients with advanced solid malignancies: Phase I and expansion cohort results. *First Author: Gerald Steven Falchook, Sarah Cannon Research Institute at HealthONE, Denver, CO*

Background: PEN-866 is a miniature drug conjugate which links a HSP90 binding small molecule to a SN-38 cytotoxic payload. HSP90 is highly expressed in advanced malignancies. PEN-866 targets and binds to activated tumor HSP90 protein, releases its cytotoxic payload, and results in complete tumor regressions in multiple xenograft models. This first-in-human study assessed safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of PEN-866. **Methods:** Patients (pts) with progressive, advanced solid malignancies were enrolled in escalating cohorts of 2-9 pts. The primary objective was to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of PEN-866 given weekly (3 out of 4 weeks in a 28-day cycle). **Results:** 30 pts were treated in 8 cohorts (range 30-360 mg flat dosing or 150–200 mg/m^2 BSA-based dosing). As of 9Jan20, the total median/mean exposure was 7.05/12.4 weeks. No dose limiting toxicities (DLTs) occurred in the first 4 cohorts (30-240 mg; 14 pts). In cohort 5 (360 mg), 1 of 3 pts had a DLT of grade (G) 3 transient diarrhea, and 2 other pts had G3 uncomplicated transient neutropenia. A change to BSA-based dosing was instituted for cohort 6 (175 mg/m^2), on which no DLTs were observed, although 1 pt experienced G3 uncomplicated transient neutropenia. At 200 mg/m^2, 2 of 5 pts experienced DLTs (G5 dehydration, G3 fatigue). The MTD and RP2D were determined to be 175 mg/m^2. The most frequent (≥20% pts) related adverse events were nausea (50%), fatigue (43%), diarrhea (40%), vomiting (27%), and anemia (23%). PK was nonlinear. Plasma exposures increased greater than dose proportionally. Median $t_{1/2}$ ~7 h. Cleaved SN38 never exceeded 3% of PEN-866 plasma AUC at all dose levels. Tissue PK confirmed tumor accumulation and retention of both the conjugate and released payload. As of 9Jan20, 26 pts were evaluable for response. 11 pts had stable disease at 8 weeks, of which 7 lasted 12–58 weeks. One pt with anal squamous cell carcinoma achieved a confirmed partial response. Decreased target lesion size was observed in 6 additional pts. **Conclusions:** PEN-866 was well tolerated and demonstrated preliminary evidence of antitumor activity. PEN-866 will be evaluated in Phase 2a expansion cohorts enrolling multiple solid tumors (NCT03221400). Clinical trial information: NCT03221400. Research Sponsor: Tarveda Therapeutics, Inc.

3516 Poster Discussion Session; Displayed in Poster Session (Board #246), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Utility of circulating tumor DNA (ctDNA) versus tumor tissue clinical sequencing for enrolling patients (pts) with advanced non-colorectal (non-CRC) gastrointestinal (GI) cancer to matched clinical trials: SCRUM-Japan GI-SCREEN and GOZILA combined analysis. *First Author: Akihiro Ohba, National Cancer Center Hospital, Tokyo, Japan*

Background: We recently reported that clinical assessment of genomic biomarkers using ctDNA had advantages over tumor tissue-based sequencing for enrollment into matched clinical trials across a wide range of GI cancers. Herein we investigated the utility of ctDNA in non-CRC cancers in a SCRUM-Japan GI-SCREEN and GOZILA combined analysis. **Methods:** In GI-SCREEN, tumor tissue samples of pts with non-CRC were analyzed by a next generation sequencing (NGS)-based assay, Oncomine Comprehensive Assay, since Feb 2015. In GOZILA, plasma samples of non-CRC pts were analyzed by an NGS-based ctDNA assay, Guardant360, since Feb 2018. **Results:** As of Apr 2019, 2,952 pts in GI-SCREEN and 633 pts in GOZILA were enrolled. Baseline characteristics between the groups were well matched except that GOZILA included more pancreatic ($P < 0.0001$) and liver cancers ($P = 0.016$) but fewer gastric cancers ($P < 0.0001$) and GIST ($P = 0.020$) than GI-SCREEN. The success rates of the tests were 86.6% in GI-SCREEN and 87.3% in GOZILA ($P = 0.649$). Median turnaround time (TAT) was 37 days in GI-SCREEN and 12 days in GOZILA ($P < 0.0001$). The proportion of cases with actionable alterations detected (tissue vs blood; 29.8% vs 46.8%, $P < 0.0001$) and enrolled into matched clinical trials (4.8% vs 6.5%, $P = 0.286$) for each group by cancer type are shown in the Table. Pts with upper GI cancers, especially those in GOZILA, were more often enrolled into matched trials; trial enrollment for those with hepatobiliary and pancreatic (HBP) or other cancers was similar regardless of testing method. Median time from GI-SCREEN or GOZILA enrollment to clinical trial enrollment was 5.0 and 1.0 months (mo), respectively ($P < 0.0001$). Objective response rates (ORR) and progression-free survival (PFS) were not significantly different (tissue vs. blood; ORR: 14.6 vs. 26.3%, P = 0.30: median PFS: 3.3 vs. 2.6 mo, P = 0.71). **Conclusions:** Clinical sequencing of ctDNA, with its shorter TAT, contributed to rapid enrollment of non-CRC pts into matched clinical trials compared to those tested by tumor tissue sequencing, particularly for those with upper GI cancer, without compromising efficacy. Clinical trial information: UMIN000029315.Research Sponsor: SCRUM-Japan.

	Actionable alterations-Tissue (n = 855)	Matched trial-Tissue (n = 41)	Actionable alterations-Blood (n = 292)	Matched trial-Blood (n = 19)
Upper GI	346 (23.4%)	24 (6.9%)	84 (35.3%)	14 (16.7%)
HBP	401 (36.6%)	14 (3.5%)	196 (56.8%)	5 (2.6%)
Others	108 (37.5%)	3 (2.8%)	12 (29.3%)	0 (0%)

3517 Poster Discussion Session; Displayed in Poster Session (Board #247), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Pan-tumor analyses of kinase fusions detected in circulating tumor DNA (ctDNA) and concordance with paired tissue. *First Author: Jessica Kim Lee, Foundation Medicine, Inc., Cambridge, MA*

Background: Oncogenic kinase gene fusions are targetable with approved and investigational therapies and can also emerge as acquired resistance (AR) to targeted therapy. To understand the clinical validity of liquid biopsy comprehensive genomic profiling (CGP) to detect kinase fusions, we compared patient-matched plasma and tissue-based CGP. **Methods:** Hybrid capture-based CGP was performed on 28,743 plasma and 325,131 tumor tissue samples in the course of clinical care. Complete exonic regions of 13 kinases involved in oncogenic fusions plus select introns in *ALK, EGFR, FGFR2/3, PDGFRA, RET,* and *ROS1* were sequenced to capture fusions with well characterized breakpoints. ctDNA fraction was estimated by maximum somatic allele frequency (MSAF). **Results:** 86% of cases had detectable ctDNA in plasma (MSAF > 0). Kinase fusions were detected in 2.1% of ctDNA cases (478/23,294) and were most prevalent in patients (pts) with bladder cancer (4.5%), non-small cell lung cancer (NSCLC) (4.3%), and cholangiocarcinoma (3.9%). The most commonly rearranged kinases were *ALK* (60%, 162/271) and *RET* (19%, 51/271) in NSCLC, *FGFR2* (85%, 11/13) in cholangiocarcinoma, and *FGFR3* (88%, 7/8) in bladder cancer. *ALK* fusions were detected in 26% (54/207) of fusion+ non-NSCLC cases. Paired tissue and ctDNA samples where ≥1 sample harbored a kinase fusion were available for 147 pts; median time between sample collection was 150 days (interquartile range: 444 days). Positive percent agreement (PPA) to tissue and liquid biopsies was 76% and 80%. Median MSAF in concordant and discordant ctDNA samples was 2.3% and 0.41% ($p = 0.04$) and median time between specimen collection for concordant and discordant pairs was 110 and 344 days ($p = 0.04$). PPA to tissue and liquid was 86% and 88% for pairs collected < 60 days apart (n = 53), versus 70% and 74% for pairs collected > 60 days apart. 6 pts with paired samples all collected > 196 days apart (median 593 days) had initial tissue samples with *EGFR* driver mutations and had an acquired kinase fusion (4 *ALK*, 1 *FGFR2*, 1 *FGFR3*) in the 2nd ctDNA sample, likely representing AR. **Conclusions:** Kinase gene fusions identified by tissue-based CGP were detected by liquid biopsy CGP in 85% of temporally-matched plasma samples. Kinase fusion detection by liquid biopsy CGP is feasible and had high PPA to tissue-based CGP. Subsequent sampling by liquid biopsy identified acquired fusions in *EGFR* driver positive cases consistent with known mechanisms of resistance to EGFR inhibitors suggesting utility of liquid biopsy at progression to identify targetable mechanisms of AR. Research Sponsor: Foundation Medicine.

3518 Poster Discussion Session; Displayed in Poster Session (Board #248), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Early plasma circulating tumor DNA (ctDNA) changes to predict response to first-line pembrolizumab +/- chemotherapy in non-small cell lung cancer (NSCLC). *First Author: Biagio Ricciuti, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: ctDNA shedding into plasma can be prognostic in lung cancer, and changes in plasma ctDNA levels correlate with response to systemic therapy. However, is unknown whether early detection of ctDNA levels change predicts response to first-line pembrolizumab +/- chemotherapy. We hypothesized that serial assessment of plasma ctDNA by next generation sequencing would enable early detection of response to immunotherapy in NSCLC prior to radiological assessment. **Methods:** Patients (pts) with advanced NSCLC who received first-line treatment with pembrolizumab +/- platinum doublet chemotherapy at the Dana-Farber Cancer Institute were enrolled in this study. Plasma collected from pts prior to starting therapy and serially after starting therapy was analyzed by NGS using enhanced tagged-amplicon sequencing (eTAm-Seq) of hotspots and coding regions from 36 genes (InVisionFirst-Lung). ctDNA allele fractions (AF) change was correlated with treatment responses. **Results:** Among 38 pts who received first-line pembrolizumab +/- platinum/pemetrexed, 9 (23.7%) had no ctDNA detected at baseline while 29 had alterations detected. Pembrolizumab was administered as monotherapy in 19 of the 29 pts (65.5%) and in combination with chemotherapy in 10 (34.5%). The median time to the first ctDNA assessment was 21 days (IQR:21-24). Pts who had a decrease in the max AF at the first blood drawn compared to pre-treatment AF had a significantly higher response rate to treatment with pembrolizumab +/- platinum doublet chemotherapy than those with an AF increase (64.5% vs 7.7%, $P < 0.01$). The median PFS (mPFS) and median OS (mOS) were significantly longer among pts with early AF decrease compared to those with an AF increase mPFS: 13.7 vs 3.4 months, HR:0.20, $P < 0.01$; mOS: 32.8 vs 14.7 months, HR:0.06, $P < 0.01$). The median change in allele fraction at the first on-treatment blood draw was -90% (range: -100 to +65), -71% (range: -100 to +100) and +35% (range: +17 to +100) in pts with subsequent radiological response (N = 11), stable disease (N = 11) and progressive disease (N = 7), respectively ($P < 0.01$). Among the 9 cases with no detected ctDNA at baseline, 2 pts with emergence of cfDNA within 8 weeks developed progressive disease. In the other 7 cases, ctDNA remained undetected. **Conclusions:** In pts with advanced NSCLC, rapid decreases in ctDNA prior to radiological assessment correlated with clinical benefit. These results suggest a potential role for ctDNA as an early pharmacodynamic biomarker of response or resistance to immunotherapies. Research Sponsor: None.

3519 Poster Discussion Session; Displayed in Poster Session (Board #249), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Acquired genomic alterations in circulating tumor DNA from patients receiving abemaciclib alone or in combination with endocrine therapy. *First Author: Matthew P. Goetz, Mayo Clinic, Rochester, MN*

Background: An understanding of the mechanisms of acquired resistance to CDK4 & 6 inhibitors, either alone or with endocrine therapy (ET), is an unmet need. Abemaciclib is a CDK4 & 6 inhibitor approved for treatment of HR+, HER2- advanced breast cancer (ABC). Here we evaluated acquired genomic alterations detected in circulating tumor DNA (ctDNA) from patients (pts) treated with abemaciclib + nonsteroidal aromatase inhibitor (AI) or placebo + AI in MONARCH 3 or abemaciclib monotherapy in nextMONARCH 1. **Methods:** MONARCH 3 randomized postmenopausal women with HR+, HER2- ABC with no prior systemic therapy in the advanced setting to abemaciclib (150 mg Q12H) or placebo + AI. nextMONARCH 1 randomized women with HR+, HER2- metastatic breast cancer who had progressed on or after prior ET and CT to abemaciclib (150 mg Q12H) + tamoxifen, abemaciclib (150 mg Q12H), or abemaciclib (200 mg Q12H) + loperamide. Plasma from pts in the abemaciclib or placebo + AI arms (MONARCH 3) or abemaciclib monotherapy arms (nextMONARCH 1) was analyzed by the Guardant360 assay to identify potential tumor-related genomic alterations including point mutations, indels, amplifications, and fusions acquired at EOT in comparison with baseline. **Results:** For MONARCH 3, commonly acquired alterations at EOT included *ESR1* (17%), *TP53* (10%), *EGFR* (8%), *FGFR1* (7%), and *PDGFRA* (7%) in the abemaciclib + AI arm, and *ESR1* (31%), *TP53* (10%), and *BRCA1* (7%) in the placebo + AI arm. Acquired alterations more frequent for abemaciclib + AI pts included *RB1* (6%), *MYC* (5%), and *AR* (5%), compared to 0% in the placebo + AI arm ($p = 0.008$ *RB1*; $p = 0.015$ *MYC* or *AR*). In contrast, acquired *ESR1* alterations were less frequent with abemaciclib + AI vs placebo + AI (17% vs 31%, $p = 0.038$). In nextMONARCH 1, the most commonly acquired alterations with abemaciclib monotherapy were in *TP53* (10%), *EGFR* (9%), *RB1* (9%), *MYC* (9%), and *MET* (8%). In addition, acquired alterations in *ESR1* (6%) and *AR* (3%) were also found. *PIK3CA* alterations were not frequently acquired (abemaciclib + AI 1%, placebo + AI 6%, abemaciclib monotherapy 5%). **Conclusions:** Acquired genomic alterations potentially associated with emerging mechanisms of resistance to abemaciclib alone or in combination with AI may include *RB1*, *MYC*, or *AR* alterations, while the acquisition of *ESR1* alterations was less common in pts treated with abemaciclib + AI compared to placebo + AI. These findings are hypothesis-generating and provide insight into mechanisms of resistance to abemaciclib vs ET. Clinical trial information: NCT02246621, NCT02747004. Research Sponsor: Eli Lilly and Company.

3520 Poster Session (Board #250), Fri, 8:00 AM-11:00 AM

An open-label, multicenter, phase II study of ceritinib in patients with advanced ALK+ non-lung solid tumors and hematological malignancies (ASCEND-10). *First Author: Victor Moreno, START Madrid-FJD, Fundación Jiménez Díaz University Hospital, Madrid, Spain*

Background: Prior studies have confirmed the efficacy and safety of ceritinib in patients (pts) with advanced *ALK*+ non-small cell lung cancer (Soria, et al, Lancet 2017; Shaw et al, Lancet Oncol 2017; Cho et al, JTO 2019). Ceritinib also demonstrated antitumor activity in pediatric pts with *ALK*+ inflammatory myofibroblastic tumor (IMT) and ALCL (Georger et al, ASCO 2015 [abstract#10005]). Long-term clinical benefits of ceritinib treatment were shown in pts with anaplastic large cell lymphoma (ALCL) (Richly et al, Blood 2015). The aim of the current study was to examine ceritinib efficacy and safety in pts with advanced *ALK*+ non-lung solid tumors and hematological malignancies. **Methods:** In this open-label, multi-arm, phase 2 (NCT02465528) trial, adult pts with *ALK* gene abnormalities who had received ≥1 prior systemic therapy were administered oral ceritinib 750 mg/day, under fasted conditions. Primary endpoint: investigator assessed disease control rate (DCR); secondary endpoints: investigator assessed overall response rate (ORR), duration of response (DOR), time to response (TTR), progression-free survival (PFS), and safety. **Results:** Overall, 22 pts (ALCL [n = 1], IMT [n = 4], glioblastoma multiforme [GBM, n = 12] and others [n = 5]) were enrolled; median (m) age: 52.5 years; male: 50%; Stage ≥IV: 95.4%. Key efficacy results are shown in the Table. mTTR in pts with confirmed complete response (CR) or partial response (PR) [n = 4] was 7.4 (range, 6–25) weeks. mDOR was not reached. mPFS (95% CI) was 2.6 (1.6, 3.7) weeks. Most common adverse events (AEs; ≥30%) were: diarrhea and nausea (59.1% each), vomiting (50.0%) and increased alanine aminotransferase (31.8%). Most common grade ≥3 AEs (≥10%): hyperglycemia (18.2%), increased gamma-glutamyl transferase, thrombocytopenia, and anemia (13.6% each). Clinical trial information: NCT02465528. **Conclusions:** Ceritinib 750 mg/day under fasted conditions showed antitumor activity in pts with *ALK*+ ALCL and IMT; however, data interpretation is limited due to the small sample size. Safety findings were consistent with the known ceritinib safety profile.Research Sponsor: Novartis.

	ALCL (n = 1)	IMT (n = 4)	GBM (n = 12)	Others* (n = 5)	All pts (n = 22)
CR, n (%)	1 (100.0)	0	0	0	1 (4.5)
PR, n (%)	0	3 (75.0)	0	0	3 (13.6)
SD, n (%)	0	0	0	2 (40.0)	2 (9.1)
ORR: CR+PR, % (95% CI)	100.0 (2.5, 100.0)	75.0 (19.4, 99.4)	0 (0, 26.5)	0 (0, 52.2)	18.2 (5.2, 40.3)
DCR: CR+PR+SD, % (95% CI)	100.0 (2.5, 100.0)	75.0 (19.4, 99.4)	0 (0, 26.5)	40.0 (5.3, 85.3)	27.3 (10.7, 50.2)

*Pts with primary tumor in soft tissue (n = 3), colon (n = 1) and stomach (n = 1).
SD, stable disease.

3522 Poster Session (Board #252), Fri, 8:00 AM-11:00 AM

Longitudinal cumulative dose: A novel measure to assess multiple dimensions of chemotherapy adherence over time. *First Author: Michael Webster-Clark, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Adjuvant chemotherapy regimens take months to complete. Despite this, trials and observational studies evaluate chemotherapy adherence via measures assessed at the end of treatment (e.g. number of patients missing any dose, relative dose intensity [RDI]). This approach misses information that impacts outcomes, like treatment delays. We propose longitudinal cumulative dose (LCD) as a way to integrate the impact of dose reductions, missed doses, and dose delays at each cycle over time. **Methods:** We obtained data from the 2,246 participants in the Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer (MOSAIC). We evaluated proportions of patients stopping treatment early and reducing (based on protocol), missing, or delaying a dose in each arm for each chemo agent at each visit. We obtained LCD, the fraction of the final standard dose a participant reached by a given day, for each participant and each chemo agent. We compared LCD medians over time and at the end of a standard regimen (24 weeks) between treatment arms and by age and performance status. We assessed agreement between oxaliplatin LCD and RDI with Fleiss' kappa (Table). **Results:** Participants randomized to FOLFOX were more likely than those randomized to 5FU to stop treatment, reduce doses, miss doses, or delay visits; these differences increased over time. Median LCD for oxaliplatin in the FOLFOX arm at 24 weeks was 77%. Graphs of median LCD for 5FU showed a clear difference between arms (FOLFOX arm median LCD: 81%; 5FU arm median LCD, 96%). While 5FU LCD decreased with age in the FOLFOX arm (median LCD in those age <40: 85%; 40-64, 82%; 65-75, 76%), it was similar across ages in the 5FU arm (median LCD 94%, 96%, and 96%, respectively), with smaller performance status trends. RDI and LCD showed fair agreement (Fleiss' kappa=0.34); 19% of those with RDI over 85% had LCD under 60%. **Conclusions:** Visualizing LCD highlighted the timing and scale of deviations from standard administration, with major differences in 5FU LCD across arms. Next steps include evaluating if LCD predicts clinical outcomes. Research Sponsor: Patient Centered Outcomes Research Institute.

Comparison of oxaliplatin LCD versus RDI.

	RDI <60%	RDI 60%-85%	RDI > 85%
LCD <60%	133	62	84
LCD 60%-85%	55	165	25
LCD >85%	10	244	332

3523 Poster Session (Board #253), Fri, 8:00 AM-11:00 AM

A phase Ib study of simmitecan (LP) single-agent and in combination with 5-fluorouracil/leucovorin (5-FU/LV) or thalidomide (T) in patients with advanced solid tumor. *First Author: Jifang Gong, Gastrointestinal Medical Oncology, Beijing Cancer Hospital, Beijing, China*

Background: Simmitecan (LP), a novel 9-substituted lipophilic camptothecin derivative, is a potent inhibitor of topoisomerase I with anti-tumor activity single agent or in combination with other anti-tumor agents, i.e. thalidomide or anti-PD-1 antibody in xenograft models. In this phase Ib study (NCT02870036), we evaluate the safety and anti-tumor effects of LP as monotherapy or in combination therapies in patients (pts) with advanced solid tumors. **Methods:** This open-label, multi-cohort phase Ib study was conducted at 3 academic centers in China. Eligible pts had advanced cancer without standard treatment options. Prior irinotecan treated failure pts was eligible. In the single agent study, enrolled pts was allocated to received intravenous(iv) 50, 80, or 120 mg/m^2 of LP Q2W to determine the safety of LP. After single agent study finished, enrolled pts allocated in LP+5-FU/LV cohorts received 50, 65, or 80 mg/m^2 of LP then LV 400 mg/m^2 and 5-FU bolus at 400 mg/m^2 followed by 5-FU continuous iv of 2400 mg/m^2 Q2W; pts in LP+T cohorts received LP 65 mg/m^2 Q2W + thalidomide 50mg QD or thalidomide 100mg QD, or LP 80 mg/m^2 Q2W + thalidomide 50mg QD. Treatment repeated in 28-day cycles until disease progression or unacceptable toxicity. **Results:** Between October 2016 to February 2019, 41 pts, median age of 55.1 (range 29-69) years, were enrolled, 13 in LP monotherapy, 10 in LP + 5-FU/LV and 18 in LP + T. Over all, no dose limited toxicity (DLT) occurred. The most common (≥20%) grade 3/4 AE among three regimens was neutropenia (44%, 70% and 89% respectively in LP, LP+5FU/LV and LP+T),and treatment related SAEs were similar, i.e. anemia and febrile neutropenia (11.1% each) in LP, diarrhea (10%) in LP+5-FU/LV, febrile neutropenia (5.6%) in LP+T. Majority of enrolled pts (24/41, 59%) had progressed on prior irinotecan, nevertheless, partial response (PR) was observed in 1 colorectal cancer pt treated with LP 80 mg/m^2 + thalidomide 50mg. Disease control rate (DCR, SD≥12 weeks or CR or PR) were 60%, 80% and 61% and median progress free survival were 2.71, 4.17 and 2.76 months respectively in LP, LP + 5-FU/LV and LP+T cohorts. **Conclusions:** This study showed the safety profiles are manageable, either LP monotherapy or combination therapies, no DLT or safety concern was elicited in combination compared to single agent, and the LP + 5-FU/LV regimen showed higher DCR. A phase II study in pts with metastatic NEC is on-going to explore safety and efficacy of LP + 5-FU/LV regimen combined with toripalimab, an anti-PD-1 antibody. Clinical trial information: 02870036. Research Sponsor: Shanghai HaiHe Pharmaceutical Co.,Ltd.

3524 Poster Session (Board #254), Fri, 8:00 AM-11:00 AM

Intratumoral exposure levels of pentaglutamated pemetrexed following treatment with LEAF-1401 and pemetrexed. *First Author: Gwangseong Kim, L.E.A.F. Pharmaceuticals LLC, Woburn, MA*

Background: The activity of pemetrexed is highly dependent on the intracellular enzyme folypolyglutamate synthase (FPGS) which adds glutamates to pemetrexed and yields very potent pemetrexed polyglutamates. Pemetrexed pentaglutamate (tetraglutamated pemetrexed) is 80-fold more potent than pemetrexed in inhibiting thymidylate synthase. Yet it is a poor drug candidate because it cannot readily cross the negatively charged cell membrane due to its own negative charge. We are developing LEAF-1401, a novel nanoliposomal encapsulation of gamma L-pentaglutamated pemetrexed. Because liposomes can readily be taken up by tumor cells, for its anti-tumor effect, LEAF-1401 can directly deliver pentaglutamated pemetrexed into tumor cells, bypassing the need for transmembrane folate carriers and FPGS which are both downregulated in resistant tumors. **Methods:** To measure drug levels in tumor, blood and various tissues (biodistribution), *in vivo* testing of LEAF-1401 and pemetrexed was conducted in a CT-26 murine colorectal carcinoma xenograft model. Animals were treated with a single dose of either LEAF-1401 (80mg/kg; equivalent to 32 mg/kg pemetrexed) or pemetrexed (118mg/kg). Tumor growth inhibition and clinical assessments were conducted. Animals were sacrificed: 5 mice per timepoint in each group and tumor, blood, liver, spleen and other tissues were harvested. Pentaglutamated pemetrexed levels were quantitatively analyzed by LC/MS/MS. **Results:** Compared to pemetrexed, LEAF-1401 treatment resulted in a 19-fold increase in exposure levels of pentaglutamated pemetrexed in the tumor and significant tumor growth inhibition. Plasma levels of pentaglutamated pemetrexed were high with LEAF-1401, but undetectable with pemetrexed. Like other liposomes, LEAF-1401 also resulted in accumulation of pentaglutamated pemetrexed in the liver and spleen (See Table below). Treatment appeared to be generally well tolerated. **Conclusions:** LEAF-1401, given at approximately a quarter of the equivalent pemetrexed dose, resulted in a 19-fold increase in pentaglutamate pemetrexed in tumor tissue compared to regular pemetrexed. LEAF-1401 represents a promising new class of novel nanoliposomal antifolates, that enhance the intratumoral delivery of potent polyglutamate antifolates, and improve antitumor activity while retaining an acceptable safety profile. Research Sponsor: L.E.A.F. Pharmaceuticals.

	Tissue Pentaglutamated Pemetrexed Levels (AUC: h*mg/mL)	
	LEAF-1401 dosed group	Pemetrexed dosed group
Tumor	0.38	0.02
Blood (plasma)	76.37	< LLOQ
Liver	9.22	< LLOQ
Spleen	1.35	0.0004

3525 Poster Session (Board #255), Fri, 8:00 AM-11:00 AM

Liquid biopsies to enable non-invasive real-time functional chemoresistance profiling in solid organ cancers. *First Author: Dadasaheb B Akolkar, Datar Cancer Genetics Limited, Nasik, India*

Background: Despite the development of targeted therapy agents and immune checkpoint inhibitors (ICI), cytotoxic anticancer agents remain the mainstay of treatment in several solid organ cancers. However, instances of innate and acquired resistance towards these anticancer agents can lead to treatment failures, which remain undetectable until clinical or radiological manifestation of symptoms suggestive of disease progression. There are presently no viable means or markers to detect or monitor for chemoresistance in real time. Owing to this unmet need, cancer treatment strategies face risks of failure and poor outcomes. **Methods:** We obtained 15 mL blood from 3,662 patients with various solid organ cancers, of various states and including treatment-naïve and pretreated patients. Circulating Tumor Associated Cells (C-TACs) were enriched and harvested from PBMCs using an epigenetically activating medium that is cytotoxic towards non-malignant epithelial and hematolymphoid cells in blood, but confers survival benefit on apoptosis resistant cells of tumorigenic origin (Circulating Tumor Associated Cells, C-TACs). In a subset of patients, fresh tumor tissue was also obtained from which viable tumor derived cells (TDCs) were obtained. Viable TDCs and C-TACs were treated with a panel of anticancer agents and the surviving cell fraction estimated to determine chemoresistance. **Results:** Among the 1,325 therapy naïve patients, resistance towards treatment agents was observed in C-TACs from 56.3 % of samples. Among 2,201 pretreated patients' samples, resistance towards treatment agents was observed in C-TACs from 77.8% of samples. The increased resistance in C-TACs from pretreated patients indicated that the C-TACs had been resistance-educated by prior therapies. In a subset of patients, Chemoresistance profile of C-TACs was observed to be 96.9% concordant with that of tumor derived cells (TDCs) which were concurrently obtained from tumor tissue indicating that C-TACs accurately represent chemo-antecedents of the tumor. **Conclusions:** Non-invasive chemoresistance profiling of C-TACs is a viable strategy to monitor treatment efficacy in real time. Adoption of this strategy in the clinic will not only guide treatment selection with reduced risk of failure, but will also enable timely therapeutic course correction upon detection of acquired chemoresistance. Research Sponsor: None.

3526 Poster Session (Board #256), Fri, 8:00 AM-11:00 AM

Pharmacokinetics, safety, and early activity of a nanoparticle micellar formulation of docetaxel in women with metastatic breast cancer: Results of two randomized trials (phase I and II). *First Author: Markus Joerger, Department of Oncology/Hematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland*

Background: Docetaxel micellar (DM) is a nano-sized particle formulation of docetaxel in which a retinoic acid derivative is used as solubilizer with a high drug to excipient ratio possibly resulting in reduced systemic toxicity or hypersensitivity reactions due to the excipient. DM is given without standard use of premedication, avoiding steroid-associated immunosuppression. Here we present the pharmacokinetics (PK) after a single dose of DM or polysorbate-solubilized docetaxel (D) as well as safety and early activity including overall response rate (ORR) in female patients with metastatic breast cancer. **Methods:** The PK study was a two-cycle, cross-over study where 30 patients were included and randomized to either DM followed by D or D followed by DM, both given as a 1-hour intravenous infusion at a dose of 100mg/m^2. The phase II study was a prospective, multicenter, open-label, third-party blinded, randomized, parallel group, active-controlled study including 200 patients to compare the early activity and safety of DM and D, both given as 100 mg/m^2 1-hour intravenous infusion every 21 days (1 cycle) for a total of 6 cycles. **Results:** Bioequivalence of total docetaxel in plasma, AUC0-last and Cmax, was demonstrated for DM compared to D. The incidence of adverse events was higher in the D arm than in the DM arm for the majority of SOCs and PTs in the phase II study. Overall, Grade 3 or 4 AEs were reported for 82.7% of patients from DM arm and 99.0% of patients from D arm. Twelve (12.2%) patients in the DM arm and 24 (24.0%) patients in the D arm needed at least one dose reduction due to AEs. The primary efficacy endpoint in the phase II study was based on the assessment according to Response Evaluation Criteria in Soldid Tumors (RECIST) 1.1 and non-inferiority was not reached based on the pre-defined non-inferiority margin. A post-hoc analysis investigating the ORR based on tumour assessment at the end of chemotherapy, and non-inferiority of DM as compared to D was shown (ITT population). **Conclusions:** DM is bioequivalent to D regarding total drug in plasma and provides a docetaxel formulation that spares patients steroid premedication. An improved safety profile for DM compared to D was shown while additional efficacy data is needed for future development of DM. Eudra CT: 2012-005161-12 and 2013-004889-33. Clinical trial information: 2012-005161-12 and 2013-004889-33. Research Sponsor: Oasmia Pharmaceutical AB.

3527 Poster Session (Board #257), Fri, 8:00 AM-11:00 AM

Liquid biopsy: A community-based oncology practice experience. *First Author: Khalil Choucair, Kansas University School of Medicine, Wichita, KS*

Background: Liquid biopsy is a promising and minimally invasive genetic test examining plasma circulating tumor DNA. Coupled with the rapidly developing next-generation sequencing (NGS) technologies, it holds the potential for implementation in selecting signal-matched therapeutic options. **Methods:** A retrospective chart review was conducted on adult patients with advanced solid tumors whose tumors were tested with Guardant360 assay, between December 2018 and December 2019. A total of 178 patients were referred for testing by 12 oncologists within a single community cancer center. **Results:** Referral rates varied widely (2.25% - 22%). The majority of patients (98%) were tested upfront for molecular marker evaluation, in either newly diagnosed advanced cancer patients, or in recurrent patients without enough tissue for testing. Other patients (2%) were evaluated after failure of 1 st line therapy to assess for acquired mutations. A total of 18 histological types were tested, with lung (LCa; n = 90; 50.56%), breast (BCa; n = 31; 17.42%), and colorectal (CRCa; n = 14; 7.87%) cancers being the most common types. In 86.11% of all tests (n = 180), $\geq$ 1 alteration was detected, while 13.89 % of tests did not reveal any tumor-related mutation, and were considered negative. The average number of alterations per test was 3.1 ($\pm$2.14; n = 481), and varied across types: CRCa (4.36), prostate cancer (2.73), BCa (2.97), and LCa (2.59), had the highest average number of alterations per test. Similarly, LCa (48.44%), BCa (19.13%), and CRCa (12.68%), harbored most of the detected somatic alterations (n = 481). Of all the alterations of practical significance (n = 457), *TP53* (32.17%), *PIK3CA* (8.53%), *EGFR* (7.66%) and *KRAS* (7.22%), were the most commonly altered genes. Only 1 patient had a positive MSI-H status, amenable to immune-therapy. Of those with positive test results (n = 155), 31 (20%) had $\geq$ 1 FDA approved, target-matched therapeutic opportunity. Similarly, 71 patients (45.81%) had $\geq$ 1 target-matched therapeutic opportunity, outside current indications. Lastly, when no FDA-approved target-matched therapy was available (n = 39), results from liquid biopsy testing offered signal-based clinical trial opportunity in 39/39 patients. **Conclusions:** Implementation of NGS-based liquid biopsy testing is feasible within a community practice. In the era of precision oncology, such assays have the potential to expedite the efforts towards target-matched therapies and signal-based clinical trial opportunities. Further studies are warranted to identify the most-cost effective testing strategies. Research Sponsor: None.

3528 Poster Session (Board #258), Fri, 8:00 AM-11:00 AM

Exosomal circular RNAs derived from serum: Promising biomarkers for therapeutic targets and prognosis of triple-negative breast cancer (TNBC). *First Author: Sujin Yang, Department of General Surgery, the First Affiliated Hospital with Nanjing Medical University, Nanjing, China*

Background: Exosomes are well known by the "exosomal shuttle" that delivers oncogenic microRNAs (miRNAs), mRNAs, circular RNAs (circRNAs) and proteins to the recipient cells and tumor microenvironment, and may be used as promising biomarkers for disease diagnosis. This study aims to provide a theoretical basis to use stable exosomal circRNAs as new biomarkers for predicting the development, metastasis and therapeutic targets of TNBC. **Methods:** A strategy combining RNA-sequencing technique, bioinformatic analysis and RT-qPCR was used to determine the level of differential expressed circRNAs in serum exosomes samples (n = 43) from TNBC patients compared with non-TNBC patients. The expression of circHSDL2 were also detected in tumor tissues (n = 20) from TNBC patients and breast cancer cell lines by qRT-PCR. Cell cycle analysis, the wound healing assays and transwell assays were used to investigate the function of circHSDL2 in proliferation, invasion and metastasis of TNBC cells. FISH, dual-luciferase reporter and functional assays were performed to confirm the interaction between circHSDL2 and let-7a-2-3p in TNBC cells. **Results:** We profiled the circRNAs in the serum exosomes samples from TNBC patients and non-TNBC patients by RNA sequencing and detected 803 significantly differentially-expressed circRNAs. After bioinformatic analysis, circHSDL2 was chose to further study. RT-qPCR results showed that higher expression of circHSDL2 in TNBC cell lines and tumor tissues from TNBC patients. Moreover, overexpression of circHSDL2 promoted TNBC cells proliferation and invasion, while knockdown of circHSDL2 inhibited TNBC cells proliferation and invasion. Mechanistically, circHSDL2 acted as a "miRNAs sponge" to absorb let-7a-2-3p; let-7a-2-3p inhibited TNBC cell invasion and metastasis. Kaplan-Meier plots showed lower expression of let-7a-2-3p was connected to poor prognosis in TNBC metastasis patients from TCGA database. **Conclusions:** The expression of circHSDL2 was found significantly upregulated in serum exosomes and tumor tissues from TNBC patients. Moreover, circHSDL2 could promote cell proliferation, invasion and metastasis in TNBC cells. CircHSDL2 might be function as competing endogenous RNAs (ceRNAs) by targeting let-7a-2-3p in the progression of TNBC. Therefore, this study provides a fresh perspective on novel therapeutic targets and potential biomarkers for TNBC from exosomal circRNAs. Research Sponsor: National Natural Science Foundation of China (No. 81872365).

3529 Poster Session (Board #259), Fri, 8:00 AM-11:00 AM

MSK-ACCESS for noninvasive somatic mutation profiling of lung cancers utilizing circulating tumor DNA. *First Author: Emily S. Lebow, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Circulating cell-free DNA (cfDNA) next-generation sequencing (NGS) is a promising strategy for non-invasive molecular profiling of cancers. MSK-ACCESS (Analysis of Circulating cfDNA to Evaluate Somatic Status) is a hybridization-capture targeted NGS assay that detects somatic variants in select exons of 129 genes with matched white blood cell sequencing. We present the initial clinical experience with MSK-ACCESS among patients with advanced non-small cell lung cancer (NSCLC). **Methods:** Patients with stage IV NSCLC underwent prospective MSK-ACCESS testing at initial diagnosis or progression of disease on targeted therapy between June 2019 and January 2020. A subset of patients had matched tissue-based NGS testing with the MSK-IMPACT 468 gene assay. We assessed oncogenic driver detection, turnaround time, plasma-tissue concordance, and matching to therapy. National Comprehensive-Cancer Network designated driver alterations were included in evaluation of tissue-plasma concordance (EGFR, ALK, KRAS, MET, RET, BRAF, HER2, ROS1, NTRK). Turnaround time was compared by a two-sided Wilcoxon signed-rank test. **Results:** A total of 201 patients with NSCLC had MSK-ACCESS testing at initial diagnosis (n = 79) or following progression of disease (n = 122). The median turn-around-time from plasma collection to MSK-ACCESS report was 16 days (range: 9 – 36 days) compared to 19 days from lab receipt of tissue to report (range: 12 – 57) for MSK-IMPACT ($p < 0.001$). Among patients with a driver detected on MSK-ACCESS, 100% (92/92) had an identical driver detected on MSK-IMPACT. Among patients with a driver detected on MSK-IMPACT, 75% (92/123) had an identical driver detected on MSK-ACCESS. This rate was similar among patients who were treatment-naive (74%; 64/86) and had disease progression (76%, 28/37) at the time of MSK-ACCESS. MSK-ACCESS identified driver alterations that directly guided first-line targeted therapy (n = 18) with response in all patients with available radiographic follow-up (n = 10), including a patient without confirmatory tissue testing. MSK-ACCESS identified resistance alterations among patients with disease progression including EGFR T790M, EGFR C797S, ROS1 G2032R, as well as a BRAF fusion. **Conclusions:** MSK-ACCESS successfully identified driver alterations with high concordance to tissue-based testing, directly guided patients to therapy with clinical responses, and detected known and novel resistance mechanisms. This assay warrants further clinical development to guide and facilitate precision oncology. Research Sponsor: None.

3530 Poster Session (Board #260), Fri, 8:00 AM-11:00 AM

Exploitation of treatment induced tumor lysis to enhance sensitivity of ctDNA analysis: A first-in-human pilot study. *First Author: Daniel Adam Breadner, London Regional Cancer Program, London, ON, Canada*

Background: Blood based liquid biopsies examining circulating tumour DNA (ctDNA) have increasing applications in non-small cell lung cancer (NSCLC). Limitations in sensitivity remains a barrier to ctDNA replacing tissue-based testing. There is a paucity of data regarding the dynamics of ctDNA levels in the hours to days following a new treatment. We hypothesize that chemotherapy or radiation will yield an increased abundance of ctDNA in plasma by inducing tumor lysis, allowing for the detection of genetic alterations that were occult in baseline testing. **Methods:** Two prospective cohorts of 20 patients (pts) with stage III/IV NSCLC were enrolled. Cohort 1 (C1) contained pts starting the first cycle of platinum doublet chemoradiation (C1a, n=10) or the first cycle of platinum doublet cytotoxic chemotherapy ± immunotherapy without radiation (RT) (C1b, n=10). Cohort 2 (C2) contained pts receiving palliative RT alone. Two baseline samples were collected, the first ≤ 14 days prior to starting treatment and one immediately prior to treatment. In C1, subsequent samples were collected 3, 6, 24 and 48 hours post initiation of chemotherapy. Pts in C2 had samples collected immediately prior to RT fractions 2, 3, and 4. Samples were analyzed for ctDNA using the 36-gene amplicon-based NGS Inivata InVisionFirst-Lung assay. **Results:** Complete results were available for the first 35 of 40 enrolled pts, C1a – 10 pts, C1b – 9 pts, C2 – 16 pts. Detectable ctDNA was present at baseline in 27 pts (77%), 4 additional pts (11%) had detectable ctDNA in post treatment samples. Four of the patients with detectable ctDNA at baseline (15%) had new genetic alterations detected in post treatment samples. A total of 8/35 pts (23%) had new genetic alterations detected in the post treatment samples. Mutant molecule numbers increased with treatment in 23 of 31 (74%) pts with detectable ctDNA, C1 - 13 of 19 pts (68%) and C2 - 10 of 16 pts (63%). ctDNA levels peaked a median of 2.2 hours (IQR: 1.5 – 2.9 hours) after the initiation of chemotherapy and a median of 1 day (IQR: 1-2 days) after radiation was commenced. The percentage increase in ctDNA levels was a median of 29% (IQR: -18 to +112%) in C1. C2 had a median increase of 16% (IQR: 0 to +131%). **Conclusions:** ctDNA levels increase in the hours to days after starting treatment. ctDNA testing in the acute post treatment phase can yield results that were not evident in pretreatment testing. Application of this principle could improve ctDNA utility as an alternate to tissue-based testing and improve sensitivity for the detection of treatment-resistant clones. Research Sponsor: None.

3531 Poster Session (Board #261), Fri, 8:00 AM-11:00 AM

Longitudinal and personalized detection of circulating tumor DNA (ctDNA) for monitoring efficacy of atezolizumab plus bevacizumab in patients with unresectable hepatocellular carcinoma (HCC). *First Author: Chih-Hung Hsu, National Taiwan University Cancer Center, Taipei City, Taiwan*

Background: ctDNA has emerged as a promising biomarker for noninvasive monitoring of treatment response and disease progression in many tumor types. However, the clinical use of ctDNA in patients with HCC has not been established. Here, we evaluated longitudinal and personalized detection of ctDNA for monitoring the treatment response to atezolizumab (atezo) + bevacizumab (bev) in patients with unresectable HCC not previously treated with systemic therapy. **Methods:** A subset (n = 48) of 104 patients with HCC who enrolled in Arm A of GO30140 (NCT02715531; Phase 1b) and received atezo + bev treatment were included in this study. These patients had 10 CR, 11 PR, 12 SD and 15 PD per IRF-assessed RECIST 1.1. Serial plasma samples were collected at baseline (Cycle [C]1 Day [D]1), during treatment (C2D1, C4D1) and at disease progression. Somatic mutations in individual tumors were identified via whole exome sequencing of archival tumor tissues or fresh biopsies collected before treatment. Personalized ctDNA assays (Signatera 16-plex multiplex PCR next-generation sequencing assay) specific to each patient's tumor mutational signatures were successfully designed for 47 of 48 patients. **Results:** At C1D1, a median of 25.7 ng of cell-free DNA was extracted from 2-mL plasma samples. ctDNA was detected in 45 of 47 patients (96%), with a median of 70.6 mean tumor molecules/mL of plasma (MTM/mL) and a median of 1.8% mean variant allele frequency (mean VAF) in plasma. Higher ctDNA levels detected at C1D1 appeared to be associated with increased tumor burden ($P < 0.03$). Dynamic changes in ctDNA levels post-treatment were associated with response at C4D1. ctDNA status changed from positive at baseline to negative in 7 of 10 CR (70%), 3 of 11 PR (27%), 1 of 11 SD (9%) and 0 of 11 PD (0%) patients. Longer PFS was observed in patients whose ctDNA became undetectable post-treatment. The median PFS in patients with ctDNA present vs cleared at C4D1 was 6.5 months and not reached, respectively (HR, 12 [1.7-93], log-rank $P < 0.00029$). **Conclusions:** Our study showed that Signatera, a personalized and tumor-informed ctDNA assay, could be used as a sensitive method for detecting ctDNA in patients with unresectable HCC. More importantly, our results illustrate the promise of ctDNA as an emerging biomarker that may potentially help to monitor treatment responses and disease progression in patients with HCC. Research Sponsor: F. Hoffmann-La Roche, Ltd.

3532 Poster Session (Board #262), Fri, 8:00 AM-11:00 AM

Comprehensive genomic profiling of 216 Chinese patients with renal cell carcinoma. *First Author: Congwang Zhang, GloriousMed Technology Co., Ltd., Shanghai, China*

Background: Renal cell carcinoma (RCC), a global public health problem, has exhibited a gradual rise in incidence. Unfortunately, the scarcity of effective biomarkers in the clinical became a major limitation of the progress of biological therapies. Therefore, it is imperative to accurately comprehend RCC genomic profiling for exploring its clinical treatment strategies. **Methods:** Formalin Fixed Paraffin Embedded (FFPE) tumor and matched blood samples of 216 Chinese RCC patients were obtained for next-generation sequencing (NGS)-based 620 cancer genes panel assay and RCC genomic profiling was evaluated. **Results:** In our Chinese RCC cohort, multiple histological subtypes, encompassing clear cell (96/216, 44.44%), papillary (14/216, 6.48%), chromophobe (2/216, 0.93%), and undefined subtypes (104/216, 48.15%) were included. The top ranked genomic alterations in Chinese RCC patients were VHL (45.83%), PBRM1 (17.1%), BAP1(13.89%), TP53 (10.65%), SETD2 (9.29%), MTOR (8.67%), ARID1A (5.6%), PTEN (5.09%). Interestingly, BAP1, PBRM1 were co-mutated with VHL, and MET, NF2 were mutually exclusive with VHL (all $p < 0.05$). Of these patients, 87.9% (190/216) of RCC patients had at least one genomic alteration, indicating the potential clinical benefits of targeted therapies. Out of 15 most common canonical pathways, potentially targetable genomic alterations were mainly identified in HIF (45.83%), chromatin remodeling (42.59%), PI3K/AKT (24.07%), DNA damage response (19.44%), RTK-RAS (18.06%), TP53 (15.74%), NOTCH (9.72%), Hippo (9.72%), and WNT (5.56%) pathway. Additionally, HIF pathway was commonly co-altered with chromatin remodeling pathway, and WNT and NOTCH pathways were significantly co-altered with TP53 pathway. Rare mutation types such as CDKN2A-DMRTA1 and HOOK1-ALK were also detected. Across samples, the median TMB was 2.2 (0-18.6) mutations/Mb. Only 2 Chinese RCC patients had TMB-high (> 10 mutations/Mb). **Conclusions:** Our results displayed the landscape of genomic alterations in 216 Chinese RCC patients. The genomic alterations identified in our study may provide an opportunity to discover potential strategies for targeted and immunotherapy in RCC. Future studies should account for these genomic alterations. Research Sponsor: None.

3533 Poster Session (Board #263), Fri, 8:00 AM-11:00 AM

Genomically informed longitudinal monitoring of circulating tumor DNA (ctDNA) to predict outcomes of cancer therapy. *First Author: Mohamed Alaa Gouda, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Short fragments of ctDNA can be detected and quantified from blood samples of patients with cancer. We hypothesize that dynamic changes in quantity of ctDNA in patients with advanced solid cancers during the first few weeks of therapy can predict treatment outcomes reported by standard imaging. **Methods:** We enrolled patients with advanced cancers treated with experimental therapies, who had blood collection for ctDNA isolation and testing at baseline, mid-cycle and at the time of restaging imaging. Patients who were treated with multiple treatment lines were included with separate record for each therapy. Genomically informed molecular testing of ctDNA was performed using unamplified droplet digital PCR (QX200, Bio-Rad) designed based on known molecular profile of tumor tissue and ctDNA was quantified as aggregate variant allele frequency (VAF%) for detected molecular aberrations. Patients were classified based on results of their first restaging imaging as responders (complete [CR] or partial response [PR]) vs. non-responders (stable disease [SD], progressive disease [PD]) and progressors (PD) vs. non-progressors (CR, PR, SD). **Results:** Total of 85 patients who received 132 courses of therapies between May 2012 and June 2019 were analyzed. Breast (N = 21), melanoma (N = 14) and cholangiocarcinoma (N = 14) were most frequent tumor types. Aggregate VAF at mid-cycle was higher in non-responders (3.98%) compared to responders (0.40%, P = 0.016) and in progressors (4.40%) compared to non-progressors (2.10%, P = 0.019) as measured by 5% trimmed mean. Similarly, aggregate VAFs at first imaging restaging was higher in non-responders (5.10%) compared to responders (0.10%, P = 0.001) and in progressors (10.80%) compared to non-progressors (0.90%, P < 0.001). Progressors demonstrated increase in ctDNA VAF at the time of the first imaging restaging compared to decrease in non-progressors (0.7% vs. -4%, P = 0.015). In addition, increase in ctDNA VAF at the first imaging restaging was associated with more PD (44% vs. 8%, P = 0.019) and less PR/CR (0% vs. 31%, P < 0.001). Median time-to-treatment failure was shorter in patients with increase in ctDNA VAF at the time of the first imaging restaging (52 days vs. 89 days, P = 0.002). **Conclusions:** Dynamic changes in quantity of blood-derived ctDNA within the first few weeks of therapy correspond with treatment outcomes reported by the first restaging imaging and time-to-treatment failure. Research Sponsor: NCI NIH Cancer Center support grant, Rising Tide Foundation, Sabin Family Foundation.

3534 Poster Session (Board #264), Fri, 8:00 AM-11:00 AM

Subcellular partitioning of Kaiso (ZBTB33) as a biomarker to predict overall breast cancer survival. *First Author: Sandeep K Singhal, Department of Pathology, School of Medicine and Health Sciences, University of North Dakota, Grand Forks, ND*

Background: The epigenetic transcriptional regulator, Kaiso (ZBTB33) has been identified as a member of the C2H2 zinc finger proteins containing a BTB/POZ -zinc finger family of transcription factors that are implicated in development of cancer. Although, our understanding of clinical relevance of subcellular distribution (cytoplasmic/nuclear) Kaiso in the growth and survival of human Breast cancer (BC) is limited. **Methods:** We examined a cohort of 555 BC patients who underwent surgery for their primary BC in Greenville, NC using AI and SM approach. **Results:** The sub-classification BC shows, cytoplasmic Kaiso is differentially enriched in ER- BC (p=0.001) compared nuclear Kaiso (p=0.8) and is significantly enriched in the more aggressive classes LumB (p=0.0017), HER2+ (p=0.05) and TNBC (p=6.1e-07) with respect to LumA BC patients. Additionally, the survival analysis of different compartments of Kaiso demonstrates that high cytoplasmic Kaiso (HR = 16.29 (7.6 – 34.8), p = 5.5e−13) is much more predictive of poor survival compared to nuclear Kaiso (HR = 2.83 (2.02 – 3.8), p = 6.1e−11). At gene expression level, ZBTB33 mRNA levels do not correlate with either nuclear (Spearman correlation: -0.03157, p= 0.7267) or cytoplasmic levels (Spearman correlation: -0.03526, p= 0.6962) of Kaiso. Surprisingly, ZBTB33 mRNA abundance is predictive of poor overall BC survival as demonstrated in two independent publicly available BC cohorts Metabric (HR = 2.14 (1.49 − 3.08), p = 2.7e−05) and Gyorffy B et al. (HR = 1.81 (1.55 − 2.12), p = 2.5e−14). Nuclear and cytoplasmic levels of Kaiso do not show significant differences based on race p=0.27 and p=0.1 respectively. **Conclusions:** Our data suggest subcellular distribution of high Kaiso is associated with poor prognosis of BC survival and subcellular localizations of Kaiso may play differential biological roles in BC prognosis. Research Sponsor: the NCI and the National Institute on Minority Health and Health Disparities, Bethesda Maryland, 20892, The NIH/NCI Cancer Center Support Grant P30CA013696, the Susan G. Komen (Sponsor ID: SAC160072) Grant in support of the Triple-Negative Breast Cancer i.

3535 Poster Session (Board #265), Fri, 8:00 AM-11:00 AM

Circulating stromal cells as a potential blood-based biomarker for screening invasive solid tumors. *First Author: Daniel Adams, Creatv MicroTech, Inc., Monmouth Junction, NJ*

Background: Peripheral blood allows for a simple non-invasive method for isolating various cancer associated circulating stromal cells (CStCs) which may predict for cancer presence. Cancer Associated Macrophage-Like cells (CAMLs), a specific CStC, are phagocytic myeloid cells that derive from an immunological response to cancer and emanate from primary tumors. Using a filtration platform we screened the peripheral blood of untreated newly diagnosed cancer patients (n = 308) for CAMLs. In parallel, we screened patients with newly diagnosed non-malignant diseases, i.e. lupus, benign cysts, etc. (n = 39), and healthy control samples (n = 76). We found that CAMLs are highly prevalent (87%) in the blood of cancer patients, but uncommon in non-malignant conditions (20%) & absent in healthy individuals (0%). **Methods:** Anonymized peripheral blood were taken from 308 cancer patients after confirmation of invasive malignancy [stage I (n = 76), stage II (n = 73), stage III (n = 72), stage IV (n = 65) and unstaged non-metastatic (n = 22)] with pathologically confirmed lung (n = 65), pancreas (n = 53), breast (n = 52), prostate (n = 40), esophageal (n = 30), renal cell (n = 18), hepatocellular (n = 15), neuroblastoma (n = 10), melanoma (n = 8), and other (n = 17). Further, anonymized blood was taken from patients with untreated non-malignant conditions including benign breast masses (n = 19), lupus (n = 11), liver cirrhosis (n = 5), benign prostatic hyperplasia (BPH) (n = 3), and viral infection (n = 1); or from healthy control volunteers (n = 76). CAMLs were isolated from whole peripheral blood by the CellSieve™ microfiltration technique and defined as enlarged, multinuclear cells with cytokeratin and/or CD45/CD14 positive. **Results:** CAMLs were found in 87% of all cancer patients regardless of stage, ~5.4 CAMLs/7.5mL blood. Specifically, CAMLs were found in 80% of Stage I, 90% Stage II, 89% Stage III, and 97% Stage IV patients. No CAMLs were found in any healthy controls, but were found in 26% of benign breast masses, 18% of lupus, 0% of BPH and 0% of cirrhosis. In total, CAML sensitivity in cancer vs healthy was 87% (CI95% 82-90%), specificity = 100% (CI95% 95-100%), PPV = 100% (CI95% 100%), NPV = 67% (CI95% 58-71%). CAML sensitivity in cancer vs benign was 87% (CI95% 82-90%), specificity = 80% (CI95% 64-91%), PPV = 97% (CI95% 95-98%), NPV = 43% (CI95% 35-51%). **Conclusions:** CAMLs, a Circulating Stromal Cell subtype, is a sensitive blood based biomarker found in all stages of cancer that is rare in non-malignant conditions and absent in healthy individuals. Research Sponsor: U.S. National Institutes of Health, Other Government Agency.

3536 Poster Session (Board #266), Fri, 8:00 AM-11:00 AM

Clinical potential of ctDNA-based TMB in small cell lung cancer recieving chemoradiotherapy. *First Author: Ying Jin, Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, Department of Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences & Zhejiang Cancer Hospital, Zhejiang Key Laboratory of Radiation Oncology, Hangzhou, China*

Background: Small cell lung cancer (SCLC) is an aggressive tumor with poor prognosis. Chemotherapy and / or radiotherapy is the main choice of SCLC treatment. Circulating tumor DNA (ctDNA) has received substantial attention in recent years owing to the potential of patient stratification and monitoring. Here, we assessed the value of prediction and prognosis using ctDNA in SCLC. **Methods:** SCLC patients (pts) with limited-stage disease (LD) receiving chemoradiotherapy and extensive-stage disease (ED) receiving chemotherapy were enrolled. Baseline plasma samples were collected for NGS using a 1021-gene-panel. Mutational features and blood-based tumor mutation burden (bTMB) were analyzed using ctDNA. pyClone software was used to cluster the mutations. The mutations in the cluster with the highest cancer cell fraction (CCF) were defined as clonal mutations. Progression-free survival (PFS) was followed. **Results:** 58 SCLC pts (35 LD and 23 ED) and 58 plasma samples were enrolled. Smoking pts accounted for 84% (49/58). In all samples, recurrent genes were TP53 (86%), RB1 (57%), LRP1B (34%), CREBBP (26%), and MLL3 (22%). The median of bTMB and clone count were 7.9 [0-26] and 7 [0-25]. Significant higher bTMB and clone count were observed in ED pts compared with LD (Mann Whitney test, p = 0.019 and p = 0.041, respectively). Mutated *CREBBP* (10/23 ED versus 5/35 LD) was enriched in ED (Fisher exact test, p = 0.017 and OR = 0.223). Mutations in NOTCH signaling pathway were enriched in ED (l6/23 ED versus 13/35 LD, p = 0.031, OR = 0.265). In LD group, there were trend toward prolonged PFS in pts with higher bTMB(p = 0.065), and pts with higher clonal bTMB (cbTMB) exhibited significant longer PFS (p = 0.016, HR 0.37, 95% CI [0.12-1.11]). Patients with alteration in PIK3CA showed shorter PFS than wild type (p < 0.001, HR 0.11, 95% CI [0-2.86]). There were no significant difference in median PFS in LD stage pts with any detectable pathway alterations. Whereas, LD pts whose ctDNA contained RTK-RAS signaling pathway alterations exhibited shorter PFS than pts without those alterations (p = 0.135). In ED pts, NOTCH1 gene wild type displayed longer PFS than mutant type (p = 0.036, HR 0.38, 95% CI [0.1-1.53]). There were no difference in PFS between pts with higher and lower bTMB and cbTMB. **Conclusions:** ctDNA can characterize the mutational feature of SCLC. There are differences in the molecular characteristics between ED and LD pts. Clonal bTMB is a potential prognostic biomarker for LD SCLC chemoradiotherapy. The prognostic marker of ED chemotherapy is different from LD. Research Sponsor: None.

3537 Poster Session (Board #267), Fri, 8:00 AM-11:00 AM

Circulating tumor DNA dynamics to predict cancer recurrence/metastasis in Chinese pathologic stage I lung adenocarcinoma. *First Author: Chao Cheng, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*

Background: Pathologic(p)stage I lung adenocarcinoma (LUAD) patients exhibit high levels of genetic heterogeneity and the association between the genomic characteristics of (p)stage I LUADs and tumor recurrence remains poorly understood. Circulating tumor DNA (ctDNA) monitoring after resection represents a useful tool to predict response to therapy and tumor recurrence but its application in (p)stage I LUAD patients remains controversial. In addition, it is of great clinical interest to decipher the difference of genetic features between ground-glass opacity (GGO) and solid nodules (non-GGO) subgroups. **Methods:** Tumor tissues and matched post-operative plasma samples were collected from a total of 86 Chinese (p)stage I LUAD patients who were enrolled in a clinical study (NCT03172156). Comprehensive genomic profiling was performed using capture-based hybrid next generation sequencing by targeting 422 cancer relevant genes. **Results:** *EGFR* and *TP53* represent commonly mutated genes in this cohort of (p) stage I lung adenocarcinoma, followed by alterations in *ALK*, *PIK3CA*, *STK11*and *MYC*. For a median follow up period of 21.54 months after surgical resection, we observed that ctDNA positivity significantly correlated with an increased probability of early tumor recurrence or metastasis (P= 0.03, HR = 7.9), and in particular, the *EGFR* mutation status of ctDNA samples rather than that of primary tumor samples significantly correlated with shorter disease-free survival (DFS). Further comparison between GGO and non-GGO subgroups indicated that the frequency of *TP53* mutations in non-GGO was markedly higher than that in GGO (48% vs 20%, $P<$ 0.05). In addition, pathway analysis showed that the epigenetic regulation pathway was more frequently affected in the GGO subgroup, while impaired apoptosis/cell cycle pathway was more enriched in the non-GGO LUADs. **Conclusions:** Our data show that ctDNA positivity, including the *EGFR* mutation status, significantly correlated with early relapse or metastasis after surgery, representing a useful tool to predict treatment response and tumor relapse in (p)stage I LUAD patients. Mutated *TP53* was more abundant in non-GGO comparing to GGO (p)stage I LUADs that may act as potential oncogenic driver in LUAD development and/or disease progression. Clinical trial information: NCT03172156. Research Sponsor: National Natural Science Foundation of China (81572391), National Natural Science Foundation of China (11671409) and the Project for Science and Technology Development of Guangdong Province, China (2017A020215167).

3538 Poster Session (Board #268), Fri, 8:00 AM-11:00 AM

Evaluation of Genexus system that automates specimen-to-report for cancer genomic profiling within a day using liquid biopsy. *First Author: Siew-Kee Kee Low, Cancer Precision Medicine Center, Japanese Foundation for Cancer Research, Tokyo, Japan*

Background: Genomic profiling of patients' tumors using NGS system help in facilitating molecular-guided therapy. The turnaround time from specimen to report by the NGS system is important to deliver result timely for clinical decisions. The Genexus Integrated Sequencer automates all steps of the targeted NGS workflow starting from nucleic acid of formalin-fixed paraffin-embedded tissues or plasma that significantly reduce laborious procedures. Importantly, the whole specimen-to-report workflow delivers results in a single day. In this study, we evaluated detection rate of alteration using Oncomine Precision Assay (OPA) on Genexus system with cell-free DNA (cfDNA) from non-small cell lung cancer (NSCLC). **Methods:** Among the cfDNA from 48 plasma samples of NSCLC were evaluated, 19 were newly-diagnosed cases with *EGFR* mutations in cancer tissues and 29 cases were patients who experienced progression of disease after first line of EGFR, ALK or ROS1-targeted therapy. 13-20ng of input cfDNA were subjected to automated Genexus Integrated Sequencer for library construction using OPA panel, templating and sequencing. OPA panel covers actionable hotspot mutations, copy number gains or loss, fusion drivers. The concordance of mutation profiles between the tumor tissue and cfDNA and detection of a resistance mutation(s) during molecular-targeted therapy were evaluated. **Results:** The sequencing resulted in median overall reads of 8,698,358, median overall depth of 30,648 (range 15,069-48,707) and median molecular coverage of 1,595 (range 859-2,550). Among 48 samples examined, 44 were detected to carry at least one somatic mutation, giving the detection rate of 92%. A total of 17 of 19 newly diagnosed EGFR-positive patients were also detected to carry *EGFR* mutations. Importantly, these 17 patients carry the same mutation that was found in tissue samples implying complete concordance. In addition, we found novel resistance mutations in plasma of the patients who were under EGFR, ALK or ROS1 targeted therapies. **Conclusions:** Genexus Integrated Sequencer is a fully automated and highly accurate NGS system with a 1-day turnaround time that could assist clinicians to make more timely decision. Novel actionable, resistance mutations were detected using OPA panel that provide potential options for molecular-guided therapy and may help the better understanding of resistance mechanism of targeted therapy. Research Sponsor: Council for Science, Technology and Innovation (CSTI), cross-ministerial Strategic Innovation Promotion Program (SIP), "Innovative AI Hospital System".

3540 Poster Session (Board #270), Fri, 8:00 AM-11:00 AM

A pan-cancer analysis of ARID1A as a potential biomarker for immune checkpoint therapy. *First Author: Dongyong Yang, Department of Pulmonary and Critical Care Medicine, Second Affiliated Hospital of Fujian Medical University, Quanzhou, China*

Background: AT-rich interactive domain 1A (ARID1A), encoding a subunit of the BAF (SWI/SNF) chromatin remodeling complex, is correlated with the origination and progress of tumor. Previous research on ARID1A gene revealed that ARID1A deficiency was associated with mismatch repair (MMR) and higher tumor mutation burden (TMB) level in cancer, which might cooperate with immune checkpoint blockade therapy. **Methods:** Next generation sequencing (NGS) data of 10336 pan-cancer patients were obtained from the MSK-IMPACT Clinical Sequencing cohort (MSKCC). NGS data of 15849 pan-cancer patients from Chinese clinical dataset were analyzed to explore the association between ARID1A gene mutation and TMB. TMB was defined as total number of somatic non-synonymous mutations in coding region. 853 advanced NSCLC patients from two independent cohorts (OAK study cohort and POPLAR study cohort) were used to analyze the correlation between ARID1A alteration and the efficacy of immune checkpoint blockade immunotherapies (ICIs). **Results:** In total, 8.62% (891/10336) of pan-cancer patients in MSKCC harbored ARID1A mutation and 8.47% (3188/37628) in Chinese cohort. In MSKCC cohort, the highest ARID1A mutation frequency tumor type was endometrial cancer (31.64%, 69/218), bladder cancer (26.95%, 114/423) and hepatobiliary cancer (17.18%, 61/355) come in second and third, respectively. While in Chinese cohort, the top three ARID1A mutation frequency tumor types were endometrial cancer (39.29%, 88/224), gastric carcinoma (17.80%, 318/1787) and urothelial carcinoma (17.18%, 83/483), respectively. ARID1A gene mutation was also associated with higher TMB in the Chinese pan-cancer cohort ($P < 0.0001$). The highest medium TMB level of ARID1A mutation tumor type was Urothelial carcinoma with 18.63 Muts/Mb (n = 65). In addition, the TMB level and prognositic analysis were performed on patients in two independent NSCLC cohorts with ICIs, TMB level of ARID1A mutant group was higher than wild-type group with significant difference ($P < 0.0001$). The overall survival (OS) of ARID1A mutation group were significantly shorter than wild-type group (OS, median, 6.80 vs 10.28 months; HR, 1.47; P = 0.0474), and a decreasing trend on progression-free survival (PFS) without significant difference (median, 1.46 vs 2.99 months; HR, 1.27; P = 0.1584). **Conclusions:** The results indicated that ARID1A gene mutation was associated with a higher TMB level in Chinese pan-cancer patients, and patients harboring these genes mutations might easily benefit from ICIs. Research Sponsor: None.

3541 Poster Session (Board #271), Fri, 8:00 AM-11:00 AM

The predictive role of plasma mutant allele fraction to antiangiogenic drugs in patients with mCRC: An expanded analysis of surrogate biomarkers of response to first-line treatment with bevacizumab. *First Author: Giulia Martini, Medical Oncology, Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy*

Background: So far, no biomarkers of response to anti-angiogenic drugs are available in colorectal cancer (CRC) treatment. Liquid biopsy tracks dynamic mutational changes in CRC patients (pts). RAS mutant allele fraction in plasma (plMAF) is an independent prognostic marker in metastatic CRC (mCRC). We explored the predictive value of plMAF in RAS mutant pts treated in 1st line with chemotherapy +/- bevacizumab (bev). **Methods:** A multicentric prospective/retrospective analysis was conducted. We collected data from 226 mCRC pts and selected the subset not eligible for metastasis resection with basal plMAF sample evaluable for RAS mutant MAF quantification with digital PCR (BEAMing). Pts were stratified as high ($\geq$ 5.8%) or low ($<$ 5.8%) plMAF. We investigated associations between clinicopathological variables and progression-free survival (PFS) stratified by plMAF RAS levels using Cox regression models and survival data were calculated by Kaplan-Meier method. Computational analysis of baseline CT scan data extracted 93 radiomics features of all the lesions per patient including 1) 1st class from density histogram distribution and texture analysis by 2) 2nd order and 3) higher order feature classes. The radiomic features distribution between pts with high and low plMAF was assessed with Student's t-test analysis. **Results:** From October 17 to May 19, 63 basal plasma samples were analysed with BEAMing. 42 pts (67.7%) were classified as high and 21 pts (32,3%) as low plMAF. In high plMAF subgroup, a statistically significant longer PFS favouring FOLFOX+bev was observed, compared to FOLFOX alone (10.7 vs 6.9 mts; HR: 0.30; p = 0.002). In low RAS plMAF subgroup, no differences in terms of PFS were observed in either arm (8.9 vs 8.7 mts; HR: 0.7; p = 0.6). Multivariate PFS model showed no association between RAS plMAF and clinicopathological variables, except for high RAS plMAF and treatment benefit with FOLFOX+bev. The CT-radiomics signature, that may translate tumor vascularization, differentiated patients with high vs low plMAF (p = 0.002). 58 patients (92%) had similar radiomic score; 5 patients with high plMAF (8%) presented very heterogeneous radiomic score distribution. **Conclusions:** Tumor-borne RAS plMAFs may constitute a potential predictive biomarker of efficacy for anti-angiogenic drugs in mCRC. Next steps will include the identification of -histological, transcriptomic and radiomic- surrogate biomarkers of response that reflect tumor irrigational status. Research Sponsor: aecc.

3542 Poster Session (Board #272), Fri, 8:00 AM-11:00 AM

Analytical validation of digital cytometry (iSort) for leukocyte enumeration using stored blood. *First Author: Aaron M. Newman, Stanford Cancer Institute, Stanford, CA*

Background: Blood leukocyte enumeration is a cornerstone for clinical diagnosis and immune monitoring of diverse cancers and immunotherapies. Existing methods rely on intact/living cells and can thus be limiting due to handling time constraints and need for predefined antibody panels. While indirect cytometry methods including digital cytometry can overcome this limitation on archival specimens, their clinical performance has not been extensively characterized. We developed iSort, a novel transcriptome deconvolution method based on CIBERSORTx. Here, we comprehensively evaluated iSort and validated it against established diagnostic standards. **Methods:** We recruited 36 healthy adult blood donors and characterized their blood leukocyte profiles. We used several established clinical cytometry methods requiring intact cells in a CLIA laboratory including Complete Blood Count [CBC] and 6-color TBNK [TBNK]. We also immunophenotyped leukocytes by a research flow cytometry panel (FACS) and by mass cytometry (CyTOF). We then used these techniques as standards for validating leukocyte populations enumerated by iSort. iSort was performed on whole blood through deconvolution of 22 subsets from RNA-Seq. We assessed iSort's analytical detection performance by spiking purified lymphocyte subsets into lymphodepleted human blood and by simulating blood mixtures using defined leukocyte mixtures within latin square designs. We assessed iSort concordance with an FDA approved IVD assay (TBNK) comparing distinct RNA-Seq library preparation chemistries. **Results:** iSort was highly correlated with TBNK/CBC across CD4 T, CD8 T, B cells, NK cells, monocytes, and neutrophils ($r \geq 0.95$). When comparing correlations to TBNK/CBC, we found no significant differences between iSort, CyTOF, and FACS, nor between RNA-Seq library chemistries. iSort demonstrated high linearity at low abundance levels (0.1 - 1%, $r = 0.99$, B-cells spiked into lymphodepleted blood samples after Rituximab) and at higher abundance levels (0.5 - 90%, $r > 0.99$) across lymphoid and myeloid subsets. iSort also showed high reproducibility among triplicate blood tubes for each population (median CV = 11%). **Conclusions:** iSort digital cytometry achieves highly accurate and robust leukocyte enumeration for diverse hematopoietic subsets. Given its favorable performance against existing clinical standards that require intact/living cells, iSort is a promising approach for the development of immunotherapy biomarkers. Research Sponsor: CiberMed, Inc.

3543 Poster Session (Board #273), Fri, 8:00 AM-11:00 AM

Noninvasive identification of lineage-specific circular RNA for ER-positive breast cancer. *First Author: Jason Brown, Department of Internal Medicine, University of Michigan, Ann Arbor, MI*

Background: Non-invasive testing in plasma using RNA biomarkers has been limited by exoribonuclease-mediated degradation of RNA. Circular RNA (circRNA) are covalently closed RNA structures that resist this degradation due to their circular structure. Therefore circRNA are more stable than their linear counterparts. CircRNA are formed by alternative backsplicing of the 3' end of a downstream exon to the 5' end of an upstream exon. Here, we propose a novel method for non-invasive identification of circRNA and demonstrate circularized forms of several lineage and cancer specific targets for estrogen receptor-positive breast cancer. **Methods:** Capture RNA sequencing on cancer tissue was previously performed to determine the relative expression of potential circRNA isoforms in breast cancer patients. These isoforms as well as those predicted by intron length were screened using a quantitative PCR-based assay on ER-positive breast cancer cells. RNA extracted from breast cancer cells are exposed to ribonuclease R to demonstrate stability of circRNA. CircRNA derived from targets with known universal expression are used as positive controls as well as for analysis on plasma. **Results:** We identify the circRNA isoforms with highest expression for five genes, including ESR1, that are differentially expressed in ER-positive breast cancer compared to other cancers and normal breast tissue. We determine that the circRNA corresponding to all five targets is specifically expressed in breast cancer cell lines with at least 1000-fold higher expression than in non-ER positive breast cancer cell lines. We demonstrate that the highest expressing circRNA isoforms are resistant to degradation by ribonuclease R, whereas corresponding linear mRNA is susceptible. We also demonstrate the presence and stability of positive control circRNA in plasma from patients without cancer. **Conclusions:** CircRNA are promising biomarkers for early non-invasive detection of cancer due to their stability in plasma. This assay reliably detects ER-positive breast cancer specific circRNA, and exoribonuclease resistance has been validated. Application of this diagnostic assay to plasma from breast cancer patients is underway. Research Sponsor: U.S. National Institutes of Health.

3544 Poster Session (Board #274), Fri, 8:00 AM-11:00 AM

Circulating microtumors: A functional hallmark for cancer detection and management. *First Author: Vineet Datta, Datar Cancer Genetics Limited, Nasik, India*

Background: There are presently no accepted non-invasive means for detection of cancers in asymptomatic individuals or suspected cases. Radiological and serological investigations, though non-invasive, are not confirmatory and necessitate an invasive biopsy to establish malignant status of suspected findings. Invasive biopsies, in turn, face challenges due to non-representative tumor tissue or in cases where biopsy is impossible or unviable. We hypothesized that Circulating Microtumors (also called as C-ETACs: Circulating Ensembles of Tumor Associated Cells) in peripheral blood are universally present in solid organ cancers and their detection can be linked to malignant status. **Methods:** We obtained peripheral blood from 14,138 patients with various solid organ cancers as well as 10,625 asymptomatic individuals with age associated elevated risk of cancer. Out of the 14,138 patients with cancer, 25.1 % had local (non-metastatic) disease and 56.4% had metastatic disease as confirmed by radiological evaluation. C-ETACs were enriched and harvested from PBMCs using an epigenetically activating medium that is cytotoxic towards non-malignant epithelial and hematolymphoid cells in blood but confers survival benefit on apoptosis resistant circulating cells of tumorigenic origin and their heterotypic clusters (C-ETACs) in peripheral blood. Viable C-ETACs were identified and further characterized by immunocytochemistry (ICC) profiling. **Results:** C-ETACs were detected in 89.7% of samples from solid organ cancers irrespective of stage, treatment or present radiological status. C-ETACs were rarely detected (3.0%) in asymptomatic individuals. The asymptomatic individuals where C-ETACs were detected are being followed up periodically so as to enable detection of cancer based on clinical or radiological manifestation of symptoms. **Conclusions:** C-ETACs are ubiquitous in cancers and unexpected in asymptomatic individuals. Detection of C-ETACs in asymptomatic individuals may be indicative of risk of latent undiagnosed malignancy. The non-invasiveness of this approach makes it convenient for screening large populations for cancer. Research Sponsor: None.

3545 Poster Session (Board #275), Fri, 8:00 AM-11:00 AM

Identification of *FGFR2/3* fusions from clinical cfDNA NGS using a de novo fusion caller. *First Author: Arielle Yablonovitch, Bioinformatics, Guardant Health, Redwood City, CA*

Background: *FGFR2/3* rearrangements are promising therapeutic targets, especially in advanced urothelial cancer (aUC) with FDA-approved erdafitinib. Liquid biopsy is an attractive non-invasive method to identify these fusions, but detection in cfDNA is technically challenging due to low tumor shedding levels, short molecules, and wide variation in gene partners. To address this, we developed an assembly-based fusion detection algorithm to call rearrangements in a *de novo* fashion without reliance on a fixed partner set and applied it to $>$ 15,000 clinical samples. **Methods:** A cohort of 15,218 patients with mixed cancer types (including 698 aUC patients, as well as breast, cholangiocarcinoma, colorectal, and gastric), plus 276 healthy control samples were previously tested with Guardant360(R), a clinical 74-gene cfDNA NGS-based assay. The median unique molecule coverage was approximately 3,000 molecules sequenced to 15,000x read depth. Samples were reanalyzed *in silico* using the novel algorithm: in brief, reads aligned to candidate fusion breakpoints were assembled into de Bruijn graphs. Resulting contigs were aligned to the reference and filters were applied to remove technical artifacts. **Results:** The majority of *FGFR2* (86%) and *FGFR3* fusion partners (73%) in the mixed cancer cohort were observed only once, consistent with previous reports (Helsten 2016). *FGFR3-TACC3* was the most common fusion, occurring in 72% of *FGFR3* fusion-positive patients. In 37% of *FGFR2* fusion positive patients, the *de novo* caller detected partners not previously described. In the aUC cohort, *FGFR3* fusions were detected in 3.3% of patients, with 8/10 (80%) partner genes/intergenic regions occurring only once, which is in line with previous reports (Nassar 2018). No fusions were identified in 276 healthy control samples. In the mixed cancer cohort, common mutations co-occurring with *FGFR2* fusions were *FGFR2* N549K, *PIK3CA* H1047R, and *TP53* R175H (5.6% each); *KRAS* Q61H was observed in 28% of patients with *FGFR3* fusions. **Conclusions:** *FGFR2/3* fusion partners detected by a highly specific assembly-based *de novo* fusion caller were heterogeneous and individually rare, highlighting the importance of a *de novo* approach. We observed an *FGFR3* fusion prevalence in cfDNA from aUC patients that is comparable to previous reports for tissue testing, demonstrating an ability to capture targetable genomic rearrangements with plasma-based NGS in this patient population. Research Sponsor: Guardant Health.

3546 Poster Session (Board #276), Fri, 8:00 AM-11:00 AM

Demonstrating the value of liquid biopsy for lung cancer in a public health care system. *First Author: Rosalyn A. Juergens, Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada*

Background: Given the challenges of molecular profiling in patients with advanced lung cancer, this prospective study examines clinical outcomes and utility of liquid biopsy in treatment naive stage IV lung adenocarcinoma patients (Cohort 1) and in the setting of resistance to targeted therapy (Cohort 2; not reported here). **Methods:** This study is being conducted at 6 Canadian centres (NCT03576937) using Guardant 360 (G360), a validated cell-free DNA next-generation sequencing assay that identifies variants in 74 cancer-associated genes, including fusions and copy number gain. Cohort 1 (N = 150) includes patients with treatment-naïve advanced non-squamous lung carcinoma, ≤10 pack-year smoking history, and measurable disease. Patients received standard of care tumour tissue (TT) molecular profiling (*EGFR, ALK +/- ROS1*) and liquid biopsy (LB). The primary endpoint was response rate to first-line therapy (RECIST 1.1); secondary endpoints include incremental targetable alterations identified through G360 (*EGFR, ALK, BRAF, ERBB2, KRAS (G12C), NTRK, MET (amplification, exon 14 skipping), RET, ROS1*), turn-around time (TAT) and successful molecular profiling rates. **Results:** To date, 84 eligible patients with clinical data have been accrued to Cohort 1. Median age is 64 (range 23-91), 64% are female, 85% never smokers, 96% have adenocarcinoma. Actionable targets have been identified in 55% of patients using G360 (*EGFR/ALK* in 37%), 39% using standard TT profiling. Eight *EGFR/ALK* aberrations were identified in TT but not LB, while 6 were identified in LB but not TT. TT profiling for *EGFR/ALK* was unsuccessful in 8% of patients (insufficient tissue, failed biopsy). Fourteen patients (17%) had no ctDNA alterations detected by G360 (low disease burden vs. non-shedding). Of 75 patients receiving first-line treatment, 57% received targeted therapy, 28% chemotherapy combinations, 11% checkpoint inhibitors and 4% were observed. Treatment decisions were informed by G360 alone in 37% and by G360+TT results in 27% (by physician report). Among 46 evaluable patients, ORR was 54% (25/46). Using G360, ORR was 75% (15/20) in those with actionable alterations and 38.5% (10/26) in those without. Using TT, ORR was 67% (14/21) in those with actionable alterations and 44% (11/25) in those without. Mean TAT was 7.9 days (SD+/-1.7) for LB vs 19.9 days (SD+/- 9.8) for TT. **Conclusions:** Liquid biopsy using G360 identifies actionable targets beyond tissue profiling alone in newly diagnosed lung cancer patients, has faster TAT and yields similar outcomes with targeted and non-targeted therapy. Clinical trial information: NCT03576937. Research Sponsor: Guardant Health, Other Foundation.

3547 Poster Session (Board #277), Fri, 8:00 AM-11:00 AM

The prevalence of $KRAS^{G12C}$ mutations utilizing circulating tumor DNA (ctDNA) in 80,911 patients with cancer. *First Author: Kyaw Thein, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Kirsten rat sarcoma viral oncogene homolog (KRAS) is the most commonly mutated proto-oncogene identified in cancer and still remains an arduous therapeutic challenge. Recently, $KRAS^{G12C}$ mutation has become special interest since it has now been considered potentially druggable after the introduction of covalent small-molecule $KRAS^{G12C}$ inhibitors. Advances in next-generation sequencing (NGS) and embracing utilization of ctDNA have uncovered more genetic alterations in many cancers. We present a comprehensive analysis on the prevalence of $KRAS^{G12C}$ mutations identified by ctDNA. **Methods:** We conducted a 5-year (July 2014 to June 2019) retrospective review of ctDNA NGS analysis in the Guardant360 CLIA database inclusive of treatment-naïve and previously treated patients with metastatic solid tumors. Data were retrieved from the 80,911 unique patients with ctDNA detected. Clonality and co-occurrence of cancer type were analyzed. Clonality was defined as variant allele fraction(AF) / maximum somatic AF in the sample. **Results:** 80,911 patients, which included more than 100 tumor histologies, were identified. 2,985 patients (3.7%) with > 40 tumor types had $KRAS^{G12C}$ mutations identified in ctDNA. $KRAS^{G12C}$ prevalence by cancer type were as follows: sarcomatoid lung carcinoma (13.5%), lung cancer NOS (9%), large cell lung carcinoma (9%), lung adenocarcinoma (7.4%), NSCLC (6.9%), carcinoma of unknown primary (CUP) (4.1%), lung carcinoid (4%), CRC (3.5%), squamous cell lung carcinoma (2%), small cell lung carcinoma (1.5%), pancreatic ductal adenocarcinoma (PDAC) (1.2%), cholangiocarcinoma (1.2%), bladder cancer (0.6%), ovarian cancer (0.6%) and breast cancer (0.3%). 53 additional patients with $KRAS^{G12C}$ were identified across 24 other tumor types. The $KRAS^{G12C}$ mutation was found to be clonal (clonality > 0.9%) in the majority of patients with lung adenocarcinoma, NSCLC, CUP, squamous cell lung carcinoma, and PDAC, compared to patients with CRC and breast cancer who had bimodal distribution of clonal and sub clonal mutations. **Conclusions:** To our knowledge, this is the largest analysis on the prevalence of $KRAS^{G12C}$ mutations identified by ctDNA. Our study demonstrated the feasibility of utilizing ctDNA to identify $KRAS^{G12C}$ mutations across solid tumors with the highest prevalence in lung cancer as previously reported in tissue. The clonality information available from ctDNA-based genotyping may provide insights into the clinical efficacy of targeting $KRAS^{G12C}$ in different tumor types. Research Sponsor: None.

3548 Poster Session (Board #278), Fri, 8:00 AM-11:00 AM

Exploring the Cancer Genome Atlas (TCGA) for the molecular profile of young onset colorectal cancers. *First Author: Seyed Ali Khalessi Hosseini, NYU Langone Medical Center, New York, NY*

Background: Colorectal cancer (CRC) incidence and mortality has been declining, in part due to increased implementation of screening, but the incidence among patients under 50 (young onset, YO) is increasing at a rate of 2% per year. The cause of this increasing incidence remains poorly understood, but differences in mutation profiles can help understand pathogenesis, prognosis, and identify targets for therapy. **Methods:** Genomic and clinical data for 488 TCGA CRC patients was used to evaluate differences in genetic alterations between YO and patients over 50. Chi-squared tests were used to determine differences in somatic mutation frequency in critical pathways implicated in CRC: DNA MMR, P53, WNT, RAS-MAPK, PI3K/AKT/mTOR, and TGF-B pathways. For 85 of the patients, proteomic data via RPPA was also available and analyzed. **Results:** The average age of included patients was 66 (SD 12.8). 76 (12.2%) were under 50 at time of diagnosis. When comparing YO with those over 50, there were no differences in microsatellite instability, histologic type (adeno or mucinous), location (colon or rectal), tumor size, or metastasis. YO patients were more likely to have nodal involvement (p = 0.007) and higher histological grade (p = 0.022). YO patients were more likely to have mutations in the MMR pathway (43% vs 23%, p = 0.002) and the PI3K/AKT/mTOR pathway (70% vs 54%, p = 0.024). Specifically, YO were more likely to have mutations in MSH2 (7% vs 1%, p = 0.001), MSH6 (24% vs 7%, p = 0.000); ATM (46% vs 30%, p = 0.015); FZD10 (7% vs 2%, p = 0.007); ERBB2 (15% vs 7%, p = 0.027); PIK3R1 (20% vs 9%, p = 0.014), PTEN (61% vs 35%, p = 0.000), and TGFBR2 (13% vs 4%, p = 0.004). When looking at proteomic data, YO were more likely to have decreased expression of MSH2 (p = 0.003) and MSH6 (p = 0.005). **Conclusions:** Patients with YO CRC are more likely to have somatic mutations in genes involved in the MMR pathway and the PI3K/AKT/mTOR pathway. Specifically, in MSH2, MSH6, ATM, FZD10, ERBB2, PIK3R1, PTEN and TGFBR2. When including proteomic data, significant differences were only seen in expression of MSH2/6. Some of these genes (e.g. ERBB2/HER2) are targets for existing therapies, and others are being actively investigated as potential therapeutic targets. Establishing differences in tumor genetic profiles is a first step towards understanding the increase in YO CRC, and simultaneously identifies targets for therapy. However, because of post-transcriptional changes (e.g. RNAi, methylation), genetic profiling alone cannot always reliably establish differences in protein expression, and thus therapy targets. Research Sponsor: None.

3549 Poster Session (Board #279), Fri, 8:00 AM-11:00 AM

Phase I expansion study of XMT-1536, a novel NaPi2b-targeting antibody-drug conjugate (ADC): Preliminary efficacy, safety, and biomarker results in patients with previously treated metastatic ovarian cancer (OC) or non-small cell lung cancer (NSCLC). *First Author: Debra L. Richardson, Stephenson Cancer Center/Sarah Cannon Research Institute at the University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: XMT-1536 is a first-in-class ADC targeting the sodium-dependent phosphate transport protein NaPi2b, broadly expressed in NSCLC and ovarian cancer. XMT-1536 utilizes the Dolaflexin platform to deliver 10-12 DolaLock auristatin payload molecules per antibody. In the dose-escalation portion of the Phase I study (NCT03319628), XMT-1536 showed clinical activity at doses >20mg/m^2 with confirmed responses and prolonged stable disease in heavily pretreated OC and NSCLC patients, without preselection for NaPi2b expression. XMT-1536 was generally well-tolerated without the severe toxicities observed with other ADC platforms such as neutropenia, peripheral neuropathy, or ocular toxicity (Tolcher et al., ASCO 2019; Richardson et al., SGO 2020). Here, we report on the expansion (EXP) cohort, which included patients with fewer prior lines of therapy, in the ongoing Phase I study. **Methods:** Doses administered intravenously every 4 weeks (q4w) of 36 and 43 mg/m^2 were evaluated in two cohorts (1) high grade serous ovarian, fallopian tube, or primary peritoneal cancer (OC) with up to 4 prior lines of therapy and (2) NSCLC adenocarcinoma; prior treatment with a platinum-based therapy, immune checkpoint inhibitor, and TKI, if indicated. Archival tumor tissue and tissue from a new tumor biopsy were required for retrospective evaluation of NaPi2b expression. **Results:** As of 10 February 2020, 23 patients (19 OC and 4 NSCLC) were enrolled in the EXP cohort: 16 dosed at 36 mg/m^2 and 7 dosed at 43 mg/m^2. Adverse events were generally similar to those previously reported, including transient AST elevation, fatigue, nausea, and pyrexia. Clinical responses and stable diseases have been observed. Efficacy data (objective response rate) and initial correlation of NaPi2b score with clinical response will be reported. Available data from all patients with data cutoff in May 2020 will be included. **Conclusions:** Overall, XMT-1536 treatment demonstrated clinical activity in high grade serous ovarian cancer and NSCLC adenocarcinoma and was generally well-tolerated with no new safety signal trends identified in the EXP. Clinical efficacy and the relevance of NaPi2b expression for treatment with XMT-1536 will be presented. Clinical trial information: NCT03319628. Research Sponsor: Mersana Therapeutics.

3550 Poster Session (Board #280), Fri, 8:00 AM-11:00 AM

First-in-human dose-escalation study of anti-EGFR ADC MRG003 in patients with relapsed/refractory solid tumors. *First Author: Rui-hua Xu, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: MRG003 is a novel antibody drug conjugate (ADC) composed of a fully human anti-EGFR IgG1 monoclonal antibody conjugated to a microtubule disrupting agent monomethyl auristatin E (MMAE). MRG003 is presently being tested in an ongoing phase I study for safety, pharmacokinetics, and preliminary antitumor activity in patients (pts) with solid tumors (CTR20180310). **Methods:** In the phase I dose escalation study of a traditional (3+3) design, pts with relapsed or refractory cancers received single agent MRG003 once every 3 weeks (Q3W) for a maximum of 8 treatment cycles. The starting dose of MRG003 is 0.1 mg/kg, followed by 0.3, 0.6, 1.0, 1.5, 2.0, 2.5, and 3.0 mg/kg. Observations included adverse events (AEs), dose-limiting toxicity (DLT), and antitumor activity which is assessed every two cycles. **Results:** A total of twenty-two pts with colorectal (CRC, n = 15), nasopharyngeal (NPC, n = 3), head and neck (H&N, n = 2), esophageal (EC, n = 1), and duodenal (DC, n = 1) cancer were enrolled in the dose escalation. The median age of pts was 56.5 years. The MTD identified was 2.5 mg/kg. Commonly observed adverse events were anemia (50%), AST increase (41%), decreased appetite (41%), rash (36%), pruritus (36%), asthenia (36%), and proteinuria (32%). Majority of AEs were mild to moderate in severity. EGFR expression in patients' tumor samples was determined retrospectively by a validated IHC method in a central laboratory. Nine out of 22 pts tested were EGFR positive. Among these 9 EGFR positive pts, one with NPC in the 2.5 mg/kg cohort had partial response, four had stable disease (one with H&N in the 1.5 mg/kg, one each with NPC and H&N in the 2.0 mg/kg, and one with EC in the 2.5 mg/kg cohorts). The disease control rate (DCR) at doses ≥1.5 mg/kg was 100% for the EGFR positive pts. **Conclusions:** The dose escalation study of MRG003 showed manageable safety profiles and encouraging preliminary antitumor activity in pts with EGFR-positive solid tumors. MRG003 is currently being evaluated as a single agent in phase I dose expansion cohorts to further assess safety, PK, and antitumor activity. Clinical trial information: CTR20180310. Research Sponsor: Shanghai Miracogen Inc.

3551 Poster Session (Board #281), Fri, 8:00 AM-11:00 AM

First-in-human phase I study of ALT-P7, a HER2-targeting antibody-drug conjugate in patients with HER2-positive advanced breast cancer. *First Author: Yeon Hee Park, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: ALT-P7 is an antibody-drug conjugate, in which two molecules of monomethyl auristatin E (MMAE) are site-specifically conjugated to a cysteine-containing peptide motif of trastuzumab variant. This is the first-in-human study evaluating safety and pharmacokinetics of ALT-P7 in patients with HER2-positive advanced breast cancer. **Methods:** This was an open label, 3+3 dose-escalation phase 1 trial. Eligible patients were with HER2-positive advanced breast cancer progressive to at least two kinds of prior anti-HER2 treatment. ALT-P7 at doses from 0.3mg/kg to 4.8mg/kg were intravenously administered once every 3 weeks. Dose limiting toxicities were evaluated over the first cycle of 21 days. Primary objective was to define the maximum tolerated dose. **Results:** ALT-P7 were administered in 27 patients (n=4 at 0.3mg/kg, n=3 at each of 0.6, 1.2, 2.4, 3.6, 4.2, 4.5 mg/kg, n=5 at 4.8mg/kg) between Jan 2018 and Feb 2020. The median number of previous line of systemic therapy was six, including median four prior anti-HER2 agents. The most common grade (G) 3/4 adverse event (AE) was neutropenia (n=4). The other common drug-related AEs of all grade were myalgia (n=9), fatigue (n=7), sensory neuropathy (n=6), alopecia (n=6), pruritus (n=6), and neutropenia (n=6). Dose limiting toxicities(DLTs) were observed in three patients at 4.8mg/kg (G4 febrile neutropenia, G4 thrombocytopenia, G4 hyperbilirubinemia, G3 myalgia, G4 hyponatremia). No DLTs have been observed up to 4.2mg/kg, and safety evaluation at 4.5mg/kg is currently ongoing. Toxicokinetic analysis for total antibody, drug-conjugated antibody, and free payload suggested that there were no accumulation of ALT-P7 upon repeated injection. In 22 patients with response evaluation, disease control rate at 6 weeks of ALT-P7 treatment was 77.3%(17/22) and partial response was achieved in two out of fifteen patients with measurable lesion. The median PFS at doses from 2.4 to 4.8mg/kg was 6.2 months (95% CI 2.5-9.9 months). **Conclusions:** ALT-P7 was well tolerated to a dose of 4.2mg/kg in heavily pretreated HER2-positive advanced breast cancer. DLTs were observed at 4.8mg/kg, and 4.5mg/kg is under evaluation. The observed clinical activity warrants further evaluation in a phase 2 trial. Clinical trial information: NCT03281824. Clinical trial information: NCT03281824. Research Sponsor: Alteogen, Inc., Korea Drug Development Fund (KDDF) funded by MSIT, MOTIE and MOHW

3552 Poster Session (Board #282), Fri, 8:00 AM-11:00 AM

A phase I/II study of rovalpituzumab tesirine in delta-like 3-expressing, advanced solid tumors. *First Author: Aaron Scott Mansfield, Mayo Clinic, Rochester, MN*

Background: Delta-like 3 (DLL3) is highly and specifically expressed in solid tumors, such as neuroendocrine carcinomas (NECs), malignant melanoma (MM), and medullary thyroid carcinoma (MTC). Rovalpituzumab tesirine (Rova-T) is a DLL3-targeting antibody-drug conjugate. **Methods:** This Phase 1/2 study (NCT02709889) enrolled patients with relapsed/refractory DLL3+ (>1% by IHC) advanced solid tumors and ECOG performance status of 0-1. Rova-T was given IV at 0.2, 0.3, or 0.4 mg/kg on d 1 of each 6-wk cycle (q6wk) for dose escalation (3+3 design) in disease-specific cohorts in Phase I. The recommended Phase 2 dose (RP2D) was tested in Phase II. Safety and dose-limiting toxicities (DLTs) were primary endpoints; efficacy outcomes were secondary endpoints. **Results:** The study enrolled 200 patients; 101 had NECs (large cell NEC [n=13], neuroendocrine prostate cancer [n=21], high-grade gastroenteropancreatic NEC [n=36], other [n=31]) and 99 had other solid tumors (MM [n=20], MTC [n=13], glioblastoma [GBM; n=23], other [n=43]). The median age was 61 y (range, 28-84); 63% were male. The RP2D was 0.3 mg/kg q6wk for 2 cycles in all cohorts. There were 7 DLTs in 5 patients: 2 with 0.2 mg/kg (Grade [Gr] 3 photosensitivity reaction, Gr 3 dyspnea), 2 with 0.3 mg/kg (1 with Gr 2 effusion, Gr 3 tumor lysis syndrome, and Gr 3 rhabdomyolysis; 1 with Gr 4 kidney injury), and 1 with 0.4 mg/kg (Gr 4 thrombocytopenia). Despite only 1 DLT identified with 0.4 mg/kg, the totality of the safety data suggested that this dose is not well tolerated. Common adverse events (AEs) in patients given 0.3 mg/kg (n=145) are shown (Table). Serious AEs occurred in 77/145 patients (53%), most commonly (≥3%) malignant neoplasm progression (n=18; 12%), pleural effusion (n=7; 5%), pericardial effusion (n=6; 4%), and dyspnea (n=5; 3%). The objective response rate (ORR) was 11% (21/200): 14 had NEC, 2 had MM, 2 had MTC, 2 had small cell carcinoma (SCC) not of lung origin (all partial responses), and 1 had GBM (complete response). In patients with NECs given 0.3 mg/kg, ORR, clinical benefit rate, and progression-free survival trended in favor of those with high DLL3-expressing tumors (≥50% by IHC) which represented 51% of NECs. **Conclusions:** Rova-T was tolerable in patients with advanced solid tumors at 0.3 mg/kg q6wk for 2 cycles. Antitumor activity was observed in patients with NEC, MM, MTC, SCC, and GBM. Clinical trial information: NCT02709889.Research Sponsor: Abbvie, Inc.

AEs in ≥30% of patients given 0.3 mg/kg q6wk Rova-T (n=145).

AE, n (%)	Any Gr	Gr ≥3
Any	144 (99)	99 (68)
Fatigue	75 (52)	6 (4)
Nausea	53 (37)	5 (3)
Thrombocytopenia	48 (33)	22 (15)
Pleural effusion	48 (33)	4 (3)
Peripheral edema	44 (30)	1 (1)

3553 Poster Session (Board #283), Fri, 8:00 AM-11:00 AM

Phase I study of mesothelin-targeted immunotoxin LMB-100 given as a long infusion with or without nab-paclitaxel. *First Author: Guillaume Joe Pegna, National Cancer Institute Center for Cancer Research, Bethesda, MD*

Background: LMB-100 recombinant immunotoxin consists of a mesothelin-binding Fab for targeting a modified *Pseudomonas* exotoxin A payload. Previous Phase 1 clinical testing of a 30-minute LMB-100 "short" infusion format identified a serum half-life of ~1 hour. Pre-clinical data suggested that extending infusion time could improve anti-tumor efficacy by increasing tumor cell duration of exposure to LMB-100. The primary objective of this study was to determine the safety and tolerability of administering LMB-100 in a long infusion format over 24-48 hours alone or with nab-paclitaxel chemotherapy in patients with mesothelin-expressing solid tumors. **Methods:** Patients (n = 15) with pancreatic adenocarcinoma and other mesothelin-expressing solid tumors (n = 3; mesothelioma, colon, and ampullary cancers) treated on 3 dose levels received long infusion of LMB-100 (65 or 100 mcg/kg/day) for 24 hour on Days 1 and 4 (n = 6) or 48 hour on Day 1 (n = 9) with or without a loading dose (40 mcg/kg over 30 minutes) for up to 2 cycles. In the second arm, patients (n = 5) with pancreatic adenocarcinoma were treated with LMB-100 over 24 hours on Day 1 concurrently with nab-paclitaxel (125 mg/m^2) for up to 3 cycles. **Results:** DLT of proteinuria (grade 3) in one patient and acute kidney injury (grade 1) in one patient were observed amongst patients receiving 100 mcg/kg/day over 48 hours and 24 hours, respectively. No objective responses were seen but all patients receiving nab-paclitaxel had > 50% decrease in CA 19-9. Patients at all single agent dose levels (8 of 10 evaluable) developed high titer anti-drug antibodies (ADAs) against LMB-100. Those with ADAs (8 of 8) had undetectable cycle 2 peak plasma LMB-100 concentration. Development of high titer ADAs occurred more frequently with long infusion than seen previously with "short" infusion LMB-100. Most long infusion patients (19 of 20) developed increased serum IL-6 within 24 hours of LMB-100 infusion. However, the systemic inflammatory response to LMB-100 (as measured by increased serum CRP) which occurs in most "short" infusion patients was not observed. **Conclusions:** Long infusion format LMB-100 is generally well tolerated but immunogenicity limits treatment to 1 effective cycle. No antitumor efficacy of the single agent was observed. Clinical trial information: NCT02810418. Research Sponsor: U.S. National Institutes of Health.

3555 Poster Session (Board #285), Fri, 8:00 AM-11:00 AM

Anaplastic lymphoma kinase (ALK) partners identified by next-generation sequencing in Chinese patients with solid tumors. *First Author: Sheng Yang, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Anaplastic lymphoma kinase (ALK) rearrangement is a validated therapeutic driver gene in non-small cell lung cancer (NSCLC). More than 30 different fusion partner genes of ALK in NSCLC have been reportedand most of these ALK fusions respond well to ALK inhibitors crizotinib. With the development of next-generation sequencing (NGS), more novel partners for ALK rearrangement have been identified. Here, we aimed to report the landscape of ALK rearrangement in Chinese patients with solid tumors. **Methods:** Tissue or blood samples were subjected to NGS in a College of American Pathologists-certified and Clinical Laboratory Improvement Amendments-accredited lab for ALK arrangement. **Results:** In total, we profiled more than 40,000 patients, among which 72 cases with 52 ALK fusion partner, harboring 17 reported partners and 35 novel partners. The average ALK rearrangement patients' age was 53 years (range, 17-76 years). Among all the ALK fusion cases (n = 72), lung cancer were the largest proportion with 77.8% (n = 56), colorectal cancer accounted for, 5.5% (n = 4), liver cancer accounted for 4.2% (n = 3), biliary cancer, melanoma, carcinosarcoma and inflammatory myofibroblastic tumor accounted for 2.8% (n = 2) respectively, and only one case (n = 1) was malignant peritoneal mesothelioma. The most common ALK fusion partners were KIF5B (n = 6), DCTN1 (n = 5) and STRN (n = 5). In 38 cases, 35 novel ALK fusion partners were discovered. The novel CLIP4-ALK, EHBP1-ALK, PLB1-ALK occurred twice in 6 patients, which were two lung cancer patients with CLIP4-ALK fusion, two lung cancer patients with PLB1-ALK fusion, one hepatic cellular cancer patients with EHBP1-ALK, and one melanoma patients with EHBP1-ALK. There were two special lung cancer cases with two ALK fusions. One case detected the novel LRIG1-ALK fusion and novel PLB1-ALK fusion, the other case detected novel GLI3-ALK fusion and reported HIP1-ALK fusion. **Conclusions:** Novel ALK fusions are detected in patients with not only NSCLC but also other solid tumors. NGS fusion assay is an optional method for screening novel fusions. Research Sponsor: None.

3556 Poster Session (Board #286), Fri, 8:00 AM-11:00 AM

High intratumoral tryptophan metabolism is a poor predictor of response to pembrolizumab (pembro) in metastatic melanoma (MM): Results from a prospective trial using baseline C11-labeled alpha-methyl tryptophan (C11-AMT) PET imaging for response prediction. *First Author: Jorge D. Oldan, Department of Radiology, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Molecular imaging of metabolic pathways critical for effector T cell response other than glucose could predict response to PD1 inhibitors. We have previously shown that high expression of tryptophan metabolic pathway enzymes in stage III/IV melanoma correlates with reduced abundance of tumor-infiltrating lymphocytes (TILs, ASCO 2019, e21014). Here we investigated C11-AMT, a PET tracer that images tryptophan metabolism, as a predictor of response to pembro in patients (pts) with PD1 inhibitor-naïve MM. **Methods:** In this trial (NCT03089606) pts must have had measurable MM by RECIST, have undergone IV contrast CT, FDG-PET, and C11-AMT PET scan (30-40 min dynamic imaging), plus a mandatory tumor biopsy prior to pembro treatment. **Results:** 21 pts (16 males; 15 stage IV; median age 61) had all 3 baseline scans and evaluable research biopsies. 13 pts were non-progressors (CR = 4, PR = 6, and SD = 3). At a median f/u of 13.7 mons (2.8-25.1+), 6 pts are dead from MM, 11 are alive without MM and 4 are alive with MM. 46 tumor lesions were assessed by all 3 scans. Of the pts with tumor lesion, C11-AMT PET $SUV_{max} < 7$ and skewness $< +0.3$ of the tumor lesion with the highest C11-AMT SUV_{max} was associated with non-progression by RECIST ($SUV_{max} < 7$/skewness $< +0.3$ in progressors vs. non-progressors; Fisher's 2-tail test $p = 0.055$). The corresponding association between baseline FDG-PET ($SUV_{max} < 14$ and skewness $< +0.3$) with treatment response was insignificant ($p = 0.08$). There was a weak (Spearman $\rho = 0.33$) but significant correlation ($p = 0.001$) in SUV_{max} between FDG-PET and C11-AMT among the 46 tumors analyzed. There was no significant correlation between melanoma-specific expression of the tryptophan- (TPH1, TPH2, IDO1, TDO2, LAT1) and glucose-metabolizing enzymes (GLUT1, HK1, HK3) by immunohistochemistry. Response to pembro trends to associate with present TILs (Fisher's $p = 0.087$). **Conclusions:** Baseline C11-AMT PET imaging using simple radiomics measures (highest metabolic activity, SUVmax, and tumor heterogeneity, skewness) may better predict clinical benefit from pembro in MM than FDG PET. Variability in C11-AMT's SUV_{max} cannot be solely explained by FDG-PET's SUV_{max}, suggesting that these two imaging modalities may provide complementary information about intratumoral metabolic dysregulation that may relate with pembro response. Texture analysis using LifeX v4.0 will be presented at the meeting. Clinical trial information: NCT03089606. Research Sponsor: Merck.

3557 Poster Session (Board #287), Fri, 8:00 AM-11:00 AM

First in-human study of in vivo imaging of ex vivo labeled CAR T cells with dual PET-MR. *First Author: Ritu Singla, Cell Therapies, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: This is a first in human in-vivo biodistribution of ex-vivo labelled CAR T cells assessed in a cohort of patients. Cells were labelled with novel Cu-64 labelled superparamagnetic iron oxide nanoparticles (SPION) and infused IV into patients with solid tumors & tracked using clinical dual PET-MR. The study validates the clinical translation of CAR T cell in-vivo tracking in real time. **Methods:** Cu-64 radioisotope was bound to silica coated SPION using electrolysis plating with tin & palladium seeding. Cellular uptake of Cu-64 SPION was facilitated with a transfecting agent. Functional assays including ^{51}Chromium release, cytometric bead array demonstrated that labelling process did not affect cytotoxicity & cytokine secretion (TNFα & IFN-g). T cells were transduced with retroviral vector constructs encoding for second-generation chimeric T-cell receptor specific for carbohydrate Lewis Y antigen. Modified T-cells were expanded ex-vivo & were labelled with Cu-64 (~300 MBq) prior to re-infusion (3 $x10^8$ labelled cells). Scanning is performed with Siemens 3T dual PET-MR scanner. **Results:** In this first in human in-vivo study (HREC/16/PMCC/30) a cohort of patients received ex-vivo labelled CAR T cells to determine how many labelled cells distribute to solid tumor sites within 3-5 days. Our results demonstrate that cells can be efficiently labelled (≤60%) with high cell viability (≥85%) at a sensitivity sufficient to detect labelled cells at tumor site for up to 5 days. An observed trend in SUV_{mean} & SUV_{max} provided insight into efficacy & individual response to therapy. Early time points showed moderate uptake of labelled cells in lungs posterior basal segments without increased activity over next few days, suggesting a transient process. Mild, diffuse bone marrow & relatively intense uptake of labelled cells in liver & spleen suggests margination of cells to reticulo-endothelial system. Distinct PET signal at some of the tumor sites at 24 h suggests antigen specific localization & time taken to reach these sites. Excretion via hepatobiliary indicated reabsorption from GI tract & re-circulation of labelled cells. Minimal uptake in brain & heart supported safety profile of labeling agent. **Conclusions:** This is first in human in-vivo study to provide highly valuable visual and dynamic data in real time and provides insight into individual responses to therapy. CAR T cell functionality largely remain unchanged due to labeling process. The findings indicate that labelled cells traffic to tumor sites at later time points & remain persistent for extended period of time. Research Sponsor: Juno Therapeutics, Australian Global Innovation Linkage Grant.

3558 Poster Session (Board #288), Fri, 8:00 AM-11:00 AM

Clinically aggressive malignancies associated with STK11 germline mutations (STK11GCa): A comprehensive genomic profiling (CGP) study. *First Author: Ethan Sokol, Foundation Medicine, Inc., Cambridge, MA*

Background: Germline mutations in the *STK11* (*LKB1*) mTOR pathway gene are associated with Peutz-Jehger's Syndrome and a variety of malignancies of variable clinical aggressiveness. Recent evidence also links *STK11* inactivation with failure to benefit from anti-cancer immune checkpoint inhibitor (IO) therapy in NSCLC. **Methods:** Using hybrid capture based CGP on extracted tumor DNA and a published "somatic-germline-zygosity" SGZ data analysis algorithm on 212,470 samples of clinically advanced malignancies, we identified 103 (0.05%) STK11GCa inactivating base substitutions or indels. Tumor mutational burden (TMB) was determined on up to 1.1 Mbp of sequenced DNA and microsatellite instability (MSI) was determined on 114 loci. PD-L1 expression was determined by IHC (Dako 22C3). **Results:** 57 (55%) STK11GCa cases were NSCLC, 7 (7%) STK11GCa cases each were CRC, breast, pancreatic and unknown primary carcinomas, and 3 (3%) were gynecologic cancers. Amongst all samples included in this analysis, *STK11* germline alterations were found in 0.15% NSCLC, 0.03% CRC, 0.03% breast, 0.08% pancreas, 0.06% unknown primary carcinoma and 0.03% of gynecologic cancers. Additional malignancies harboring STK11GCa included melanoma, gastroesophageal, HNSCC, bladder, HCC, lymphoma and mesothelioma. In STK11GCa, the median patient age at sequencing was 61 years (range 2 to > 89 years); gender distribution was 52% female and 48% male. STK11GCa cases had a median of 6.5 genomic alterations (GA)/tumor and *KEAP1*, another IO resistance gene, was co-altered in 10%. Currently untargetable GA were detected in *TP53* (50%), *KRAS* (38% with 9% in potentially targetable G12C), *CDKN2A* (32%), *CDKN2B* (22%), *SMARCA4* (19%), *MYC* (11%), and *APC* (10%). Potentially targetable GA, which have also been linked in some studies to IO efficacy, included GA in *BRAF* (10%), *EGFR* (9%) and *PBRM1* (4%). No targetable gene rearrangements or fusions were identified. No MSI High cases were identified. The median TMB was 5 mut/Mb with 23 % >10 mut/Mb and 4% >20 mut/Mb. 15% of 20 evaluated STK11GCA cases were PD-L1 high (>50% tumor cell staining). **Conclusions:** STK11GCa include a wide variety of primary tumors with a paucity of co-occurring targetable GA. Although these tumors have significant PD-L1 staining and a subset harbor other markers of potential IO efficacy, the inactivated *STK11* in these tumors may contribute to IO resistance and lack of responsiveness to immunotherapies. Research Sponsor: Foundation Medicine Inc.

3559 Poster Session (Board #289), Fri, 8:00 AM-11:00 AM

A prospective study of prognostic role of plasma circulating tumor DNA (ctDNA) in patients (pts) with early-stage malignancies. *First Author: Mikhail Fedyanin, Federal State Budgetary Institution N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russian Federation*

Background: Recently, conflicting evidence has emerged showing the association of ctDNA level and cancer progression. The aim of our study was the development of a method for detecting ctDNA in plasma and the investigation of the prognostic value of ctDNA retention after surgery in the prospective way. **Methods:** This prospective, single-center, sample collection study; pts with early-stage malignancies of the different origin were included. Tumor somatic mutations were determined by target sequencing of DNA from FFPE tumor blocks. Sequencing was performed using the custom NGS panel covering regions of frequent somatic mutations in 50 genes. Tumor-specific mutations were monitored in plasma samples taken before and after surgery. The median time between surgery and plasma collection was 7 days (5-15). Mutations of plasma ctDNA were determined by ddPCR. The plasma sample was considered "positive" if the content of ctDNA was more than 0.5 copies of mutant DNA in ml plasma. We needed 265 pts for improving 1-year disease free survival (DFS) from 60% to 80% with α=0.01, β=0.1, 10% loss of f.-up and duration of the study for 2 years. **Results:** The study comprised 271 pts with various cancers including colorectal – 91 (33,6%), pancreatic – 37 (13,7%), breast – 66 (24,4%), lung – 35 (12,9%) and gastric cancer – 42 (15,5%). Pts with stage I was 50 (18,5%), stage II – 118 (43,5%) and stage III – 103 (38%). The median time of the f.-up was 9 mos. (1-37). No significant association was found between the level of ctDNA before surgery and DFS either in the general group or in groups stratified by tumor sites (HR 2.4, 95%CI 0.8-7.1, p=0.12 and HR 1.5, 95%CI 0.4-6.3, p=0.5, correspondingly). ctDNA was detected in the plasma after surgery in 57 (10%) pts: 9 (9.9%) cases of colorectal, 10 (27%) - pancreatic, 9 (13.6%) - breast, 19 (54.3%) - lung, and 10 (23.8%) - gastric cancer. Progression of the disease was detected in 28/57 (49%) pts with ctDNA(+) and 17/214 (8%) - in ctDNA(-) pts ($p<0.001$). One-year DFS in ctDNA(+) and ctDNA(-) pts were 57% and 87%, respectively (HR 6.1, 95%CI 3.3-11.2, $p<0,001$). ctDNA positivity after surgery was an independent negative prognostic factor according to Cox regression model fitted to T, N, and adjuvant chemotherapy (HR 5.7, 95%CI 3.1-10.8, $p<0.001$). **Conclusions:** These results demonstrate the prognostic significance of ctDNA persisting after surgery in pts with the early stage of the different malignancies. Further clinical validation of this approach is required in trails with modifications of the adjuvant treatment, according to the content of ctDNA. Research Sponsor: This research is conducted under the auspices of the experimental governmental assignment of the Ministry of Health of the Russian Federation and coordinated by the FSBI "Center for Strategic Planning and Management of Biomedical Health Risks".

3560 Poster Session (Board #290), Fri, 8:00 AM-11:00 AM

Validation of RecurIndex (RI) for patients with early-stage breast cancer enrolled in a Taiwanese multicenter study. *First Author: Yi-Hsuan Lee, Departments of Pathology, National Taiwan University Hospital, Taipei, Taiwan*

Background: Numerous prospective studies, predominantly in Caucasian population, have proven the clinical utility of using multigene expression tests to prevent over-treatment in early breast cancer (EBC) patients. Since racial and ethnic disparities exist in genetic and biological factors that could influence the disease, the primary purpose of this study is to access the clinical utility of RecurIndex, a recurrence risk test, that is based on a genomic profiling derived from Asian women. **Methods:** A total of 298 patients with EBC, luminal subtype (85.6%), HER2 subtype (7.7%) and triple-negative subtype (6.7%), were enrolled in a retrospective study across Taiwan medical centers. Kaplan Meier and Cox Proportional Hazards model were used to, respectively, identify independent prognostic factors and calculate the survival rates. The prediction model was then tested using the area under the receiver operating characteristic curve (AUC). The primary endpoint was distant recurrence-free survival (DRFS). **Results:** The 10-year DRFS was significantly higher in the good-prognosis group than the poor-prognosis group (92.0% [95% CI, 86.1-98.2] versus 63.0% [95% CI, 49.9-79.5]) (Table). The overall hazard ratio for distant recurrence was 1.031 (95% CI, 1.017 ± 1.046) per RI score increment. In addition, in a subset of 179 cases (60.1%), the model yielded an 82.3% correct classification rate for predicting DR with a sensitivity of 87.0%, a specificity of 68.6% and negative predictive values of 97.3%. **Conclusions:** The present study provides robust evidence of the clinical utility of RI-DR to predict clinical outcomes. RecurIndex could be used to determine the utility of chemotherapy in Asian patients, especially in hormone-receptor positive and HER2 negative disease, leading to a meaningful reduction in adjuvant chemotherapy recommendations. Research Sponsor: Amwise Diagnostics Pte. Ltd.

Kaplan-Meier estimates of distant recurrence-free survival rates by RI-DR risk classification.

Risk group	10-year DRFS (%)	P value	Crude hazard ratio (95% CI)
All patients (n=298)		0.0011	
Good prognosis (n=145)	92.0		----
Poor prognosis (n=153)	63.0		3.621 (1.59 - 8.27)
Luminal patients (n=255)		0.0200	
Good prognosis (n=141)	91.6		----
Poor prognosis (n=114)	65.4		2.729 (1.13 - 6.58)
HER2/TNBC patients (n=43)		0.2500	
Good prognosis (n=4)	100.0		----
Poor prognosis (n=39)	61.2		----

Key words: Early breast cancer, Asian women, genomic assay, clinical utility, recurrence index (RI), distant recurrence (DR).

3561 Poster Session (Board #291), Fri, 8:00 AM-11:00 AM

Molecular profiling of metastatic breast cancer (MBC) and target-based therapeutic matching in an Asian tertiary phase I oncology unit. *First Author: Robert John Walsh, Department of Haematology-Oncology, National University Cancer Institute, National University Health System, Singapore, Singapore*

Background: Somatic profiling of MBC has highlighted actionable mutations and driven trials of matched targeted therapy (tx). Previous phase I studies have reported improved outcomes following matched therapies with tumour molecular profiles. Here, we review next generation sequencing (NGS) and treatment outcomes of Asian MBC patients (pts) in the phase I unit of a tertiary centre. **Methods:** Pts with MBC referred to a phase I unit underwent NGS (n = 152). Tumour tissue was sequenced via the amplicon based Ion Ampliseq Cancer (IAC) v2 (50 genes) platform from 2014-2017 prior to institutional change to Foundation Medicine 1 (FM1) (324 genes) 2017-2019. Patients were counselled on findings and enrolled onto matched therapeutic trials where available. **Results:** NGS was successfully performed in 107 pts (IAC 46%, FM1 54%) of which tumour subtypes include hormone receptor positive 63%, triple negative breast cancer (TNBC) 28% and Her2 positive 19%. Median lines of prior tx for MBC was 4 (range 0-12). 89% had prior chemotherapy (CT), 57% prior endocrine therapy (ET). 72/107 (67%) sequenced patients had further treatment and 18 (25%) were matched to tx based on NGS findings (15 clinical trial, 3 off trial). Matching rates on both NGS platforms were similar (IAC 22% *vs* FM1 28%). Mutated pathways with potential matched tx included PIK3CA/AKT/PTEN (52%), DNA damage response (DRR) (15%), and FGFR (11%) pathways. *PIK3* mutations were seen in 43% and associated with higher number of metastatic sites (p = 0.03); most prevalent aberrations were *PIK3CA H1047R* (41%) and *PIK3CA E542K* (13%). Matched cases were more heavily pretreated (mean lines of prior tx 5.3 matched *vs* 3.7, unmatched p = 0.05), and showed a median progression free survival (mPFS) of 24 weeks [w] and clinical benefit rate (complete/partial response or stable disease $\geq$ 12 weeks) of 53% on matched tx. Comparison by NGS platform showed improved mPFS for matched vs unmatched pts sequenced on FM1 *vs* IAC (FM1: 26 *vs* 19w, HR = 0.76 [95% CI: 0.3-1.9]; IAC: 8 *vs* 12w; HR = 1.21 [95% CI: 0.5-2.8]). Interestingly, 1 pt with *SMARCB* mutation, reportedly associated with the FGFR pathway, had a PFS of 70w on tx with a pan-FGFR inhibitor after progressing on 3 prior lines of tx (ET and CT). **Conclusions:** Molecular profiling of MBC in a phase I unit led to matched tx in 25% of cases. Matched pts showed encouraging mPFS with a suggestion of benefit in those matched after sequencing on a broader gene panel (FM1). Research Sponsor: NCIS Centre Grant - NMRC/CG/M005/2017_NCIS.

3562 Poster Session (Board #292), Fri, 8:00 AM-11:00 AM

Exomes and transcriptomes to reveal actionable findings in patients with negative-targeted panel sequencing. *First Author: Eric Y. Zhao, Canada's Michael Smith Genome Sciences Centre, Vancouver, BC, Canada*

Background: Next generation sequencing targeted panels increasingly inform clinical decisions, but may miss actionable findings detectable by whole exome sequencing (WES) and RNA-seq. There has been no direct comparison of WES plus RNA-seq against targeted panel sequencing to determine its added utility. To address this, we performed WES and RNA-seq analysis in a cohort of 100 patients with no actionable findings on prior panel sequencing. **Methods:** Ontario-wide Cancer Targeted Nucleic Acid Evaluation (OCTANE; NCT02906943) has sequenced 2,106 patients using a 161-gene Oncomine or 555-gene Hi5 panel. 100 patients (98 Hi5, 2 Oncomine) were chosen for further sequencing. Tumor (100x coverage) and normal (50x) exomes and tumor transcriptomes were sequenced on Illumina HiSeq2500 or NextSeq550. Interpretation included knowledgebase annotation (e.g. OncoKB, CIViC), mutation signatures, homologous recombination deficiency (HRD) scores, gene expression, and pathway analysis. Findings were deemed "actionable" if they could directly inform management or trial eligibility. **Results:** WES and RNA-seq identified one or more novel actionable findings in 38 patients. Of these, the main actionable finding was tumor mutation burden (TMB), mutation signature, or HRD score in 19 (50%), a copy number variant in 16 (42%), a fusion in 2 (5%), and a point mutation in 1 (2.6%). WES identified a *MALAT1-GLI1* fusion in a cancer of unknown primary (CUP) whose transcriptome was consistent with gastric cancer, together suggesting the diagnosis of a rare gastroblastoma. To date, two cases have received exome-supported targeted therapy: (1) a metastatic high grade serous ovarian cancer, HRD-high, treated with olaparib then cisplatin for a combined 15 months, and (2) a metastatic neuroendocrine rectal tumor with RICTOR amplification treated with everolimus starting in Dec 2016 until last follow-up in Sep 2019. Of 62 patients with no actionable finding, expanded sequencing identified one or more known cancer drivers in 25 (40%): 17 CNVs, 3 fusions, and 5 point mutations or indels. In 16 patients, an oncogenic variant found on panel was not captured by WES, and may represent artifacts, germline mutations, or subclonal/localized variants. **Conclusions:** WES and RNA-seq expanded detection of actionable biomarkers and oncogenic mutations, especially CNV, TMB/signatures, and HRD. Two cases have undergone exome-supported targeted treatment. We performed the first WES of a rare gastroblastoma, originally a CUP but reclassified by expanded fusion detection and RNA-seq. Research Sponsor: The Government of Ontario and The Princess Margaret Cancer Foundation.

3563 Poster Session (Board #293), Fri, 8:00 AM-11:00 AM

Machine learning radiomics signature on magnetic resonance imaging associated with phenotypes and disease-free survival in patients with breast cancer (RBC-01): A registry-based, multicenter cohort study. *First Author: Herui Yao, Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Department of Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China*

Background: The early stage breast cancer patients can vary in disease-free survival (DFS), innovative predictors evaluate the prognostic capacity are urgently needed. We aimed to develop and independently validate a radiomics signature based on MRI associated with phenotypes and DFS in patients with breast cancer and to establish a radiomics nomogram that incorporates the radiomics signature and clinicopathological findings using computational algorithms. **Methods:** In this multicenter, retrospective, cohort study, we analyzed preoperative contrast–enhanced MRI data from the prospective cohort study (n = 123) of patients who had been treated with neoadjuvant chemotherapy in phase 3 trials and independent cohort (n = 438) at the Sun Yat-sen Memorial Hospital as training cohort to develop the radiomic signature, and validated it in validation cohort (Foshan cohort, n = 121; Dongguan cohort, n = 89) between November 17, 2011, and September 21, 2019, and validated in TGCA cohort (n = 84). Machine-learning algorithm to identify robust imaging subtypes and evaluated their clinical and biologic relevance. A nomogram combining the radiomic signature and clinicopathological findings to predict individual survival based on Cox regression model. The primary endpoint was disease-free survival (DFS). This study is registered with ClinicalTrials.gov, number NCT04003558, and Chinese Clinical Trail Registry, number ChiCTR1900024020. **Results:** A total of 855 breast cancer patients were included. Radiomics signature was generated to classify patients into high-risk and low-risk groups in the Guangzhou training cohort. Patients with low-risk scores in the training cohort had higher DFS (hazard ratio [HR] 0.55, 95% CI 0.31 to 0.99; *P*= 0.045) than patients with high-risk scores, and validated in in validation cohort (HR 0.14, 95% CI 0.03 to 0.62; *P*= 0.003). The nomogram combined radiomics score with clinicopathological factors could accurately predict DFS benefits in training cohort (C-index = 0.83; AUC, 1, 2, 3-year were 0.80, 0.85, 0.82, respectively) and validated in validation cohorts. **Conclusions:** The radiomics signature are significantly associated with the DFS in patients with breast cancer. Combining the radiomics nomogram improved individualized DFS pretiction. Clinical trial information: NCT04003558. Research Sponsor: None.

3564 Poster Session (Board #294), Fri, 8:00 AM-11:00 AM

Comparison of the clinical interpretation of high-dimensional molecular data by two molecular tumor boards. *First Author: Damian Tobias Rieke, Charité Universitätsmedizin Berlin, Berlin, Germany*

Background: The clinical interpretation of molecular data is a bottleneck of precision oncology. High-dimensional molecular data, such as RNA sequencing (RNA-seq) and whole-exome sequencing (WES), will likely increase the complexity of clinical interpretation. We compared the recommendations by two molecular tumor boards (MTBs) that independently interpreted the same high-dimensional molecular profiles. **Methods:** Patients with advanced solid tumors, no available standard therapy, an ECOG performance status of 0-1, and available fresh-frozen tissue underwent WES of tumor tissue and normal blood as well as RNA-seq of tumor tissue within the MASTER (Molecularly Aided Stratification for Tumor Eradication Research) precision oncology program of the German Cancer Consortium (DKTK). Data from 46 patients (WES and RNA-seq, n = 41; WES alone, n = 5) were independently discussed by two MTBs. Treatment recommendations were compared with regard to levels of evidence, therapeutic baskets, and types of biomarkers. **Results:** A total of 51,610 aberrations (median, 393 per patient) were considered for clinical interpretation (34,314 mutations/single-nucleotide variants, 7,115 mRNA expression changes, 6,144 DNA copy number variations, 4,037 gene fusions). 110 and 132 treatment options were identified by the two MTBs, respectively, with an overall agreement rate of 44.1%. The highest agreement rates were identified for treatment options based on clinical levels of evidence (Level 1, 60%; Level 2, 49.6%) and for poly(ADP-ribose)-polymerase inhibition (57.1%). The lowest agreement rates were identified when MTBs opted for traditional chemotherapy (0%), combination therapies (6.9%), therapies based on preclinical levels of evidence (Level 3, 35.9%; Level 4, 32%), and MAPK inhibition (35%). Similar agreement rates, ranging from 39% (gene fusions) to 54% (loss of heterozygosity), were observed for different types of biomarkers. **Conclusions:** Reproducible, evidence-based annotation of high-dimensional molecular data is feasible. Our experience provides a basis for ongoing harmonization and standardization efforts within the MTBs of the DKTK. Research Sponsor: Deutsches Konsortium für translationale Krebsforschung.

3565 Poster Session (Board #295), Fri, 8:00 AM-11:00 AM

ERBB2 amplifications and mutations in 109 advanced breast cancer patients by next-generation sequencing. *First Author: Ami N. Shah, Northwestern University, Chicago, IL*

Background: In advanced breast cancer (ABC) HER2 status is based on ASCO/CAP immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) criteria. Next generation sequencing (NGS) of tissue and blood can detect aberrations in *ERBB2* such as copy number gain/amplifications (cng/amp) and mutations. **Methods:** We retrospectively identified patients (pts) seen at Northwestern University between 2015 and 2019 with ABC and an alteration in *ERBB2* identified by tissue and/or circulating tumor DNA (ctDNA) NGS. We included pts with testing by Guardant360, TempusX, and/or FoundationOne platforms. NGS reports were evaluated for non-synonymous mutations and cng/amp. HR and HER2 status were determined based on the most recent pathologic assessment. Mutations were categorized as pathologic if they were consider oncogenic (level 1-2 evidence with direct functional data), likely oncogenic, or predicted oncogenic, based on OncoKB (Chakravarty et al., JCO PO 2017). **Results:** 109 cases of ABC (6 locally advanced, 103 metastatic) with *ERBB2* alterations were identified. Tissue NGS was available from 43%, ctDNA from 72%, and both from 19%. The positive predictive value (PPV) of *ERBB2* amp/cng by tissue NGS to predict HER2+ using the gold standard as IHC/FISH was 94% (33/35). The PPV of *ERBB2* amp by ctDNA was 93% (40/43). *ERBB2* mutations were detected in 52 pts. Of these, 23 pts were considered to harbor pathologic *ERBB2* mutations, (19 oncogenic, 2 likely oncogenic, 1 predicted oncogenic) detected by ctDNA and tissue in 4, ctDNA in 16, and tissue in 3 pts. The most frequently detected mutations were V777L and S310. Four pts had co-mutations of *ERBB2* V777L and S310F. Disease subtype among those with *ERBB2* pathologic mutations was HR+ HER2- in 57%, HER2+ in 26%, and triple negative in 17%. In all patients with serial ctDNA analysis and pathologic *ERBB2* mutations, the mutation was detected on the first analysis. Pathologic *ERBB2* mutation represented the mutant with the highest mutant allele frequency (MAF) in 30% and top 3 highest MAF in an additional 35%. *PIK3CA* was co-mutated in 48%. **Conclusions:** The PPV of *ERBB2* amp/cng by tissue and ctDNA NGS was high, and has potential utility for cancers where HER2 IHC/FISH is not standardly assessed or cases where biopsy is challenging. *ERBB2* pathologic mutations were found in all breast cancer subtypes. When present, they were identified on the initial ctDNA analysis and often represented a significant clone, supporting its role as a 'driver mutation'. Research Sponsor: None.

3566 Poster Session (Board #296), Fri, 8:00 AM-11:00 AM

Platform comparison of HTG EdgeSeq and RNA-Seq for gene expression profiling of tumor tissue specimens. *First Author: Di Ran, HTG Molecular Diagnostics, Tucson, AZ*

Background: Clinical biomarker studies are often hindered by the availability of tissue specimens of sufficient quality and quantity. While RNA-Seq is often considered the gold standard for measuring mRNA expression levels in cancer tissue, it typically requires multiple formalin-fixed paraffin-embedded (FFPE) tissue sections to extract a sufficient amount of quality RNA for subsequent gene expression profiling analysis. The HTG EdgeSeq technology is a gene expression profiling platform that combines quantitative nuclease protection assay technology with next-generation sequencing detection. Unlike RNA-Seq, the HTG EdgeSeq technology does not require RNA extraction, and can use small amounts of tissue material, typically several mm^2, to generate reproducible gene expression profiles. **Methods:** This study compares the performance of RNA-Seq and HTG's profiling panel, the HTG EdgeSeq Precision Immuno-Oncology Panel (PIP), which is designed to measure expression levels of 1,392 genes focused on tumor/immune interaction. Approximately 1,200 samples from three tumor indications (gastric cancer, colorectal cancer and ovarian cancer) were tested using both technologies. **Results:** Up to four FFPE slides were used for RNA extraction to support RNA-Seq testing; out of the 1,202 samples processed, 1,099 generated extracted RNA of sufficient quality and quantity (as measured by RNA concentration, RIN score and %DV200) to proceed to sequencing, which resulted in a pass rate of 91.4% for RNA-Seq. The HTG EdgeSeq PIP panel resulted in a pass rate of 97.3% (samples passing QC metrics) when the same 1,200 samples were tested, and required only a single FFPE section owing to the small sample requirement. The t-SNE (a non-linear dimensionality reduction method) analysis of the common 1,358 genes revealed similar clustering of the three cancer indications between the two methods. Correlations across individual genes by sample resulted in the mean Spearman correlation coefficient of 0.73 (95% confidence interval of 0.61 - 0.80). Additionally, gene-wise comparisons across all samples were also evaluated. **Conclusions:** These data demonstrate that HTG EdgeSeq gene expression panels can be used as a competitive alternative to RNA-Seq, generating equivalent gene expression results, while offering the added benefits of a small sample size requirement, lack of RNA extraction bias, and fully automated data analysis pipeline. Research Sponsor: HTG Molecular Diagnostics and Oncologie, Inc.

3567 Poster Session (Board #297), Fri, 8:00 AM-11:00 AM

Diagnosis of leptomeningeal metastasis (LM) through identification of circulating tumor cells (CTCs) in cerebrospinal fluid (CSF). *First Author: Kathleen Fenn, Department of Medicine at Columbia University Medical Center, New York, NY*

Background: Diagnosis of LM from solid tumors can be challenging. The TargetSelector (TS) CTC detection assay has demonstrated highly specific and sensitive CTC capture both for epithelial (CK+) and non-epithelial (CK-) subsets. The assay utilizes a ten-antibody (ab) capture cocktail followed by biotinylated secondary abs that bind to CTCs, enriched in a microfluidic device. TS targeted next-generation sequencing (NGS) assay detects somatic mutations in 12 breast cancer-related genes. The aim was to determine whether TS can improve sensitivity in the diagnosis of LM compared to CSF cytology by lumbar puncture (LP). **Methods:** CSF was collected prospectively from patients (pts) with a prior solid tumor diagnosis and suspicion of LM. CTCs were isolated from CSF using the TS platform. Cells were stained with cytokeratin (CK), CD45, streptavidin and DAPI. CTCs captured in a microchannel were classified as CK + or -. Peripheral blood samples obtained at time of LP underwent similar CTC analysis. Cell-free total nucleic acids (cfTNA) were extracted from plasma and CSF followed by NGS. Data analysis used the Ion Torrent Suite with annotation and report curation by Ion Reporter and Oncomine Knowledgebase Reporter software respectively. **Results:** There were 14 pts (13 women and 1 man), median age 56 years (range 32-75) with cancers of the breast (10), lung (1), colon (1), CNS lymphoma (1) or glioma (1). Pts had received a median of 2.5 lines of systemic metastatic therapy (range 0-8). CSF cytology was not sent for 1 pt and TS was not performed for 1 pt. TS and standard cytology had 89% agreement in pts with metastatic breast cancer (MBC, 8/9). Of the 6 pts for whom CTCs were detected in CSF by TS, 3 pts had + cytology (all MBC), 2 pts had - cytology and 1 pt with MBC was not tested by cytology. Of the 3 pts with + CSF by cytology (all MBC), all were detected by TS (Table). Among 5 MBC pts with CTCs present in CSF, ER status was concordant in 2 of 5 (40%). HER2 status was concordant in 3 of 4 (75%) evaluable pts and not determined in 1 pt. Analysis of cfDNA from CSF identified somatic mutations in 3 pts (TP53, PIK3CA, CCND1, respectively). In 1 of 3 pts, the mutation identified in the CSF (PIK3CA) in HR+/HER2- MBC was also identified in the blood. **Conclusions:** TargetSelector is a viable platform for the detection of breast cancer CTCs in the CSF. NGS performed on CSF samples can identify potentially actionable mutations. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

	LP CTC (+) (n = 6) no. (%)	LP CTC (–) (n = 7) no. (%)
Breast primary	5 (83)	5 (71)
Other primary	1 (17)	2 (29)
CSF cytology +	3 (50)	0 (0)
CSF mutation detected	2 (33)	1 (14)

3568 Poster Session (Board #298), Fri, 8:00 AM-11:00 AM

The utility of blood-based molecular tools-the NETest-to monitor and evaluate the efficacy of PRRT in neuroendocrine tumors. *First Author: Lisa Bodei, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Peptide receptor radionuclide therapy (PRRT) is an effective therapy for metastatic/inoperable neuroendocrine tumors (NETs). Tools to predict and monitor the efficacy of therapy are important adjuncts in the radio-oncology armamentarium. Standard blood biomarkers are not effective by new molecular based assays such as the PRRT Predictive Quotient (PPQ) and NETest are effective as real-time predictors and monitors of therapy. We aimed to prospectively evaluate whether: 1) the NETest functioned as a surrogate biomarker for image-based per RECIST evaluation of PRRT efficacy; 2) there was a correlation between changes in NETest levels during therapy, PPQ prediction and treatment efficacy. **Methods:** Three independent ^{177}Lu-PRRT-treated GEP-NET and BPNEN cohorts (Rotterdam, Netherlands: n= 41; Bad-Berka, Germany: n= 44; Meldola, Italy: n= 72). Treatment response: RECIST1.1 [Responder (stable, partial/complete response) vs Non-Responder]. Blood sampling: pre-PRRT, prior to each cycle and 6 months (median) after completion of all cycles. PPQ (positive/negative) and NETest (0-100 score) by PCR. Stable$<$40; progressive $>$ 40). CgA (ELISA) as comparator. Samples deidentified, measurement and analyses blinded. Kaplan-Meier survival and Mann-Whitney analyses. **Results:** 122 of 157 were evaluable. RECIST stabilization or response in 67%; 33% progressed. NETest significantly ($p<$ 0.0001) decreased in RECIST-"responders" (-47$\pm$3%); in "non-responders" it elevated (+79$\pm$19%, $p<$ 0.0005). NETest monitoring accuracy 98% (119/122). Follow-up levels $>$ 40 (progressive) vs stable ($<$40) significantly correlated with mPFS (not reached vs. 10 months; HR 0.04, 95%CI: 0.02-0.07). PPQ response prediction was accurate in 118 (97%); 99% accurate positive and 93% accurate negative prediction. NETest significantly ($p<$ 0.0001) decreased in PPQ-predicted responders (-46$\pm$3%) and remained increased in PPQ-predicted non-responders (+75$\pm$19%). Follow-up NETest categories stable vs progressive significantly correlated with PPQ prediction and mPFS (not reached vs. 10 months; HR 0.06, 95%CI: 0.03-0.12). In comparison, the standard biomarker, CgA, failed to predict or correlate with response to PRRT (p= NS). **Conclusions:** NETest accurately (98%) monitors PRRT response and is an effective surrogate marker for radiological response (image concordance 98%). A NETest decrease identified responders (99%) and correlated ($>$ 97%) with the pretreatment PPQ response predictor. Research Sponsor: None.

3569 Poster Session (Board #299), Fri, 8:00 AM-11:00 AM

High-risk breast cancer genes at 8q22-24 and their role in over 5,000 patients evaluated with the 70-gene risk of recurrence assay. *First Author: Sami Diab, Rocky Mountain Cancer Center-Aurora, Aurora, CO*

Background: Previous studies have shown that *CCNE2* expression is higher in patients' cancers resistant to CDK4/6 inhibitors. Increased expression of *CCNE2*, *MTDH,* or *TSPYL5*, genes contained within the 70-gene risk of distant recurrence signature (70GS), has also been implicated in breast oncogenesis, poor prognosis, and chemoresistance. These genes are located on chromosome region 8q22.1, one of the most recurrently amplified regions out of all 70GS genes in breast tumors (Fatima et al. 2017). *MYC*, located on 8q24, is overexpressed in 40% of all breast cancers (BC). Here we examined the expression of *CCNE2*, *MTDH,* and *TSPYL5* in relation to 70GS risk and the 80-gene molecular subtype signature (80GS), and their correlation with *MYC* expression in early stage BC patients. **Methods:** *CCNE2*, *MTDH*, *TSPYL5,* and *MYC* mRNA expression was measured in 5022 BC samples sent to Agendia (Irvine, CA) for 70GS and 80GS testing, which included FFPE microarray full-transcriptome data. 70GS was used to stratify patients into Ultra Low Risk (UL), Low Risk (LR), High Risk (HR), and Ultra High Risk (UH). Both 70GS and 80GS were used to classify patient samples into Luminal A, Luminal B, HER2, or Basal type. Wilcoxon rank sum test was used to assess expression differences. **Results:** The expression of *CCNE2*, *MTDH*, and *TSPYL5* significantly correlated with each other and was higher in HR patients compared to LR patients ($p < 0.001$) and higher in UH patients compared to HR patients ($p < 0.001$). Expression of these genes was highest in Basal type tumors, 83% of which were UH, followed by Luminal B type tumors, and lowest in Luminal A type tumors. *CCNE2* and *MYC* expression was elevated in LR compared to UL patients ($p < 0.001$ and $p = 0.0043$). There was no difference in *MYC* expression between HR vs. LR or UH vs. HR. Lastly, there was no association between the expression of 8q22.1 genes and *MYC* in any 70GS subgroup. **Conclusions:** Within the 70GS, *CCNE2, MTDH,* and *TSPYL5* have similar expression patterns and when overexpressed may identify an UH cohort of BC. This observation, in addition to their physical proximity at 8q22.1 suggests a possible amplicon in this region. The highest expression of *CCNE2*, *MTDH,* and *TSPYL5* associated with UH patients and is concordant with previous studies that support the role of these genes in BC metastasis. Furthermore, this analysis suggests *MYC* may not stratify patients based on metastatic potential. These data may be clinically relevant for stratifying patients in ongoing clinical trials evaluating response and resistance to targeted therapies in early stage BC. Research Sponsor: Agendia, Inc.

3570 Poster Session (Board #300), Fri, 8:00 AM-11:00 AM

Adding precision to 2018 ASCO/CAP HER2 testing guidelines in breast cancer with genomic profiling. *First Author: Adam Brufsky, Magee-Womens Hospital of UPMC, Pittsburgh, PA*

Background: Biological heterogeneity of HER2 positive breast cancers has been suggested by a modest benefit of HER2-targeted therapies reported in the APHINITY and ExteNET trials. This highlights the need for improved biomarkers that more precisely identify patients who benefit from HER2-directed agents. The 80-gene molecular subtyping signature (80GS) classifies breast tumors into Luminal, HER2 or Basal type based on the gene expression of downstream signaling pathways. Previous work showed a substantial proportion of tumors identified as HER2 equivocal or HER2 positive by 2013 ASCO/CAP guidelines may be reclassified as non-HER2 type by 80GS. In 2018, ASCO/CAP HER2 IHC/ISH classification guidelines were revised to reduce the frequency of HER2 equivocal cases, for which treatment recommendations have been ambiguous. Here we evaluated concordance between HER2 status by 2018 ASCO/CAP guideline classification and 80GS molecular subtyping. **Methods:** Pathology reports are provided by physicians for samples that are tested with the 70-gene risk of distant recurrence signature (70GS) and 80GS as part of routine diagnostic care. This analysis includes data sent to Agendia (Irvine, CA) from January 2019 to January 2020. HER2 IHC/ISH results based on ASCO/CAP 2018 guidelines were available for 1453 samples. **Results:** Of 1453 samples, 1336 (92%) were HER2 negative, 99 (7%) were HER2 positive, and 18 (1.2%) were HER2 equivocal under 2018 guidelines. 80GS reclassified 57 of 99 (58%) HER2 positive tumors as Luminal and 11 of 99 (11%) as Basal; the remaining 31% were confirmed HER2. Furthermore, 55 of 99 (55%) HER2 positive tumors were also ER and PR positive by IHC, with 48 (87%) of these reclassified as Luminal type. Of HER2 negative tumors, 80GS classified 94 of 1336 (7%) as Basal and 2 of 1336 (0.15%) as HER2. Of HER2 equivocal tumors, 16 of 18 (89%) reclassified as Luminal and 2 of 18 (11%) as Basal. **Conclusions:** In this real-world diagnostic dataset, 2018 ASCO/CAP guidelines resulted in few HER2 equivocal tumors overall, confirming the positive impact of the revised guidelines. However, 80GS reclassified 69% of HER2 positive tumors to non-HER2 molecular subtypes, suggesting these tumors may have suboptimal responses to HER2-directed therapy compared to HER2 enriched. All HER2 equivocal tumors reclassified to non-HER2 subtypes. Molecular classification by 80GS adds further precision in classifying HER2 positive patients and potential to predict responsiveness to HER2-targeted therapies. Further studies are warranted to validate the utility of HER2 status based on 80GS. Research Sponsor: Agendia, Inc.

3571 Poster Session (Board #301), Fri, 8:00 AM-11:00 AM

Genomic analysis of driver-negative lung adenocarcinoma (LA) in lifetime never smokers. *First Author: Aline Fusco Fares, Princess Margaret Hospital, Toronto, ON, Canada*

Background: Genomic events giving rise to driver negative LA in never smokers remain elusive. Here we report results of whole exome sequencing (WES) and targeted RNA sequencing in NS who had no mutation drivers found on routine clinical testing by targeted next generation sequencing (NGS). **Methods:** The cohort of never smokers with EGFR/ALK negative LA by clinical biomarker testing at Princess Margaret Cancer Centre, were first subjected to various clinical NGS profiling platforms (table). Where tissue was available, those negative for potential drivers in the clinical NGS then underwent WES (mean coverage > 200x) and Oncomine comprehensive v.3 RNA sequencing. We analyzed mutational signatures (MS) of the driver negative cohort based on the COSMIC catalog and assessed the median tumor mutation burden (mTMB mut/Mb -Megabase) in cases without a smoking MS, to avoid confounders. **Results:** Of 159 never smokers profiled with clinical NGS, potential drivers were found in 86 (54%): 75 (87%) with mutations in known LA driver genes and 11 (13%) with fusions. Among the remaining never smokers that tested negative by clinical NGS, 35 (48%) had available tissue for further testing. The Oncomine panel identified 9 cases (25%) with fusions or MET exon14 mutation (n = 7). Within the driver negative group, 24 (92%) underwent WES. Three tumors had WES base substitution patterns that were consistent with a smoking-related MS (MS4). Twenty-one patients exhibited signatures found common across all cancer types (MS 5), associated with DNA mismatch repair (MS 6, MS 20) or APOBEC over-activation (MS 2, MS13). In the driver-negative group, we identified 7 pts with somatic mutations in the KMT2 family (4 KMT2C, 4 KMT2A, 1 KMT2D), known for putative tumor suppressors and histone methyltransferases. mTMB on the driver negative group was 1.92, while one outlier with APOBEC MS and KMT2C/A mutations had a TMB of 16.8. **Conclusions:** Never smokers with driver negative LA are a heterogeneous group, with different MS and a wide TMB range. Mutations on KMT2 family are frequently found in driver negative LA in never smokers and warrant further investigations. Research Sponsor: Alan Brown Chair.

Never smokers EGFR/ALK negative with routine clinical NGS	**Drivers on NGS** N = 86 (54%)	**Mutations:** KRAS (35%) HER2 (33%) BRAF (9%) METex14 (7%) FGFR (4%)
N = 159 • 15 genes N = 89 • > 150genes N = 41 • Blood Guardant360 or Foundation blood N = 29		**Fusions:** ROS1 (6%) NRG1 (3%) RSPO2 (3%) RET (3%)
	No drivers on NGS N = 73 (46%)	**Tissue for WES and RNA panel** N = 35 (48%)
		Fusions N = 9 METex14 (20%) NTRK (3%) RSPO (3%)
		WES on driver negatives N = 24 (2 no material) KMT2 (29%), ATM (12%) SMAD4 (8%) ARID2 (4%)

3572 Poster Session (Board #302), Fri, 8:00 AM-11:00 AM

Ultrasensitive multiplex detection of structural rearrangements in *ALK*, *RET*, *ROS1* and *PD-L1* using a comprehensive next-generation sequencing assay. *First Author: Kao Chin Ngeow, Lucence Diagnostics, Singapore, Singapore*

Background: Oncogenic structural rearrangements (SR) in *ALK*, *RET* and *ROS1* are well-described in lung cancer, and confer sensitivity to targeted therapy. SR disrupting the 3'UTR of *PD-L1* gene have been reported in multiple cancer types and can potentially predict response to checkpoint immunotherapy. An amplicon-based next-generation sequencing (NGS) platform technology (AmpliMARK), previously optimized for detection of single nucleotide variations (SNVs), microsatellite instability and viral DNA, was extended to the multiplex detection of SR in *ALK*, *RET*, *ROS1* and *PD-L1* in cell-free DNA (cfDNA) and tumor tissue DNA. **Methods:** A hybrid primer-extension and adapter-ligation based method allowing detection of SR in a fusion-partner agnostic manner was utilized for multiplex target capture of genomic regions of *ALK*, *RET*, *ROS1* and *PD-L1* SR. Analytical validation was performed using admixtures of fragmented genomic DNA from an *ALK* SR-positive cell line, commercial standards containing *RET* and *ROS1* SR, and synthetic *PD-L1* SR gene constructs. Clinical performance was assessed in cfDNA samples from lung cancer patients and tumor tissue DNA samples from natural killer(NK)/T-cell lymphoma patients. **Results:** Detection of SR could be achieved to an allele frequency detection limit of 0.5% with sensitivity of 89.5% and specificity of 100% in admixture samples mimicking cfDNA. In an unselected series of 374 lung cancer cases, actionable SR for *ALK*, *RET* and *ROS1* were detected in cfDNA of 9 samples, for an overall detection rate of 2.4%, and 1.8% (3 out of 168) when restricted to treatment-naive lung cancer cases only. In 29 NK/T-cell lymphoma tumor tissue samples, 9 samples were positive for *PD-L1* SR, which were orthogonally confirmed by whole-genome sequencing, targeted sequencing or Sanger sequencing for a concordance rate of 100% across all samples. For 1 NK/T-cell lymphoma tumor tissue sample where matched plasma was available, the same *PD-L1* SR was also detected in cfDNA. **Conclusions:** We have demonstrated and validated a comprehensive amplicon-based NGS assay for ultrasensitive multiplex detection of structural rearrangements in *ALK*, *RET*, *ROS1* and *PD-L1* across both cfDNA and tumor tissue DNA in analytical and clinical contexts. Ongoing studies will further evaluate the performance and utility of this assay across a larger number of clinical samples for the detection of these SR as well as additional cancer-associated SR involving *NTRK1/2/3*, *FGFR2/3* and *TMPRSS2*. Research Sponsor: Lucence Diagnostics.

3573 Poster Session (Board #303), Fri, 8:00 AM-11:00 AM

^{89}Zr-durvalumab PD-L1 PET in recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck. *First Author: Sarah Verhoeff, Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands*

Background: Immune checkpoint inhibitors (ICI) targeting programmed cell death protein-1/ligand-1 (PD-1/PD-L1) have shown activity in R/M squamous cell carcinoma of the head and neck (SCCHN). Positron-emission-tomography (PET) with ^{89}Zr-labeled anti-PD-L1 antibodies could aid in predicting response to ICI. We present the dose-finding results of the first-in-human ^{89}Zr-durvalumab PD-L1 PET-imaging in patients with SCCHN participating in the ongoing phase II PINCH study (NCT03829007). **Methods:** Following baseline [^{18}F]FDG-PET and CT/MRI imaging, patients with incurable R/M SCCHN received 37 MBq ^{89}Zr-durvalumab and protein dose 2mg, 10mg or 50mg durvalumab. ^{89}Zr-durvalumab PD-L1 PET-scan was acquired day 5 post-injection. Plasma pharmacokinetic analyses were performed at day 0 and 5. Standardized uptake values (SUV, mean ± SD) were measured in [^{18}F]FDG-positive tumor lesion, liver, spleen, bone marrow and bloodpool. PD-L1-expression was assessed on archival tumor tissue using the Ventana PD-L1 (SP263) assay. **Results:** 14 patients were enrolled and no adverse events were reported. High tracer-retention was observed in liver and spleen, most prominent in patients receiving 2 or 10mg durvalumab. ^{89}Zr-durvalumab accumulation within tumors and between patients was heterogeneous and not all [^{18}F]FDG-positive lesions showed ^{89}Zr-durvalumab uptake. Tumor lesions were visualized best using 10 or 50mg durvalumab (SUV_{peak} 2mg: 3.86 ± 0.79, 10mg: 7.46 ± 2.18, 50mg: 5.57 ± 1.74). Tumor-to-blood-ratios for 10mg durvalumab were highest (2mg: 2.27 ± 0.33, 10mg: 3.44 ± 0.76, 50mg: 1.73 ± 0.99; p = 0.019). PK-analyses confirmed visual prolonged tracer-retention in bloodpool with increasing protein dose. PD-L1-expression was equally distributed amongst dose-groups. **Conclusions:** This is the first study to show feasibility of ^{89}Zr-durvalumab PD-L1 PET in SCCHN patients, demonstrating the highest tumor-to-blood radio with a total dose of 10mg durvalumab. So far, no correlation of tumor PD-L1 expression with ^{89}Zr-durvalumab-uptake and PD-L1 expression on archival tissue was found. Next step will be to correlate ^{89}Zr-durvalumab PD-L1 PET tumor uptake with durvalumab treatment response in the phase 2 part of the PINCH study. Clinical trial information: NCT03829007. Research Sponsor: Astra Zeneca, Radboud Institute for Health Sciences, Junior research project.

3574 Poster Session (Board #304), Fri, 8:00 AM-11:00 AM

PCR-based comprehensive genomic profiling (PCR-CGP): Feasibility from >20,000 tumor tissue specimens (TTS) and predicted impact on actionable biomarker identification versus hybrid capture (H)-CGP and plasma (P)-CGP. *First Author: Dan Rhodes, Strata Oncology, Ann Arbor, MI*

Background: Tissue-based h-CGP is increasingly utilized for treatment selection in patients with advanced solid tumors but has high tumor surface area [TSA] requirements (≥25mm^2 for leading commercial tests). P-CGP is recommended when tissue is insufficient for H-CGP. Here we assessed the feasibility and clinical impact on actionable biomarker identification of PCR-CGP. **Methods:** We performed a post-hoc, non-prespecified analysis on 21,743 consecutive subjects with advanced solid tumors who sent TTS for PCR-CGP from 5/17-12/19 as part of an ongoing observational trial at > 20 U.S. health systems (NCT03061305). PCR-CGP was performed using StrataNGS, a single-site laboratory developed test assessing all CGP biomarker classes (including microsatellite instability (MSI) status and tumor mutation burden [TMB]). We predicted actionable biomarker identification rates for PCR-CGP, H-CGP and P-CGP if applied to all U.S. patients with advanced solid tumors through incorporating population incidence, biomarker frequencies, test TSA and tumor content requirements (or cfDNA detection rates), and performance characteristics. Actionable biomarkers were the 30 in 11 tumor types from the MoIDX p-CGP local coverage determination (L38043), pan-tumor NTRK fusions and MSI, and TMB in lung cancer. **Results:** Among TTS from 21,734 patients with advanced cancer, 20,493 (94.3%) met TSA requirements for PCR-CGP (≥2mm^2) vs. 9,281 (42.7%) for H-CGP. PCR-CGP reported results for 98.0% and 95.0% of patients with large (≥25mm^2 TSA) and small (2-24mm^2) TS, respectively, in a median of 7 business days. Compared to 1,882 orthogonal actionable biomarker results, PCR-CGP accuracy was 96.6% and 96.5% in large and small TTS, respectively. Actionable biomarker frequency was highly correlated in PCR-CGP tested large vs. small TTS (r^2= 0.99), as well as in this PCR-CGP cohort vs. a MSKCC institutional pan-cancer H-CGP cohort (r^2= 0.92). If applied to all U.S. patients with advanced solid tumors, PCR-CGP has significantly greater predicted actionable biomarker identification rate (88.5%) compared to P-CGP (77.0%, N-1 chi-squared test, p < 0.0001) or H-CGP (54.3%, p < 0.0001). **Conclusions:** Half of TTS submitted for PCR-CGP did not meet H-CGP tissue requirements. PCR-CGP is feasible for the vast majority of patients and is predicted to expand the actionable biomarker evaluable proportion of patients with advanced solid tumors compared to H-CGP or P-CGP. Clinical trial information: NCT03061305. Research Sponsor: Strata Oncology.

3575 Poster Session (Board #305), Fri, 8:00 AM-11:00 AM

Hyperprogression in cancer patients on immunotherapeutic agents. *First Author: Sumi Dey, University of Michigan, Ann Arbor, MI*

Background: Patients (pts) treated with checkpoint inhibitors (CPI) may uncommonly experience accelerated progression in their tumor burden when compared to their rate of progression prior to receiving CPI. This hyperprogression has been varyingly defined and no biomarker has yet been identified. **Methods:** We reviewed the database from the Tumor Response Assessment Core (TRAC) at University of Michigan to identify these patients. Hyperprogression was defined as increase in tumor burden per specific immune RECIST criteria by at least 40% from baseline on the first follow-up scan with a minimum increase of 10 mm, and at least 2 times rate of growth than observed prior to start of CPI therapy. **Results:** Out of 741 pts who underwent baseline and 1st follow-up assessment enrolled on 118 trials, 302 (34.4%) pts received immunotherapy alone or in combination with chemotherapy/targeted agents across 49 trials. Of them, 15 pts (5%) with 5 females (33%) and median age of 63 years (range, 44 -72) met criteria for hyperprogression. The primary cancers included lung (5), colorectal (2), renal (2), biliary (1), pancreatic (1), esophageal (1), bladder (1), small bowel (1), and melanoma (1). The median time to hyperprogression was 67 (range 42-110) days, and the mean survival was 7.9 months from trial enrollment. We did not identify any clinical factor or specific CPI therapy that associated with hyperprogression. Exploratory biomarker analysis of genomic (gene panel assay) and immune subsets of tissue microenvironment (multiplex staining) is underway. **Conclusions:** This is the largest cohort investigated for hyperprogression across multiple cancers in literature. The rate of hyperprogression observed is less than previously reported in literature, and physicians need to be aware of this possibility while administering CPI to their patients. Research Sponsor: None.

3576 Poster Session (Board #306), Fri, 8:00 AM-11:00 AM

Targetable immune checkpoint molecules may be significantly differentially expressed in minority ethnicities. *First Author: Jacob J. Adashek, University of South Florida, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Studies of immune checkpoint blockade therapy (ICT) outcomes have been largely performed in melanoma and lung cancer patients, both of which are enriched for White patients. For example, a National Cancer Database study found that 97% of first-line ICT treatments in melanoma have been administered to White recipients (Patel, ASCO-SITC 2020). Given expanding indication in tumor types affecting more diverse populations, we sought to study whether minority populations might be projected to have differing checkpoint blockade response rates. **Methods:** Ethnicity information and RNAseq expression profiles and primary site information were obtained for 7087 patients from TCGA. Ethnicity was tested for association with RNA expression of targetable checkpoint genes (*PD1, PDL1, PDL2, CTLA4, IDO1, LAG3, TIM3, TIGIT, OX40, VISTA*, and *GITR*) in 5 tumor histology types by Wilcoxon methods with Benjamini-Hochberg correction for multiple hypothesis testing. A dataset of $>$ 2700 cases was obtained from NantHealth, with paired whole exome/RNAseq data. Ethnicity for 579 patients was assigned using allele-fraction from ~250 single nucleotide polymorphic sites found exclusively in 6 populations within the 1000 Genomes project. Ethnicity/checkpoint associations found in TCGA were tested within this dataset. **Results:** Within the TCGA cohort, ethnicity was not a factor in differential expression of checkpoint molecules in lung cancer. Within melanomas, in Asian patients *PDL1, CTLA4*, and *IDO1* were expressed at lower levels than in White patients (each $p = 0.04$). These associations did not remain significant after correction for multiple hypothesis testing. Breast cancers in Black patients had significantly higher *PD1, CTLA4, IDO1, LAG3, GITR*, and *OX40* expression compared to White patients, all remaining significant after correction (adj. p 3.7e-5 to 6.4e-3). Among White patients, colon cancers showed higher expression of *PDL1/2, IDO1, LAG3, TIM3*, and *GITR* (p 0.04 to 0.0017). *IDO1* was significantly higher in White patients even after correction (adj. $p = 0.03$), and lower in Black patients (adj. $p = 0.03$). **Conclusions:** Ethnicity may represent a significant factor for efficacy checkpoint blockade therapies. White breast cancer patients might be anticipated to exhibit reduced sensitivity to PD1/CTLA4 blockade, while Black colon cancer patients may exhibit reduced sensitivity to IDO1 therapies such as epacadostat. A biomarker-driven approach to patient selection may ameliorate ethnic disparities in ICT outcomes. Research Sponsor: None.

3577 Poster Session (Board #307), Fri, 8:00 AM-11:00 AM

Comparison of recurrence patterns after surgery and radiation therapy with 68Ga-PSMA-11 PET/CT in nonmetastatic castrate-sensitive prostate cancer patients: A single-center post-hoc retrospective analysis in 787 patients. *First Author: Wesley R Armstrong, Ahmanson Translational Theranostics Division, University of California, Los Angeles, CA*

Background: 20 to 50% of prostate cancer (PCa) patients undergoing radical prostatectomy (RP) or definitive radiation therapy (dRT) will experience disease recurrence. However, anatomical recurrence patterns may differ depending on the therapeutic approaches. The aim of this post-hoc retrospective analysis was to investigate if the relapse pattern as assessed by 68Ga-PSMA-11 PET/CT was different depending on the type of local pelvic therapy (RP, dRT, salvage RT (SRT), pelvic lymph node dissection (PLND), pelvic lymph node RT (PLNRT)) in patients with non-metastatic castrate sensitive (nmCS) recurrent disease after primary definitive therapy. **Methods:** Patients who underwent a 68Ga-PSMA-11 PET/CT for nmCS PCa recurrent disease after primary definitive therapy were screened from a database of 4 prospective studies (NCT02940262, NCT03515577, NCT04050215, NCT03582774). Patients who underwent primary staging ($n = 95$), without definitive therapy ($n = 68$), with known metastatic disease (M1) ($n = 68$) or with castrate resistant (CR) disease ($n = 291$) were excluded. We examined the relationship between recurrence patterns as assessed by 68Ga-PSMA-11 PET/CT (PROMISE criteria) and prior local treatments: i) RP, ii) dRT, iii) RP + SRT. **Results:** 787 patients were included in the analysis. Positive scan rates were 60%, 94% and 75% in RP, dRT and RP + SRT populations, respectively. Median pre-scan PSA levels were 0.50 (0.02-72.5) ng/ml, 4.4 (0.1-202) ng/ml, and 1.07 (0.04-33) ng/ml for patients who underwent RP ($n = 464$), dRT ($n = 109$) and post-RP SRT ($n = 214$). Median time to first recurrence was 27.7 after RP and 54.6 months after dRT ($p = < 0.0001$). Patients who underwent RP had lower local recurrence (LR) pattern (T+) rates by PSMA PET than those with dRT (99/464; 21% vs 69/109; 63%; $p = < 0.0001$). Nodal metastasis (N1) positivity rate was similar between RP and dRT (179/464; 39% vs 43/109; 39%; $p = 0.87$). Extrapelvic metastasis (M1) positivity rate was lower for RP than dRT (93/464; 20% vs 51/109; 47%; $p = < 0.0001$). Median time from post-RP SRT to second recurrence was 22.3 months. In patients who had a second recurrence after RP and SRT the positivity rate of LR (T+), N1 disease and M1 disease by PSMA PET/CT was 12% (24/214), 46% (99/214) and 44% (95/214). **Conclusions:** In this cohort of patients with nmCS PCa recurrent disease after primary definitive therapy, the patterns of failure differ based on prior local treatments. Research Sponsor: None.

3578 Poster Session (Board #308), Fri, 8:00 AM-11:00 AM

Highly accurate automated tissue classification using deep learning on digital pathology images: A novel tool for resolving conflicts in diagnosis. *First Author: Stephen Charles Benz, NantOmics, LLC, Santa Cruz, CA*

Background: Pathologist inspection of biopsy slides is the gold-standard for diagnosis and is crucial for effective therapy decisions. However, expert shortage is resulting in turnaround times exceeding College of American Pathologists' (CAP) standards (Alshieban, 2015). Further, discrepancy between diagnoses can exceed 4% (Mukhopadhyay, 2018), and 2% of cases are designated as 'carcinoma of unknown primary' (CUP) negatively affect outcomes due to difficulty selecting therapies (Rassy, 2020). Here we sought to aid in diagnosing patients from whole-slide images (WSIs) using deep neural networks. **Methods:** $>$ 6.3K high-resolution H&E-stained diagnostic WSI of formalin-fixed paraffin-embedded (FFPE) tumor block slices were selected from TCGA sources. Slide images were obtained from 30 different cancer subtypes including 368 Breast (5.6%), 324 Colon (5.12%), 287 Lung Adenocarcinoma (LUAD) (4.5%), Lung Squamous-Cell carcinoma (LUSC) (4.5%), and Stomach Adenocarcinoma (4.3%). Local regions containing tumor tissue were automatically identified by training an *Inception V3* deep-learning network as previously presented. A separate *Inception V3* network was trained to classify the primary tissue of 200mm^2 tumor regions in 60% of the images, which was validated in the remaining 40% testing cohort. **Results:** The proposed deep-learning model was 92.7% accurate in identifying the primary tissue within the test set of WSIs. As expected, most misclassification occurred in highly-related tissue-types: Rectal cancers misclassified as colon (25%) and vice versa (4.8%), uveal melanomas misclassified as cutaneous melanomas (18.6%), cholangiocarcinomas as hepatocellular carcinomas (8.6%), and LUSC misclassified as LUAD (6.0%) and vice versa (3.4%). Combining related tissues, the classifier achieves 94.6% accuracy across 24 primary types. Unexpectedly, cutaneous melanomas samples were misclassified as breast (9.1%) and LUSC (5.6%), suggestive of related molecular phenotypes. **Conclusions:** By focusing machine-vision attention on tumor regions, the automated system approaches pathologist accuracy. Used in conjunction with molecular profiling, rates of CUP or misdiagnosis can feasibly be minimized to improve patient care. This system is currently being validated in an external set of $>$ 4K unselected clinical cases from the NantHealth database. Research Sponsor: ImmunityBio.

3579 Poster Session (Board #309), Fri, 8:00 AM-11:00 AM

A phase Ib study of oral Chk1 inhibitor LY2880070 as monotherapy in patients with advanced or metastatic cancer. *First Author: Wilson H. Miller, Segal Cancer Center, Jewish General Hospital, Rossy Cancer Network, McGill University, Montreal, QC, Canada*

Background: LY2880070 (LY) is an orally-administered, selective adenosine triphosphate-competitive inhibitor of checkpoint kinase 1 (Chk1). LY blocks the checkpoint response, and Chk1 inhibition results in mitotic catastrophe to produce apoptosis. **Methods:** This 2-part, open-label multicenter study explores the safety, pharmacokinetics (PK) and anti-tumor activity of LY in patients with advanced or metastatic cancers. The primary objective of this study was to determine the maximum tolerated dose (MTD) for multiple escalating oral doses of LY. Secondary objectives were to: 1) Characterize the dose-limiting toxicities (DLTs) and overall safety profile for LY; 2) Evaluate the PK of LY; and 3) Evaluate the anti-tumor activity of LY. Patients received LY orally in 21-day cycles in two treatment arms: 1) A multiple ascending dose (MAD) arm in patients with normal/intermediate CYP2D6 metabolism; or 2) An arm with LY administered as monotherapy to CYP2D6 poor metabolizers. **Results:** The MTD in normal/intermediate CYP2D6 metabolizers was 200 mg BID daily. A dose of 400 mg QD was not tolerated even with the use of anti-emetics. However, BID administration (same total daily dose) made LY tolerable. Dose-limiting toxicities were predominantly vomiting, nausea, and fatigue, and appeared to be correlated with C_{max}. The mean half-life was 5.35 (+/- 2.3) hours. BID dosing provided maintenance of the AUC (3271.4 h•ng/mL 200 mg BID vs 3377.9 h•ng/mL 400 mg QD) while lowering C_{max} (350.0 ng/mL 200 mg BID vs 691.9 ng/mL 400 mg QD) and increasing C_{min}, compared to QD dosing of the same total daily dose. Importantly, BID administration of 200 mg LY resulted in a median C_{min} at steady-state that remains above the IC_{80} for 12 h/day and above the IC_{50} for 24 h/day. Five patients had a best response of SD for a duration of $\geq$ 6 cycles. **Conclusions:** LY was tolerated in a daily BID schedule. The toxicity profile can be modulated by changing the dosing frequency from QD to BID while administering the same daily dose. LY may be a potential combination therapy with DNA damaging agents. Study #: NCT02632448. This study is sponsored by Esperas Pharma Inc., 1255 boul. Robert-Bourassa #1610, Montreal, Qc, H3B 3X3. Clinical trial information: NCT02632448. Research Sponsor: Esperas Pharma Inc.

3580 Poster Session (Board #310), Fri, 8:00 AM-11:00 AM

Preclinical evaluation of XPO1 inhibition in Wilms tumors. *First Author: Michael Vincent Ortiz, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: XPO1 is a nuclear export protein that selectively transports tumor and growth regulatory proteins out of the nucleus, thereby effectively inhibiting their function. We previously utilized the Virtual Inference of Protein-activity by Enriched Regulon analysis (VIPER) algorithm to discover that malignant rhabdoid tumors were dependent upon XPO1 inhibition and then evaluated a preclinical cohort using selinexor (KPT-330), the first-in-class selective inhibitor of nuclear export, to demonstrate that XPO1 inhibition was sufficient to cause cell cycle arrest, apoptosis, and disease control in multiple cell line and patient derived xenograft (PDXs) models. Our subsequent analysis revealed that the most common childhood kidney tumor, Wilms tumor, has even high higher inferred activity of XPO1 than rhabdoid tumors leading to our hypothesis that XPO1 inhibition is an effective therapeutic strategy to treat Wilms tumors. **Methods:** A panel of 9 Wilms tumor cell lines and 3 Wilms tumor PDXs were genomically characterized and tested to evaluate the pre-clinical efficacy of XPO1 inhibition in Wilms tumors. **Results:** Proliferation rate, increased XPO1 protein expression, and loss of function mutations in TP53 correlated with *in vitro* Wilms tumor cell line sensitivity to selinexor. Evaluation of co-segregation of all single nucleotide variant changes using with inferred activity of XPO1 on VIPER in all TGCA tumors demonstrates a strong association with TP53 alterations. XPO1 inhibition was effective in all Wilms tumor models tested, most significantly in MSKREN-57196, a favorable histology Wilms tumor PDX with somatic 1q gain as well as WTX and MYCN mutations, as well as in MSKREN-31827, a diffusely anaplastic TP53 mutant Wilms tumor PDX. Eltanexor (KPT-8602) is an XPO1 inhibitor with decreased CNS penetration and an improved toxicity profile; this drug was tested in these in vivo models and found to be at least as effective as selinexor. **Conclusions:** Somatic 1q gain in favorable histology Wilms tumors and TP53 mutations in diffusely anaplastic Wilms tumors have a particularly poor prognosis in the relapsed setting. Our study demonstrates that XPO1 inhibition may provide a rational therapeutic option to treat such high-risk Wilms tumors. Future clinical trials evaluating XPO1 inhibitors should evaluate its efficacy in children with relapsed Wilms tumors. Research Sponsor: Cycle for Survival, Other Foundation, U.S. National Institutes of Health, Friends and family of Caroline Bhatt.

3581 Poster Session (Board #311), Fri, 8:00 AM-11:00 AM

A phase Ib study of oral Chk1 inhibitor LY2880070 in combination with gemcitabine in patients with advanced or metastatic cancer. *First Author: Quincy S. Chu, Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada*

Background: LY2880070 (LY) is an oral, selective competitive inhibitor of checkpoint kinase 1 (Chk1). Chk1 inhibitors are known to increase the antitumor efficacy of agents such as gemcitabine (GEM), which induce replication stress. Synergy between these two agents has been applied to the clinical setting. **Methods:** This two-part, open-label multi-center study explores the safety, pharmacokinetics (PK), and anti-tumor activity of LY in patients with advanced or metastatic cancers. The primary objective of this study was to determine the maximum tolerated dose (MTD) for multiple escalating oral doses of LY in combination with GEM. Secondary objectives were to: 1) Characterize the dose-limiting toxicities (DLTs) and overall safety profile for LY; 2) Evaluate the PK of LY; and 3) Evaluate the anti-tumor activity of LY. Patients received LY in a variety of different dose regimens, in combination with GEM (50 to 800 mg/m^2) on days 1, 8, and 15 (optional) of a 21-day cycle. **Results:** The combination of LY with GEM required lower doses of both LY (vs 200 mg BID monotherapy RP2D dose) and GEM (vs approved doses). The dose levels explored ranged from LY:GEM of 10 mg QD: 800 mg/m^2 to 50 mg BID:100 mg/m^2. BID dosing of LY was implemented in order to maximize the total daily dose and avoid the adverse events that appeared to correlate with C_{max}. Treatment-emergent adverse events in $>$ 40% of patients included vomiting, nausea, and fatigue. DLTs included reduced platelet count (Gr2), fatigue (Gr3), diarrhea (Gr3), and thrombocytopenia (x2, Gr2). The $t_{1/2}$ of LY was ~ 5 h, and was not significantly affected by combination with GEM. Two patients had a best overall response of SD for a duration of $\geq$ 6 cycles, and a confirmed PR was observed in an ovarian cancer patient who had failed multiple regimens. **Conclusions:** LY was tolerated in combination with lower dose GEM. The toxicity profile can be modulated by changing the dosing frequency from QD to BID while administering the same daily dose. LY may be good candidate for combination therapy with DNA damaging agents. Clinical trial information: NCT02632448. Research Sponsor: Esperas Pharma Inc.

3582 Poster Session (Board #312), Fri, 8:00 AM-11:00 AM

Preclinical evaluation of KZR-261, a novel small molecule inhibitor of Sec61. *First Author: Eric Lowe, Kezar Life Sciences, South San Francisco, CA*

Background: Secreted and transmembrane proteins play key roles in malignant transformation and growth, including in autocrine growth factor expression, receptor oncogene signaling, and immune system evasion. Biogenesis of these proteins involves translocation of the nascent polypeptides into the endoplasmic reticulum (ER) through the Sec61 channel, providing an untapped therapeutic target for a broad spectrum of malignancies. Here we describe preclinical activity of KZR-261 and related inhibitors of Sec61-dependent protein secretion. **Methods:** Sec61 inhibition with KZR-261 and related analog KZR-834 were evaluated using cell lines overexpressing proteins of interest tagged with luciferase. In vitro anti-tumor activity was assessed against a panel of 346 cell lines across 25 tumor types. Quantitative proteomic profiling by mass spec and gene expression profiling by RNAseq were conducted following treatment in multiple solid and heme tumor cell lines. Anti-tumor efficacy was evaluated in athymic nude mice implanted with the cancer cell lines H82 (SCLC), HT29 (CRC), BxPC3 (Pancreatic), 22RV1 (Prostate), H929 (Myeloma) and RL (NHL). Activity was also evaluated in a MC38 syngeneic colon tumor model. **Results:** KZR-261 and KZR-834 exhibited nanomolar potency against many therapeutic targets, including immune checkpoints, VEGF-A, VEGFR and EGFR. Broad in vitro anti-cancer activity was observed with KZR-834, which potently decreased cell viability across both solid and heme tumor types including CRC, Pancreatic, HNSCC, HCC, Lymphoma and Myeloma. Global proteomic analysis observed more than 1.5 fold downregulation of $<$ 10% of detected Sec61 client proteins following treatment, while gene expression profiling revealed upregulation of ER stress response genes in sensitive versus resistant cell lines. Analysis of the TCGA database also found these genes upregulated in a number of different tumor types. In vivo, weekly IV administration was well tolerated and induced a dose dependent anti-tumor response at doses below the MTD in solid and heme xenograft models. In the syngeneic MC38 model, administration of KZR-834 in combination with anti-PD1 antibody resulted in greater anti-tumor activity than either single agent. **Conclusions:** Novel Sec61 inhibitors potently block expression of secreted and membrane proteins, translating into anti-tumor activity against many tumor types in vitro and in vivo, suggesting broad therapeutic potential. Clinical trials are being planned with KZR-261 to understand safety and early efficacy of this novel compound and therapeutic target. Research Sponsor: Kezar Life Sciences.

3583 Poster Session (Board #313), Fri, 8:00 AM-11:00 AM

Results of a completed phase I trial of CBL0137 administered intravenously (IV) to patients (Pts) with advanced solid tumors. *First Author: John Sarantopoulos, Institute for Drug Development, Mays Cancer Center at University of Texas Health San Antonio, San Antonio, TX*

Background: The novel curaxin CBL0137 intercalates into DNA, interfering with histone/DNA binding. Consequent trapping of histone chaperone FACT leads to MYC, NF-kB, and HSF1 inhibition, p53 activation, and an IFN response. CBL0137 shows broad nonclinical antitumor activity (Gasparian et al. Sci Transl Med. 2011; 3(95):95ra74). **Methods:** This dose-ranging study assessed the CBL0137 maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) and CBL0137 safety, pharmacokinetics (PK), and efficacy in adults with advanced treatment-refractory solid tumors. CBL0137 was administered IV on Days 1, 8, and 15 of repeated 28-day cycles until progressive disease (PD) or unacceptable toxicity. Doses were escalated using a 3+3 design based on Cycle 1 dose-limiting toxicities (DLTs). PK was assessed through 168 hours after Day 1. Efficacy was evaluated every 8 weeks. **Results:** The study enrolled 83 pts (M/F [n] = 49/34; median [range] age = 64 [33-85] years; ECOG status [n] = 1/2 [32/51]), with cancer types (n) of colorectal (23), prostate (7), glioblastoma (6), liver (6), non-small-cell (5), and others (36) across 17 dose levels from 10 to 700 mg/m^2/infusion. Durations of therapy ranged to 24 months. Cycle 1 DLTs (n type) were observed at 240 mg/m^2 (1 Gr 3 photosensitivity), 400 mg/m^2 (1 Gr 3 anemia), 700 mg/m^2 (1 Gr 4 thrombocytopenia, 1 Gr 4 neutropenia/Gr 4 thrombocytopenia), and 650 mg/m^2 (1 Gr 3 thrombocytopenia, 1 Gr 4 neutropenia/Gr 3 thrombocytopenia). Nausea and vomiting were successfully prevented with dexamethasone/serotonin antagonists. Photosensitization was effectively managed with sun protection. Peripheral venous thrombosis required central vein infusion in subjects with glioblastoma. PK showed dose-proportional increases in plasma CBL0137 area under the concentration-time curve (AUC), a high mean (range) volume of distribution (Vd) of 1,030 (655-1460) L/m^2 consistent with extensive tissue distribution and DNA intercalation, and an average mean (range) half-life ($t_{1/2}$) of 24.7 (10.3-40.7) hours without dose dependence. The best response was stable disease: 2 pts with liver cancer had tumor control for 9 and 24 months and a maximum tumor regression of 10%; 2 pts with prostate cancer had tumor regressions by 11% and 22%; 1 pt with uterine cancer had a 20% tumor regression. **Conclusions:** CBL0137 administered IV was generally well tolerated with manageable toxicities The MTD and RP2D were estimated at 540 mg/m^2 due to myelosuppressive DLTs. PK were predictable. Preliminary evidence of antitumor activity supports Phase 2 testing. Clinical trial information: NCT01905228. Research Sponsor: Incuron, Inc.

3584 Poster Session (Board #314), Fri, 8:00 AM-11:00 AM

Selpercatinib (LOXO-292) in patients with *RET*-fusion+ non-small cell lung cancer. *First Author: Koichi Goto, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Selpercatinib (LOXO-292) is a highly selective and potent small molecule RET kinase inhibitor. Here we report an update on the efficacy and safety of selpercatinib in *RET*-fusion+ non-small-cell lung cancer (NSCLC). **Methods:** Patients with *RET*-fusion+ NSCLC were enrolled to the Phase 1/2 LIBRETTO-001 trial (NCT03157128), a global, multicenter trial (16 countries, 89 sites). Following the Phase 1 dose escalation portion of the trial, patients received the recommended dose of 160 mg orally twice daily. Each cycle was 28 days. The primary endpoint was objective response rate (ORR) per RECIST 1.1. Secondary endpoints included duration of response (DoR) and safety. Per health authority agreement, the primary analysis set was defined as the first 105 consecutively enrolled patients previously treated with platinum-based chemotherapy. Treatment-naïve patients were analyzed separately. All analyses were based on a 16-Dec-2019 data cutoff date. **Results:** In the primary analysis set of platinum-treated patients (median of 3 prior systemic regimens; range 1-15), the ORR by investigator assessment was 70% (95% CI 59.8–78.1, n = 73/105). Responses did not differ by fusion partner or number or type of prior therapies, including anti-PD-1/PD-L1 agents and off-label multikinase inhibitor use. The median DoR was 20.3 months (95% CI 15.6–24.0) with 45 of 73 (62%) responders censored at a median follow-up of 14.8 months. Among 39 treatment-naïve patients, the ORR by investigator assessment was 90% (95% CI 75.8–97.1, n = 35/39, including 2 responses pending confirmation). Median DoR was not reached with 27 of 33 (82%) confirmed responses ongoing at a median follow-up of 7.4 months. In the safety analysis set consisting of all selpercatinib dosed patients (N = 702), the most common treatment-related adverse events (TRAEs) that occurred in ≥15% of patients were dry mouth (33.3%), increased AST (24.5%), increased ALT (23.8%), hypertension (23.2%), diarrhea (19.7%), and fatigue (16.8%). Only 2% (14 of 702) of patients discontinued selpercatinib for TRAEs. **Conclusions:** Selpercatinib achieved marked and durable antitumor activity in patients with *RET*-fusion+ NSCLC. Selpercatinib was well tolerated. Efficacy data assessed by independent review committee based on the 16-Dec-2019 data cutoff date will be presented. Clinical trial information: NCT03157128. Research Sponsor: Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company.

3585 Poster Session (Board #315), Fri, 8:00 AM-11:00 AM

Activity of SY-5609, an oral, noncovalent, potent, and selective CDK7 inhibitor, in preclinical models of colorectal cancer. *First Author: Liv Johannessen, Syros Pharmaceuticals, Cambridge, MA*

Background: Colorectal cancer (CRC) is driven by genetic alterations that result in constitutive activation of oncogenic transcription factors (eg β-catenin, MYC) and of mitogenic signaling and cell cycle progression (driven by oncogenic mutations in KRAS and BRAF). CDK7 is a key regulator of transcription, through phosphorylation of the CTD domain of RNA Polymerase II, and of cell cycle progression, through phosphorylation of the cell cycle kinases CDK1, 2, 4, and 6. This dual role of CDK7 suggests inhibitors of CDK7 may be effective in the treatment of CRC. SY-5609 is an oral, noncovalent, potent and highly selective CDK7 inhibitor in phase 1 clinical development for patients with advanced solid tumors including CRC (NCT04247126). Here we report on the activity of SY-5609 in patient-derived xenograft (PDX) models of CRC. **Methods:** SY-5609 was administered once daily (QD) by oral gavage for 21 days (end of treatment, EOT) to mice bearing PDX models of CRC. The relationship between SY-5609 dose, pharmacodynamic (PD) changes in xenograft tissue, tumor growth inhibition (TGI), and mouse body weight (BW) was evaluated across a range of doses. SY-5609 TGI activity was also evaluated at sub-maximum-tolerated-dose levels across a panel of 30 independent CRC models including BRAF-, KRAS-, and non-BRAF/KRAS-mutant (wild type) models (n = 10 per group). **Results:** SY-5609 induced dose-dependent TGI in BRAF-mutant CRC PDX tumors, with tumor regressions observed at well tolerated doses (no BW loss at EOT), and no tumor regrowth for 2+ weeks after treatment was discontinued. Dose-dependent TGI was associated with dose-dependent PD changes in PDX tumor tissue. Across 30 PDX models, SY-5609 at well-tolerated doses (average BW loss of 0% at EOT across all models) induced ≥50% TGI in 67% (20/30) of models. Deep responses (≥90% TGI or regressions) were observed in 23% (7/30) of models, with enrichment for deep responses in BRAF mutant models (50%, 5/10) relative to KRAS mutant (10%, 1/10), and wild type (10%, 1/10) models. **Conclusions:** Daily oral dosing of the CDK7 inhibitor SY-5609 induces robust TGI, including regressions, in CRC PDX models at well-tolerated doses. Dose-dependent TGI is associated with dose-dependent PD changes in CRC PDX tumor tissue. These results highlight the therapeutic potential of SY-5609 in CRC and support the evaluation of SY-5609 in CRC patients in early phase clinical trials. SY-5609 is in phase 1 clinical development for patients with advanced solid tumors including CRC (NCT04247126). Research Sponsor: Syros Pharmaceuticals.

3586 Poster Session (Board #316), Fri, 8:00 AM-11:00 AM

A phase I, first-in-human, open-label, dose-escalation, safety, pharmacokinetic, and pharmacodynamic study of oral TP-3654 administered daily for 28 days to patients with advanced solid tumors. *First Author: Ignacio Garrido-Laguna, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: TP-3654 is an oral, second generation, potent PIM-1 kinase inhibitor with activity against PIM 2, 3 and favorable selectivity against other kinases. These cytoplasmic serine/threonine kinases are highly expressed in many cancers and their oncogenic potential has been largely attributed to supressing apoptosis downstream of stimuli including inflammatory cytokines and other immune effectors. TP-3654 has efficacy in various hematologic and solid tumor models inducing stromal Pim-1 also has been shown to mediate various aspects of the tumor microenvironment. Thus, Pim kinases are attractive targets for the treatment of many human malignanices. **Methods:** A first in human, multicenter, phase 1, dose escalation study using a standard 3+3 design with a modified Fibonacci scheme to examine the safety and clinical activity of TP-3654 in patients with advanced solid tumors. **Results:** Ten patients were enrolled between 30Apr and 31Dec2019 receiving 480, 720, and 1080 mg respectively. Grade 3 AEs were scrotum wound infection, altered mental status, anemia, fall, and lower extremity edema, none were related to study drug and all were manageable with supportive care. There were no Grade 4 or 5 AEs and no DLTs. Median duration of SD was 5.5 months (6/10) and with prolonged SD > 16wks (4/10). One CRC patient with 4 lines of prior therapy had a 22% reduction in tumor volume (SD > 5+ mos). TP-3654 plasma PK values (C_{max}, AUC) continuously increased through all 3 cohorts. Average C_{max} (ng/mL) and $AUC_{0\text{-}24}$ (ng*hours/mL) were 195, 1965 (480mg); 357, 3310 (720mg); 735, 6922 (1080mg), respectively. PK values increased linearly with higher doses without reaching saturation. Peripheral Blood Mononuclear Cells were isolated from subjects prior and up to 24hours after treatment. Western Blot from protein lysates revealed a decrease in phosphorylation of BAD and p70s6K proteins, both regulated by PIM-1 kinase. **Conclusions:** These findings suggest that TP-3654 is tolerated as a monotherapy in patients with heavily pretreated, relapsed, and resistant solid tumors warranting further clinical development in selected indications. Research Sponsor: Tolero Pharmaceuticals.

3587 Poster Session (Board #317), Fri, 8:00 AM-11:00 AM

AVID200, first-in-class TGF-beta 1 and 3 selective and potent inhibitor: Safety and biomarker results of a phase I monotherapy dose-escalation study in patients with advanced solid tumors. *First Author: Timothy A Yap, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: AVID200 is a rationally designed first-in-class, selective inhibitor of transforming growth factor-beta (TGF-beta) that neutralizes TGF-beta 1 & 3 with pM potency and 4,000 fold selectivity over TGF-beta 2. TGF-beta 1 & 3 signaling has been associated with immune checkpoint inhibitor resistance and immunosuppression in the tumor microenvironment while TGF-beta 2 is required for normal cardiac function and hematopoiesis. **Methods:** NCT03834662 (AVID200-03) is a multicenter Phase 1 study following a standard 3 + 3 dose escalation to evaluate safety and tolerability of AVID200 given IV every 3 weeks to patients (pts) with advanced solid tumors. Peripheral target engagement was assessed in blood by ELISA and a cell-based functional assay, and in skin biopsies by immunohistochemistry (IHC). Pharmacodynamic markers of TGF-beta signal modulation and immune activation were evaluated in serum using the InflammationMAP v 1.0 (Myriad RBM) and in paired tumor biopsies by IHC and Imaging Mass Cytometry. **Results:** Nineteen pts (ECOG 0-1, median age 63 [range 39-77], 52.6% male) received AVID200 at 3 planned dose levels of 180 (N = 7), 550 (N = 6), and 1100 mg/m^2 (N = 6) (~5, 15, and 30 mg/kg). The maximum tolerated dose was not reached. Three Grade (G) 3 treatment-related adverse events (TRAEs) were reported in 2 pts (diarrhea and lipase elevation, anemia); no > G3 TRAEs were observed. Serum exposure was dose-proportional and AVID200 sequestered all active TGF-beta 1 & 3, but not beta 2, in blood across the entire dosing period at all dose levels, providing proof-of-mechanism of AVID200. SMAD2 phosphorylation in skin biopsies was detectably reduced on Day 4 at 15 and 30 mg/kg. Pro-inflammatory markers in serum were increased on Day 8 versus baseline in a dose-dependent manner. Tumor biopsies of pts treated at 15 mg/kg showed modulation of TGF-beta signaling and immune activation. A best response of RECIST stable disease > 12 weeks was observed in 2 pts: 1 with adenoid cystic carcinoma (5 mg/kg; 8.7 months); 1 with breast carcinoma (30 mg/kg; 3.1 months). **Conclusions:** AVID200 was safe and well tolerated at dose levels of 5-30 mg/kg, with peripheral target engagement across the entire dosing period. AVID200 led to TGF-beta target modulation and immune activation. These data provide proof-of-principle that AVID200-mediated selective and potent inhibition of TGF-beta 1 & 3 is feasible in the clinic. The AVID200 monotherapy data warrant exploration of rational combination with a PD-(L)1 inhibitor. Clinical trial information: NCT03834662. Research Sponsor: Forbius.

3588 Poster Session (Board #318), Fri, 8:00 AM-11:00 AM

Correlation between overall response rate and progression-free survival/overall survival in comparative trials involving targeted therapies in molecularly enriched populations. *First Author: Benjamin J. Solomon, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia*

Background: Randomized trials involving agents targeting oncogene addicted tumors have greatly increased over the past decade. Whether clinical response rates can predict or correlate with efficacy measures such as progression-free survival (PFS) or overall survival (OS) has not been established in molecularly enriched patient populations. In this meta-analysis, we investigated whether improvements in objective response rate (ORR) in comparative trials using targeted agents could serve as a potential surrogate endpoint for improvements in PFS or OS in populations with oncogene addicted cancer. **Methods:** CT.gov and MEDLINE databases were queried (using commercial text mining software I2E) for randomized, phase 3 clinical trials based on the following prospectively defined criteria: (1) use of agents targeting EGFR activating mutations (erlotinib, gefitinib, afatinib, dacomitinib, osimertinib), ALK and ROS1 rearrangements (crizotinib, ceritinib, alectinib), BRAF V600E or V600K mutations (dabrafenib), and BCR-ABL fusion protein (imatinib, dasatinib, nilotinib, ponatinib); (2) must include molecularly enriched trial populations (biomarker subgroup data included if available); (3) control arms should not include targeted agents directed towards those molecularly enriched populations. ORR, OS, and PFS data were manually extracted from the relevant studies and correlative analyses (weighted Pearson correlation) were performed. **Results:** 61 trials were identified with 15 ultimately meeting the prespecified criteria. ORR effect size (both the ORR difference and log odds ratio) and the log PFS hazard ratio were strongly correlated (-0.78, p-value = 0.0007). No significant correlation was found between ORR and OS. **Conclusions:** In our analyses, a strong correlation between ORR and PFS was found in randomized clinical trials investigating agents targeting oncogene-driven cancers. Establishing a correlation between ORR and OS was limited, most probably due to confounding factors such as treatment cross-over following progression, number of subsequent therapies and long post-progression survival in this setting. These findings further warrant the use of ORR as a surrogate for PFS in biomarker-driven studies. Research Sponsor: Eli Lilly and Company.

3589 Poster Session (Board #319), Fri, 8:00 AM-11:00 AM

Phase I study of the combination of alisertib (MLN8237) and gemcitabine in advanced solid tumors. *First Author: Jasmine Huynh, UC Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Aurora Kinase A (AKA) is a key mitotic regulator overexpressed in multiple solid tumors. This open-label dose escalation and expansion phase I study evaluated the safety and tolerability of alisertib (MLN8237), an oral AKA inhibitor, in combination with gemcitabine. **Methods:** In dose escalation, patients (pts) > 18y with refractory solid tumors received 28-day cycles of gemcitabine on days 1, 8, 15 and alisertib twice daily on days 1-3, 8-10, and 15-17. Gemcitabine was given at 1000mg/m2. Four dose levels (DL) of alisertib (20-50mg) were given per 3+3 design to investigate dose limiting toxicities (DLT) in cycle 1, to determine maximum tolerated dose (MTD) and recommended phase II dose (RP2D). In dose expansion, advanced pancreatic adenocarcinoma pts received the MTD dose twice daily on a modified dosing schedule to allow for pharmacokinetic (PK) evaluation. Anti-tumor activity was assessed by response rate (RECIST 1.1) and progression-free survival (PFS). PK evaluation of plasma gemcitabine and alisertib was performed on all pts enrolled in the dose expansion. PK sampling was performed before treatment, immediately after gemcitabine infusion, and at other pre-specified post-infusion timepoints. **Results:** Twenty-six pts were treated in total: 21 pts in dose escalation and 5 pts in dose expansion. Overall, median age was 57y [42-82]; 50% male; 62% PS 1 (16 pts); 2 [0-7] median prior therapies. In the dose escalation phase, 9 tumor types were included and NSCLC was most common (7 pts). Maximum administered dose (DL4) achieved 900 mg alisertib per cycle and was tolerated (1 DLT in 6 pts). The dose expansion phase enrolled 5 pts with advanced pancreatic adenocarcinoma; median age 63y [48-82]; 60% male; 60% PS 1 (3 pts); 2 [1-2] median prior therapies. Grade ≥3 TRAEs were observed in 73% of all pts and were predominantly hematologic, including neutropenia (54%), leukopenia (50%), and lymphopenia (31%). Similar TRAEs were seen at DL4; all 14 pts experienced neutropenia with 64% experiencing grade ≥3 neutropenia. Fourteen of 23 evaluable pts (61%) had stable disease and 2 pts (9%) had partial response (PR) as best overall response. Median PFS was 2.9 months (95% CI 2.0-4.2). Analysis of PK data is ongoing and will be reported. **Conclusions:** Alisertib can be safely administered with gemcitabine. RP2D for alisertib is 50 mg PO BID in combination with full dose gemcitabine. Best response was at least stable disease in a majority of pts with PR observed in 9% of this heavily pretreated group of patients. Most grade ≥3 TRAEs were hematologic. Results of PK studies will also be reported. Clinical trial information: NCT01924260. Research Sponsor: Takeda.

3590 Poster Session (Board #320), Fri, 8:00 AM-11:00 AM

Phase I study of IM156, a novel potent biguanide oxidative phosphorylation (OXPHOS) inhibitor, in patients with advanced solid tumors. *First Author: Sun Young Rha, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: IM156, a novel oral potent biguanide OXPHOS inhibitor of Protein Complex 1 (PC1) of the mitochondrial electron transport chain, causes AMPK phosphorylation, the downstream effects of which are detrimental to OXPHOS-dependent cancer cells prone to energy stress. Preclinical experiments with IM156 demonstrated activity in solid tumor and hematologic malignancy models as a single-agent and in combinations. **Methods:** This was an open label, first-in-human, multi-center, dose-escalation study (NCT03272256) using a 3+3 design. The primary endpoint was to determine the maximum tolerated dose and/or recommended Phase 2 dose (RP2D) based on dose limiting toxicities (DLT), safety and tolerability. Secondary endpoints included pharmacokinetics (PK), pharmacodynamics (PD) and preliminary signals of efficacy. Eligible patients were adults with advanced solid tumors refractory to standard therapies with ECOG Performance Status <2, adequate organ function, and measurable disease (RECIST 1.1 or RANO [gliomas]). IM156 was administered orally every other day (QOD) or daily (QD) in 28-day cycles. **Results:** 22 patients (gastric cancer: N = 8; ovarian cancer: N = 3; colorectal cancer: N = 3; endometrial cancer: N = 2; sarcoma: N = 2; other: N = 4) were enrolled in 7 dose cohorts (100, 200, 400, 800, and 1,200 mg QOD; 800 and 1,200 mg QD). The most frequent treatment-related adverse events (TRAEs) were gastrointestinal (nausea [N = 16, 73%], diarrhea [N = 12, 55%], and vomiting N = 11, 50%]). Nausea, reported in 3 (14%) patients, was the only Grade 3 TRAE. No DLTs were reported; the RP2D declared was 800 mg as 1,200 mg QD was associated with Grade 2/3 nausea requiring dose modifications. PK demonstrated dose-proportional increases in C_{max} and $AUC_{0\text{-}last}$ reaching the expected efficacious range. PD demonstrated a decrease in tumor growth rate in 3 patients (1,200 mg QOD: N = 2; 800 mg QD: N = 1), and a decrease in VEGF and tumor markers in a patient with gastric cancer with neuroendocrine differentiation treated at 800 mg QD who remains on study in Cycle 11. Best response was stable disease in 7 (32%) patients. **Conclusions:** IM156 is the first PC1 OXPHOS inhibitor to have been successfully tested in patients with cancer with the identification of a RP2D. It was well tolerated at dose levels active in preclinical models, and demonstrated modest clinical activity in an unselected population of patients. Subsequent development will focus on OXPHOS-dependent tumors and in combinations with agents in which OXPHOS metabolism is a mechanism of resistance. Clinical trial information: NCT03272256. Research Sponsor: Immunomet Therapeutics.

3591 Poster Session (Board #321), Fri, 8:00 AM-11:00 AM

TOOme: A novel computational framework to infer cancer tissue-of-origin by integrating both gene mutation and expression. *First Author: Wei Gao, Departments of Internal Medicine-Oncology, Fujian Provincial Cancer Hospital and Fujian Medical University Cancer Hospital, Fuzhou, China*

Background: Metastatic cancers require further diagnosis to determine their primary tumor sites. However, the tissue-of-origin for around 5% tumors could not be identified by routine medical diagnosis according. With the development of machine learning techniques and the accumulation of big cancer data from TCGA and GEO, it is now feasible to predict cancer tissue-of-origin by computational tools. **Methods:** Developed a computational framework to infer tumor tissue-o. **Results:** Applied TOOme to the TCGA data containing 7,008 non-metastatic samples across 20 solid tumors including BLCA, BRCA, CESC, COAD, GBM and so on. 74 genes by gene expression profile and 6 genes by gene mutation are selected by the random forest process, which can be divided into two categories: (1) cancer type specific genes, which are highly expressed or mutated only in one specific cancer and (2) those expressed or mutated in several cancers with different levels of expression or mutation rates. Function analysis indicates that the selected genes are significantly enriched in gland development, urogenital system development, hormone metabolic process, thyroid hormone generation prostate hormone generation and so on. According to the multiple-label classification method, random forest performs the best with a 10-fold cross-validation prediction accuracy of 96%. We also use the 19 metastatic samples from TCGA and 256 cancer samples downloaded from GEO as independent testing data, for which TOOme achieves a prediction accuracy of 89%. The cross-validation validation accuracy is better than those using gene expression (i.e., 95%) and gene mutation (83%) alone. **Conclusions:** TOOme provides a quick yet accurate alternative to traditional medical methods in inferring cancer tissue-of-origin. In addition, the methods combining somatic mutation and gene expressions outperform those using gene expression or mutation alone. Research Sponsor: None.

3592 Poster Session (Board #322), Fri, 8:00 AM-11:00 AM

Phase Ib/IIa study of GC1118 in combination with irinotecan or FOLFIRI in patients with metastatic solid tumors. *First Author: Keun Wook Lee, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea*

Background: GC1118 is a novel anti-EGFR monoclonal antibody which has a unique binding epitope and superior ligand inhibition potential. It showed promising antitumor activity as a single agent in the phase I study. This study aimed to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of GC1118 in combination with irinotecan or FOLFIRI in metastatic solid tumors and evaluate the efficacy of GC1118 plus FOLFIRI as a second line therapy for RAS and BRAF wild-type metastatic colorectal cancer. **Methods:** Phase 1b part was designed to evaluate weekly GC1118 (starting from 3 mg/kg) in combination with biweekly irinotecan (180mg/m^2) or FOLFIRI (irinotecan 180mg/m^2, leucovorin 400mg/m^2, 5-FU 400 mg/m^2 bolus, and 5-FU 2400mg/m^2 over 46hrs) in a 3+3 design. In the phase 2a part, the RP2D of GC1118 is administered in combination with FOLFIRI in a Simon's two stage design with objective response rate (ORR) as the primary endpoint. **Results:** 13 pts were enrolled in phase 1b and received 3mg/kg of GC1118 with irinotecan (N = 6) or FOLFIRI (N = 7). DLT occurred in 2 pts (G4 neutropenia, G2 rash) in irinotecan arm and 1pt (G3 neutropenia) in FOLFIRI arm with 3mg/kg of GC1118 and it was determined as MTD and RP2D. Adverse events (AE) of grade $\geq$ 3 included neutropenia (61.5 %), skin rash (15.4 %) and diarrhea (15.4%). Dose reductions due to GC1118-related AE were required in 6 (46.2%) patients. Among 10 response-evaluable pts in phase 1b, best overall response was PR in 3 and SD in 6, and median PFS was 12 months. In stage 1 of phase 2a (N = 9), 4 PR and 5 SD were observed (ORR 44.4%, 95% CI 13.7 – 78.8). We moved to stage 2, and are currently enrolling additional 20 pts. AE of grade $\geq$ 3 included neutropenia (66.7%), skin rash (22.2%) and diarrhea (11.1%). Updated data of the phase 2a part will be presented at the meeting. **Conclusions:** The MTD and RP2D of weekly GC1118 in combination with irinotecan or FOLFIRI was 3mg/kg. Preliminary results of GC1118 and FOLFIRI as a 2nd line treatment in mCRC suggests promising antitumor activity and acceptable safety profile. Clinical trial information: NCT03454620. Research Sponsor: Green Cross Corporation.

3593 Poster Session (Board #323), Fri, 8:00 AM-11:00 AM

Phase I study of regorafenib and sildenafil in advanced solid tumors. *First Author: Andrew Stewart Poklepovic, VCU Massey Cancer Center, Richmond, VA*

Background: Regorafenib (R) is an oral multikinase inhibitor with anti-angiogenic properties approved for use in several solid tumors. Sildenafil (S) is an oral phosphodiesterase-5 (PDE5) inhibitor that interacts synergistically with R in both short-term and colony formation assays to kill multiple cancer cell types. Mechanistic studies identified that PDE5 knockdown enhances R lethality, suggesting a direct target effect for S. **Methods:** A single-center, open-label, dose-escalation study was conducted in adults with advanced solid tumors. Patients (pts) took R (120 or 160 mg) and S (50 or 100 mg) once daily days 1 through 21 of each 28-day cycle. Pts remained on study treatment until progression or excessive toxicity, with response assessments every 8 wks. The maximum tolerated dose (MTD) was defined as the maximum tested dose with $\leq$1/6 pts experiencing dose-limiting toxicity (DLT), with Cycle 1 as the DLT observation period. **Results:** 32 pts were enrolled and 29 treated at 3 dose levels (DLs). Median duration of treatment was 8 (range 2 – 101) wks. One of 6 evaluable pts treated at DL2 (160 mg R + 50 mg S) experienced DLT (grade 4 lipase increase). One of 12 evaluable pts treated at DL3A (160 mg R + 100 mg S, the MTD) experienced DLT (grade 3 rash and grade 3 muscle pain). The toxicity profile was generally consistent with that seen in R monotherapy at FDA-approved doses. 10 pts had a best response of progressive disease (PD). 14 pts had a best response of stable disease (SD), 5 of whom had stable disease duration $>$ 24 wks. 5 treated pts were not evaluable for response. Notably, 2 pts with ovarian cancer and 1 with cervical cancer had stable disease $>$ 24 wks. Analyses of correlative studies to examine pharmacokinetics and drug combination pharmacodynamic effects are underway. **Conclusions:** The combination was well-tolerated. The recommended phase 2 dose is 160 mg R + 100 mg S. Objective responses were not observed, but prolonged stable disease was seen in a subset of pts. Encouraging disease control was seen in gynecologic cancers. Dosing up to 100 mg S is safe concurrently with standard doses of R, and may be considered as an adjunct to R in future trials. Evaluation of R+S in gynecologic cancers warrants further consideration. Clinical trial information: NCT02466802. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

Dose Level (mg R + mg S)	# treated pts	# DLT evaluable pts	# pts with DLTs	# Response evaluable pts	# pts with PD	# pts with SD
1 (120 + 50)	4	3	0	4	2	2
2 (160 + 50)	9	6	1	6	2	4
3A (160 + 100)	16	12	1	14	6	8

3594 Poster Session (Board #324), Fri, 8:00 AM-11:00 AM

Selpercatinib (LOXO-292) in patients with *RET*-mutant medullary thyroid cancer. *First Author: Manisha H. Shah, Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: Selpercatinib (LOXO-292) is a highly selective and potent small molecule RET kinase inhibitor. Here we report an update on the efficacy and safety of selpercatinib in *RET*-mutant medullary thyroid cancer (MTC). **Methods:** Patients with *RET*-mutant MTC were enrolled to the Phase 1/2 LIBRETTO-001 trial (NCT03157128), a global, multicenter trial (16 countries, 89 sites). Following the Phase 1 dose escalation portion of the trial, patients received the recommended dose of 160 mg orally twice daily. Each cycle was 28 days. The primary endpoint was objective response rate (ORR) per RECIST 1.1. Secondary endpoints included duration of response (DoR) and safety. Per health authority agreement, the primary analysis set was defined as the first 55 consecutively enrolled patients previously treated with multikinase inhibitors cabozantinib and/or vandetanib. Patients naïve to cabozantinib and vandetanib treatment were analyzed separately. All analyses were based on a 16-Dec-2019 data cutoff date. **Results:** In the primary analysis set of prior cabozantinib and/or vandetanib-treated patients with MTC (n = 55), the ORR by investigator assessment was 62% (95% CI 47.7–74.6, n = 34/55) and the median DoR was not reached (95% CI 18.4 months–not estimable) despite a median follow-up of 14.8 months. In cabozantinib/vandetanib treatment-naïve patients (n = 88), the ORR by investigator assessment was 69% (95% CI 58.6–78.7, n = 61/88, including 2 responses pending confirmation). Of the 59 confirmed responding patients, with a median follow-up of 8 months, responses were ongoing for 57 responders at the time of the analysis. In the safety analysis set consisting of all selpercatinib dosed patients (N = 702), the most common treatment-related adverse events (TRAEs) that occurred in $\geq$15% of patients were dry mouth (33.3%), increased AST (24.5%), increased ALT (23.8%), hypertension (23.2%), diarrhea (19.7%), and fatigue (16.8%). Only 2% (14 of 702) of patients discontinued selpercatinib for TRAEs. **Conclusions:** Selpercatinib use was associated with marked and durable antitumor activity in prior cabozantinib and/or vandetanib-treated patients and in cabozantinib/vandetanib-naïve patients with *RET*-mutant MTC, with the majority of responses ongoing in both cohorts. Selpercatinib was well tolerated. Efficacy data assessed by independent review committee based on the 16-Dec-2019 data cutoff date will be presented. Clinical trial information: NCT03157128. Research Sponsor: Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company.

3595 Poster Session (Board #325), Fri, 8:00 AM-11:00 AM

IGM-8444 as a potent agonistic Death Receptor 5 (DR5) IgM antibody: Induction of tumor cytotoxicity, combination with chemotherapy and *in vitro* safety profile. *First Author: Beatrice Wang, IGM Biosciences Inc, Mountain View, CA*

Background: Death receptor 5 (DR5) is a member of the tumor necrosis factor (TNF) receptor superfamily that multimerizes when bound to its ligand, TNF-related apoptosis inducing ligand (TRAIL), to activate the extrinsic apoptotic pathway. DR5 is broadly expressed on solid and hematologic cancers and has been targeted with both recombinant TRAIL and agonistic antibodies in the clinic. However, these therapeutics have generally been unsuccessful due to toxicity or lack of efficacy. We have developed a multivalent IgM DR5 agonist, IGM-8444, that multimerizes DR5 to selectively and potently induce tumor cell apoptosis while maintaining tolerability. **Methods:** IGM-8444 is an engineered, pentameric IgM antibody with 10 binding sites specific for DR5. Human tumor cell lines or hepatocytes were evaluated *in vitro* for dose dependent IGM-8444 induced cytotoxicity. The efficacy of IGM-8444 was evaluated with or without chemotherapy, in cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) mouse tumor models, with IGM-8444 administered at various dose levels and schedules when tumors reached approximately 100 mm^3. Sera and tumors were analyzed for biomarkers of tumor apoptosis. **Results:** *In vitro* cytotoxicity assays identified IGM-8444 activity across cell lines from 18 solid and hematologic malignancies. In IGM-8444 partially resistant cell lines, combination with chemotherapy or a Bcl2 inhibitor enhanced *in vitro* cytotoxicity. IGM-8444 was efficacious as a monotherapy in CDX and PDX tumor models including colorectal, lung, and gastric indications. In a gastric PDX model, IGM-8444 induced complete and durable dose-dependent tumor regressions. *In vivo*, combination of IGM-8444 with standard-of-care chemotherapies, such as irinotecan, led to enhanced efficacy. IGM-8444 administration increased markers of tumor apoptosis, identifying potential clinical pharmacodynamic biomarkers. At doses several log-fold higher than efficacious doses, IGM-8444 demonstrated a favorable single agent *in vitro* safety profile, with little to no *in vitro* cytotoxicity observed using primary human hepatocytes from multiple donors. **Conclusions:** These data support the clinical development of IGM-8444 in both solid and hematological malignancies as a single agent and in combination with standard of care therapy. IGM-8444 is projected for IND filing in 2020. Research Sponsor: IGM Biosciences Inc.

3596 Poster Session (Board #326), Fri, 8:00 AM-11:00 AM

Tumor-targeted oncolytic adenovirus demonstrates high cytotoxicity for human lung and renal cell carcinomas independently of the level of tumor PD-L1 expression. *First Author: Jia Yao, Emory University School of Medicine, Atlanta, GA*

Background: Immuno-checkpoint (IC) inhibitors targeting PD1-PD-L1 pathway have proven highly effective at extending survival of cancer patients. However, the clinical benefits of IC inhibitors are limited to only about 20% patients who have moderate to high levels of tumor PD1 and/or PD-L1 expression. To develop therapeutics that would provide clinical benefits to a larger proportion of cancer patients, we engineered oncolytic adenovirus for targeted infection of human tumor cells via CD46 and integrins of $\alpha 3\beta 1$ or $\alpha 6\beta 4$ classes, overexpressed on many epithelial human cancers. **Methods:** Here, we analyzed the infectivity and cytotoxicity of this novel oncolytic virus in a panel of human non-small cell lung cancers (NCSLC) cell lines, primary patient derived NSCLC xenografts, and tumor surgical explants from patients with renal cell carcinoma (RCC). **Results:** The in vitro analysis of NSCLC cells lines (N = 17) demonstrated that over 60% of them were highly sensitive to virus infection. The genome-wide transcriptional profiling showed that only 3 out of 12 cell lines that were sensitive to oncolytic virus infection, expressed PD-L1 ($>$ 4.5 Log2 RPMK). Furthermore, although the pre-treatment of these cell lines with IFN-I activated PD-L1 expression, IFN-I treatment did not reduce the efficacy of tumor cell infection by the oncolytic virus. The analysis of virus infectivity on primary human tumor cells from patients with NSCLC (N = 4) and RCC (N-24) demonstrated that primary tumors were highly sensitive to oncolytic virus infection. Specifically, tumor-targeted oncolytic virus demonstrated strong cytotoxicity in 22 out of 24 analyzed primary isolated RCC cell samples. Next, we subcutaneously grafted PD-L1-negative NSCLC A549 cells to NSG mice, treated them with oncolytic virus intravenously, and the kinetics of tumor growth and animal survival was monitored. This analysis showed that after intravenous administration, oncolytic virus was able to infect tumor cells and suppress tumor growth. Whereas the median survival in mock-treated group was 26 days, all mice survived up to 100 days post oncolytic virus therapy (endpoint). **Conclusions:** Our study showed that tumor-targeted oncolytic adenovirus infects human tumor cell lines independently of their PD-L1 expression status and is not sensitive to IFN-I inhibition. This novel tumor-targeted oncolytic virus has the potential to provide clinical benefits to cancer patients, who do not respond or became resistant to ICI drugs. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

3597 Poster Session (Board #327), Fri, 8:00 AM-11:00 AM

RICTOR amplification as a novel therapeutic target for lung cancer brain metastases. *First Author: Haiying Cheng, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY*

Background: Approximately 20% to 50% of patients with advanced lung cancer develop brain metastases, which are associated with debilitating neurologic impairment and a dismal prognosis. There have been very limited studies investigating the genomics of brain metastases in lung cancer. **Methods:** We comprehensively investigated the frequency of PI3K/AKT/RICTOR/mTOR pathway aberrations in primary and metastatic sites using an extensive database of 11845 cases of lung adenocarcinoma by NGS (FoundationOne). The potential roles of *RICTOR* amplification in the development of brain metastases were studied both in vitro and in vivo in orthotopic mouse models. **Results:** Compared to the primary tumor, *PI3K/AKT/mTOR* gene alterations were more frequent in metastatic sites, with particular enrichment noted in brain metastases. *RICTOR* amplification alone accounted for the observed higher frequency both in brain metastases (brain vs. primary: 9.73% vs 3.50%, P = 2.6E-14; brain vs. other mets: 9.73% vs. 7.3%, P = 0.03) and other metastatic sites (other mets vs. primary: 7.3% vs.3.5%, P = 10E-15), whereas the frequency of *PTEN, AKT1, PK3CA* or *mTOR* genetic alterations was not different in the primary tumor, brain and other metastatic sites. *In vitro*, inducible RICTOR knockdown in H23 lung cancer cells (parental line with *RICTOR* amplification) was associated with reduced cell migration and invasion, whereas upregulation of RICTOR in HCC827 lung cancer cells (parental line with normal *RICTOR* copy numbers) was associated with an increase of both processes. These results were confirmed with pharmacological inhibition using mTOR1/2 inhibitors with known CNS penetration. In vivo, both inducible ablation of RICTOR and the mTOR1/2 inhibitor TAK228 (Sapanisertinib) significantly inhibited lung cancer H23-R4-Luc tumor growth in the brain, including a number of near complete responses. Mechanistic studies suggest that RICTOR may regulate the brain metastasis process through AKT and CXCL12 chemokine-CXCR4 axis. **Conclusions:** *RICTOR* amplification is the first identified actionable target that is markedly enriched in brain metastases. Our study provides a strong rationale for the development of RICTOR-targeted therapeutic strategies for the treatment and/or prevention of these major causes of lung cancer morbidity and mortality. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

3598 Poster Session (Board #328), Fri, 8:00 AM-11:00 AM

Therapeutic drug monitoring of pazopanib: Using cost-neutral PK-guided interventions to optimize exposure. *First Author: Stefanie L. Groenland, The Netherlands Cancer Institute–Antoni van Leeuwenhoek, Amsterdam, Netherlands*

Background: Pazopanib is an approved treatment for renal cell carcinoma (RCC) and soft tissue sarcoma (STS). At the currently registered fixed dose of 800 mg QD, 20% of patients (pts) do not attain the efficacy threshold of $C_{min} \geq 20.5$ mg/L (Suttle et al, 2014), providing a strong rationale for therapeutic drug monitoring (i.e. individualizing the dose based on measured plasma drug concentrations). Previous studies provided cost-neutral alternatives to absolute dose increments to optimize exposure (i.e. splitting intake moments or concomitant intake with food (Groenland et al, 2020; Lubberman et al, 2019)). This study aimed to investigate the feasibility, tolerability and efficacy of TDM of pazopanib, using cost-neutral interventions. **Methods:** Patients starting treatment with pazopanib at the standard dose of 800 mg QD in modified fasting state were included in the prospective DPOG TDM study (www.trialregister.nl, NL6695). PK sampling occurred 4, 8 and 12 weeks after start of treatment, and every 12 weeks thereafter. Pazopanib concentrations were measured with LC-MS/MS and C_{min} was calculated. In case of $C_{min} < 20.5$ mg/L and acceptable toxicity, a dose intervention was recommended. As a first step, intake moments were split (i.e. 400 mg BID). Secondly, concomitant intake with food was recommended. **Results:** In total, 34 pts were included (19 STS, 15 RCC), of whom 158 PK samples were collected. Eleven pts (32%) were underdosed and had at least 1 PK sample below the target. In 24% of the pts a PK-guided intervention could be performed, which was successful in 6 pts (75%). Median C_{min} increased from 15 mg/L to 32 mg/L (p = 0.027). Eventually, 3 pts went back to 800 mg QD due to toxicity, after which C_{min} remained $\geq$ 20.5 mg/L in 2 pts. In pts with adequate exposure throughout the study, median C_{min} was 32 mg/L (range 23 – 65 mg/L). In 3 pts, a PK-guided intervention could not be performed, due to progression (n = 1) or logistical issues (n = 2). Twelve pts (35%) received a dose reduction due to toxicity (lowest dose was 200 mg QAD), exposure remained adequate at this reduced dose in all pts. For STS pts, median PFS was 19.8 months in pts with $C_{min} < 20.5$ mg/L who did need an intervention vs. 6.4 months in pts with all $C_{min} \geq 20.5$ mg/L (not significant). For RCC pts, this was 15.5 months vs. 7.4 months, respectively (not significant). **Conclusions:** This prospective study shows that PK-guided dose optimization of pazopanib using cost-neutral interventions is feasible in daily practice. A PK-guided intervention was performed in 24% of the patients, which was successful in 75% of these patients. Clinical trial information: NL6695. Research Sponsor: Unrestricted research grants by Novartis, Pfizer and Roche.

3599 Poster Session (Board #329), Fri, 8:00 AM-11:00 AM

Preliminary clinical pharmacokinetics and dose-response to support a phase II dose selection for CX-2009: A masked probody drug conjugate to CD166. *First Author: Mark Stroh, CytomX Therapeutics, Inc., South San Francisco, CA*

Background: PROBODY therapeutics are antibody prodrugs with cleavable peptide masks designed to reduce off-tumor, on-target toxicities. The mask blocks binding in the periphery and is removed by tumor-associated proteases resulting in intratumoral binding. CX-2009 is a PROBODY drug conjugate directed against CD166/ALCAM, which is a target overexpressed in carcinomas but not suitable for traditional ADC targeting because it is expressed in normal epithelium. CX-2009 is conjugated to DM4, a potent microtubule inhibitor. Here we report preliminary clinical pharmacokinetic (PK) and exploratory dose-response (DR) analyses for CX-2009 from the ongoing phase 1/2 PROCLAIM-CX-2009 study (NCT03149549). **Methods:** Human PK and anti-drug antibody (ADA) data were obtained at selected times post-dose following IV 0.25–10 mpk CX-2009 Q3W and of 6 mpk Q2W. Covariates were selected for population PK (POPPK) based on multivariate screening at $P < 0.01$. Preliminary exploratory DR analyses were conducted for selected endpoints including adverse events of special interest and response data (CR, PR, SD, and PD). **Results:** Preliminary CX-2009 PK data from 92 subjects were available as of October 2019. Median free DM4 levels circulated at ≤0.3% of Total CX-2009 (masked + activated CX-2009) levels across the 1–10 mpk dose levels. A two-compartment POPPK model with linear elimination was fit to the Intact (masked form) CX-2009 data. The preliminary CX-2009 POPPK model estimates for Intact CX-2009 clearance (CL), volume of distribution, and half-life were 0.47 L/day, 4.51 L, and 7.14 days, respectively, with 91% of CX-2009 circulating as Intact CX-2009. ADA was not a statistically significant covariate on Intact CX-2009 CL. Evidence of clinical activity was observed at doses of 4 mpk Q3W or higher. DR analysis suggested that the frequency of grade ≥3 ocular toxicity events increased significantly at dose equivalents ≥8 mpk Q3W. POPPK simulations suggested that the targeted 90 nM trough concentration (based on nonclinical data) would be contained within the 90% prediction interval of predicted Intact CX-2009 levels following CX-2009 7 mpk. **Conclusions:** Preliminary CX-2009 PK data following CX-2009 0.25-10 mpk suggest that CX-2009 circulates predominantly as Intact CX-2009, and that Intact CX-2009 PK is not strongly influenced by target-mediated drug disposition or ADA. Preliminary DR and POPPK simulations support further evaluation of 7 mpk CX-2009 Q3W in selected cohort expansions. Clinical trial information: NCT03149549. Research Sponsor: CytomX Therapeutics, Inc.

3600 Poster Session (Board #330), Fri, 8:00 AM-11:00 AM

Prophylactic dihydropyrimidine dehydrogenase (DPYD), and reactive cytidine deaminase (CDA) testing is feasible and reduces severe toxicity in Irish patients receiving 5-fluorouracil (5-FU) based chemotherapy. *First Author: Jake Murphy, Bon Secours Hospital, Cork, Ireland*

Background: 5-Fluorouracil (5-FU) steady state concentrations can vary up to fourfold among cancer patients. 5-FU intolerance and toxicity is associated with reduced activity of the key metabolic enzyme dihydropyrimidine dehydrogenase (DPD) due to polymorphisms of the DPYD gene, as well as mutations in cytidine deaminase (CDA). Since 2012, Bon Secours Hospital, Cork has implemented prophylactic DPYD screening to reduce toxicity. **Methods:** In this retrospective cohort study, 742 adult cancer patients who underwent reactive or prophylactic DPYD testing in our center between 2012 and 2019 were included. Reactively tested patients were screened prior to 2012. 5-FU related toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE) and analysed. Frequencies of polymorphisms in DPYD, affecting 5-FU metabolism in patients who experienced severe toxicity are described, in both patients who were retrospectively tested, and in our larger prophylactic patient cohort. Mutations of genes encoding CDA were also analysed. Analysis of type and severity of toxicity, and survival analysis will be presented at the Annual Meeting. **Results:** 742 patients were tested for DYPD in our centre, of which 704 were prophylactic tests. 11.4% of the patients tested prophylactically were found to have polymorphisms in the DYPD gene. Expectedly, a higher proportion of patients tested reactively were found to have polymorphisms in DYPD (21.9%). 21 out of 34 patients who had severe toxicity had CDA mutations present on testing. Further data involving classification and severity of toxicities, along with survival analysis will be presented at the Annual Meeting. **Conclusions:** The prevalence of DPYD mutations in Ireland is estimated to be 7-10%, and is putatively responsible for approximately 20% of all severe 5-FU toxicities suffered by cancer patients. Implementing prophylactic DPYD screening is beneficial in reducing toxicities in this setting. Future work will focus on phenotypic measurements of uracil metabolism and pharmacokinetic 5-FU monitoring to further reduce toxicity in patients who do not have DPYD mutations. Research Sponsor: None.

3601 Poster Session (Board #331), Fri, 8:00 AM-11:00 AM

Myelodysplastic syndrome and acute myeloid leukemia as side effect of PARP inhibitors. *First Author: Samip R. Master, Louisiana State University Health Sciences Center, Shreveport, LA*

Background: Acute myeloid leukemia(AML) and myelodysplastic syndrome(MDS) have been rarely noted in patients on PARP inhibitors. The actual incidence is unknown and it has been put has warning/precaution of FDA label for olaparib, niraparib and rucaparib. **Methods:** The FDA has made the data on the adverse effects of various treatments available to the general public through the FDA Adverse Events Reports System (FAERS) public dashboard. We investigated the adverse events reported for PARP inhibitors like olaparib, niraparib and rucaparib for the years 2017-2019 to find out the number of patients who had acute leukemia or myelodysplastic syndrome reported while on those medications. **Results:** A total of 8151 adverse events were reported between 2017 and 2019 for olaparib, niraparib and rucaparib. Out of which, 6077 were serious and 1121 deaths were reported. There were 237 reports of AML and MDS, which compromise 2.9 % of total events reported. We also looked that cyclophosphamide data for comparison purposes during the same period. There were 29,162 adverse events reported for cyclophosphamide, out of which 963 i.e. 3.3% were AML and MDS. For olaparib, 2523 adverse events were reported and 173 (6.8%) were MDS/AML. For niraparib, 5496 adverse events were reported and 41(0.7%) were MDS/AML. For rucaparib, 153 adverse events were reported and 4 (2.6%) were MDS/AML. **Conclusions:** Based on this retrospective data, AML/MDS is an adverse event in pts of PARP inhibitors and needs to be monitored. Pts on olaparib seem to have high risk of AML/MDS compared to other two to PARP inhibitors. Research Sponsor: None.

3602 Poster Session (Board #332), Fri, 8:00 AM-11:00 AM

Preliminary population pharmacokinetics supports phase II dose selection for masked anti-PD-L1 antibody CX-072. *First Author: Mark Stroh, CytomX Therapeutics, Inc., South San Francisco, CA*

Background: PROBODY therapeutics (Pb-Tx) are antibody prodrugs designed to reduce off-tumor, on-target toxicities. The mask inhibits Pb-Tx binding in the periphery yet can be removed by tumor-associated proteases, restricting target engagement to the tumor. This is the first report of preliminary clinical pharmacokinetic (PK) analysis supporting selection of the phase II dose for CX-072, an anti–PD-L1 Pb-Tx, from the ongoing phase I/II PROCLAIM-CX-072 study (NCT03013491). **Methods:** A quantitative systems pharmacology (QSP) model[1] was used to project the CX-072 plasma trough level (C_{min}) corresponding to 95% intratumoral receptor occupancy (RO). Human PK and anti-drug antibody (ADA) data were obtained at selected times postdose following IV administration of 0.03–30 mpk CX-072 in PROCLAIM-CX-072. Population PK (POPPK) modeling was performed with NONMEM v7.3.0. Exploratory analysis and simulations were done with R v3.3.1 or later. Covariates were selected for POPPK using forward addition ($P<0.05$) followed by backward deletion ($P<0.01$). **Results:** The preliminary POPPK analyses were informed using available PK data as of August, 2019 from 135 subjects receiving CX-072 Q2W as monotherapy in the dose-escalation and expansion cohorts of PROCLAIM-CX-072. A mixture model was used to capture time- and dose-dependent apparent ADA effect on clearance (CL). The preliminary POPPK model estimates for CX-072 CL and volume of distribution (Vd) were 0.306 L/day and 4.84 L, respectively. Statistically significant covariate effects included body weight on the central Vd and CL, and albumin on CL. The QSP model predicted a CX-072 C_{min} of 13–99 nM would be required for 95% intratumoral RO. POPPK simulations suggested that >95% of patients receiving CX-072 10 mg/kg Q2W would meet or exceed this targeted C_{min} regardless of ADA. Additional observed data indicated that the majority of patients receiving 10 mpk CX-072 Q3W × 4 with 3 mpk ipilimumab (IPI) Q3W × 4 in the CX-072-IPI combination part of PROCLAIM-CX-072 maintained the targeted C_{min}. Simulations did not suggest there would be a clinically meaningful change in exposure following a fixed dose of CX-072 800 mg relative to the 10 mpk weight-based dose. **Conclusions:** Preliminary PK analysis supports selection of 800 mg CX-072 Q2W as the recommended monotherapy dose and 800 mg Q3W when combined with IPI. The combination of 800 mg CX-072 + 3 mpk IPI Q3W × 4 doses, followed by monotherapy administration of 800 mg CX-072 Q2W is being further explored in phase II. Reference: 1) Stroh M et al. *CPT.* 2019(9):676-84. Clinical trial information: NCT03013491. Research Sponsor: CytomX Therapeutics, Inc.

3603 Poster Session (Board #333), Fri, 8:00 AM-11:00 AM

Final results from the phase I study expansion cohort of the selective FGFR inhibitor Debio 1,347 in patients with solid tumors harboring an FGFR gene fusion. *First Author: James M. Cleary, Dana Farber Cancer Institute, Boston, MA*

Background: Debio 1347 is a selective oral inhibitor of FGFR 1-3 tyrosine kinases. It exhibited high antitumor activity in *in vitro* and *in vivo* tumor models with FGFR1-3 gene fusions. Here we report the results of the expansion portion of a Phase 1 study of advanced solid tumors patients (pts) harboring an FGFR1-3 gene fusion. **Methods:** Pts with advanced refractory solid tumors harboring an FGFR1-3 gene fusion were enrolled. Based on results from the dose escalation portion, pts received Debio1347 80 mg once daily (qd) in 28-day cycles. Pharmacokinetics (PK) and pharmacodynamics were evaluated. The data cut-off was October 8, 2019. **Results:** Among 18 pts enrolled, 5 had primary brain tumors (PBT), 5 had cholangiocarcinoma, 2 had urothelial cancer, 2 had colon cancer, 1 patient each lung neoplasm, gastric cancer, endometrial cancer and squamous cell carcinoma of the chest wall. Tumors harbored fusions with FGFR1 (n = 1), FGFR2 (n = 8), and FGFR3 (n = 9). All had prior systemic therapy (median 3 lines; range 1-4). The most common treatment emergent adverse events were fatigue (50%), hyperphosphatemia (44.4%), anemia (38.9%), alopecia (33.3%), nausea (33.3%), vomiting (33.3%), constipation (33.3%), and palmar-plantar erythrodysesthesia syndrome (22.2%). Blurred vision was reported in 1 pt. There were no findings on ocular exams compatible with retinal detachment. No grade 3 AE related to study drug were reported. One patient needed dose reduction due to grade 2 nails toxicity. In PK analysis, plasma steady-state was rapidly achieved and serum phosphate increase correlated with Debio 1347 plasma exposure, confirming target engagement at 80 mg qd. Median follow-up was 18 weeks. Partial responses were observed in 3 pts harboring an FGFR2 fusion: 1 out of 2 colon cancer and 2 out 5 cholangiocarcinoma. Median duration of response was 16.1 weeks (range: 8.4-22.8+). Overall disease control was observed in 11 out of 14 pts without PBT (79%). Median PFS was 18.3 weeks. No signs of activity were observed in the 5 patients with PBT, all with an FGFR3-TACC3 fusion. **Conclusions:** Debio 1347 at the recommended dose of 80 mg qd was generally well tolerated and showed signs of activity in solid tumors harboring an FGFR fusion. The FUZE phase 2 clinical trial of Debio 1347 is recruiting FGFR fusion-positive advanced solid tumors irrespectively of tumor histology, excluding PBT. Clinical trial information: NCT01948297. Research Sponsor: Debiopharm International SA.

3604 Poster Session (Board #334), Fri, 8:00 AM-11:00 AM

Results of a phase Ib trial evaluating the safety and clinical activity of sapanisertib (TAK 228) in combination with serabelisib (TAK 117) and paclitaxel in patients with advanced ovarian, endometrial, or breast cancer. *First Author: Casey B. Williams, Avera Cancer Institute, Sioux Falls, SD*

Background: The link between taxane resistance and activation of PI3K/AKT/mTOR signaling suggests that by inhibiting this pathway in combination with anti-microtubule agents like paclitaxel may improve treatment outcomes in many malignancies. To investigate this further we combined the TORC 1/2 inhibitor sapanisertib (TAK-228), the PI3Kα isoform inhibitor serabelisib (TAK-117), and paclitaxel in a phase I trial to determine the safety, efficacy, and RP2D. **Methods:** Open label, cohort study using a traditional 3+3 dose escalation design with a maximum of 5 dosing cohorts. A dose expansion of cohort 4, the recommended RP2D, is planned for February 2020. **Results:** Enrollment to the DLT evaluation has been completed and the clinical results are summarized in Table. Sixteen patients have been enrolled; a majority were heavily pretreated and resistant to paclitaxel. Overall, the combination was safe and tolerable. One DLT occurred due to renal dysfunction in cohort 5. 360 adverse events have been reported, but only 28 (8%) grade 3 or 4 events. The most common events were leukopenia and non-febrile neutropenia. Two patients required dose reductions as a result of pneumonitis. The ORR is currently 46% in 13 evaluable patients. CBR is 69% and PFS is currently at 10 months. Two patients achieved a CR and three patients remain on treatment. **Conclusions:** The combination proved to be well tolerated in the doses and schedules used in cohorts 1-4 and exhibited very promising clinical activity in heavily pretreated patients. This regimen could prove to be a highly effective treatment option and a phase 2 study is warranted at the RP2D. Clinical trial information: NCT03154294.Research Sponsor: Takeda.

Pt # and Diagnosis	Cohort	Previous Lines	TAK 228/117 (mg) days 2-4, 9-11, 16-18, and 23-25	Paclitaxel Dose (mg/m2) days 1, 8, and 15	Best Response
1 (Breast)	1	3*	2/100	60	PR (PFS 9 months)
2 (Ovarian	1	12*	2/100	60	SD (PFS 9 months)
3 (Endometrial)	1	2	2/100	60	PD
4 (Endometrial)	1	6	2/100	60	PR (PFS 12 months)
5 (Breast)	2	5	2/200	60	NE
6 (Breast)	2	5	2/200	60	NE
7 (Endometrial)	2	1	2/200	60	CR (Duration of CR - 15 months)
8 (Mullerian)	3	3	2/200	80	PD
9 (Ovarian)	3	3*	2/200	80	SD (PFS 6 months)
10 (Ovarian)	3	5*	2/200	80	SD/PR (29% by RECIST) (PFS 6 months)
11 (Ovarian)	4	4	3/200	80	PD
12 (Ovarian)	4	3	3/200	80	PR (PFS 12 months)
13 (Ovarian)	4	4	3/200	80	SD (Cycle 12 and ongoing)
14 (Endometrial)	5	4*	4/200	80	CR (Cycle 9 and ongoing)
15 (Ovarian)	5	4	4/200	80	PD
16 (Ovarian)	5	6	4/200	80	DLT – Still on treatment

* Received Prior Everolimus/Temsirolimus

3605 Poster Session (Board #335), Fri, 8:00 AM-11:00 AM

Efficacy and safety of entrectinib in patients (pts) with *NTRK*-fusion positive (*NTRK*-fp) solid tumors: An updated integrated analysis. *First Author: Christian Diego Rolfo, University of Maryland School of Medicine, Baltimore, MD*

Background: *NTRK* gene fusions lead to transcription of chimeric TRK proteins with overexpressed kinase function. Entrectinib is a potent inhibitor of TRKA/B/C. In phase 1/2 studies (ALKA, STARTRK-1, STARTRK-2; EudraCT 2012-000148-88; NCT02097810; NCT02568267), entrectinib was effective in pts with *NTRK*-fp solid tumors. We present updated data in a larger population with longer follow-up. **Methods:** In this integrated analysis of adult pts from 3 phase 1/2 trials (data cut-off 31 Oct 2018), tumors were assessed by blinded independent central review (BICR) with RECIST v1.1 (end of cycle 1; then every 8 wks). Primary endpoints were overall response rate (ORR) and duration of response (DOR). Secondary endpoints were progression-free survival (PFS), overall survival (OS), efficacy in pts with/without baseline CNS disease, and safety. **Results:** There were 74 evaluable pts with advanced/metastatic *NTRK*-fp solid tumors (Table). Median duration of survival follow-up in all pts was 14.2 mo (range 0.1–29.7). BICR ORR was 63.5% (95% CI 51.5–74.4), with 5 complete responses (6.8%). Median BICR DOR was 12.9 mo (95% CI 9.3–NE); median BICR PFS was 11.2 mo (95% CI 8.0–15.7); median OS was 23.9 mo (16.0–NE). In pts with no baseline CNS disease (investigator-assessed; n=55), BICR ORR was 65.5% (95% CI 51.4–77.8) and median BICR DOR in responders was 12.9 mo (95% CI 9.3–NE). In pts with baseline CNS disease (investigator-assessed; n=19), BICR ORR was 57.9% (95% CI 33.5–79.8) and median BICR DOR in responders was 6.0 mo (95% CI 4.2–NE). Safety was in line with that previously reported; the most common ≥grade 3 treatment-related AEs were weight gain (8, 7.1%), anemia (8, 7.1%), and fatigue (7, 6.2%). **Conclusions:** In this updated analysis, including more pts and longer follow-up, entrectinib continued to demonstrate clinically meaningful responses in pts with *NTRK*-fp solid tumors, with and without baseline CNS disease. Clinical trial information: NCT02097810, NCT02568267.Research Sponsor: Ignyta/F Hoffmann-La Roche.

Baseline characteristic	*NTRK*-fp tumors (N=74)
Age (yrs): mean (SD)	56.5 (14.6)
Race,* n (%): White/Asian/Black	52 (70.3)/13 (17.6)/2 (2.7)
ECOG PS, n (%): 0/1/2	30 (40.5)/34 (45.9)/10 (13.5)
CNS mets at baseline,† n (%)	19 (25.7)
Tumor type, n	
Sarcoma	16
MASC	13
NSCLC	13
CRC	7
Thyroid	7
Breast	6
Neuroendocrine	4
Pancreatic	3
Gynecological	2
Cholangiocarcinoma	1
Gastrointestinal non-CRC	1
Neuroblastoma	1

*7 not reported. †Investigator-assessed. CRC, colorectal cancer; ECOG PS, European Cooperative Oncology Group performance status; MASC, mammary analogue secretory carcinoma; NSCLC, non-small cell lung cancer; SD, standard deviation.

3606 Poster Session (Board #336), Fri, 8:00 AM-11:00 AM

Safety and efficacy of pemigatinib plus pembrolizumab combination therapy in patients (pts) with advanced malignancies: Results from FIGHT-101, an open-label phase I/II study. *First Author: Martin Gutierrez, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ*

Background: Pemigatinib (INCB054828) is a selective fibroblast growth factor receptor (FGFR) 1–3 inhibitor with demonstrated efficacy as monotherapy in phase 1/2 (FIGHT-101) and phase 2 (FIGHT-201, -202, -203) trials in pts with advanced cancer. Here, we present preliminary safety, efficacy, and pharmacokinetic (PK) data for pemigatinib (PEMI) combined with pembrolizumab (PEMBRO), a programmed cell death protein-1 (PD-1) inhibitor, in pts with refractory advanced malignancies enrolled in the ongoing FIGHT-101 trial (NCT02393248). **Methods:** FIGHT-101 includes monotherapy (part 1 and 2) and combination therapy (part 3) cohorts. This analysis is based on pts enrolled in the PEMI + PEMBRO combination dose finding (3a) and dose expansion (3b) cohorts. Eligible adults had advanced malignancies who had progressed after prior therapy and for whom PEMBRO treatment was relevant; pts in part 3b had *FGF/FGFR* alterations. Pts received oral PEMI at 9 mg or 13.5 mg QD on an intermittent dosing (ID) schedule (21-day cycle, 14-day on/7-day off), or 13.5 mg QD on a continuous dosing (CD) schedule, plus PEMBRO 200 mg IV on day 1 of each 21-day cycle. **Results:** At data cutoff (August 30, 2019), 23 pts had received PEMI + PEMBRO; 22 (96%) had discontinued therapy (disease progression, 70%). Most frequent tumors were NSCLC (n = 3), bladder (n = 3), pancreatic, testicular, and sarcoma (each n = 2). Of 19 enrolled pts with baseline *FGF/FGFR* data; 5 had *FGFR* mutations or rearrangements. No dose-limiting toxicities occurred with PEMI + PEMBRO. The recommended PEMI dose combined with PEMBRO was 13.5 mg QD. Most frequent all-cause, all-grade (Gr) adverse events for ID (n = 17) were hyperphosphatemia (n = 14 [82%]; Gr ≥3, n = 0), anemia (n = 9 [53%]; Gr ≥3, n = 3 [18%]), and decreased appetite (n = 9 [53%]; Gr ≥3, n = 0); for CD (n = 6), hyperphosphatemia (n = 5 [83%]; Gr ≥3, n = 0), and dry mouth (n = 4 [67%]; Gr ≥3, n = 0). One pt discontinued, 2 reduced dose, and 13 interrupted dose due to AEs (none for hyperphosphatemia; dose interruption mainly for gastrointestinal AEs [n = 5]). One fatal AE occurred (suicide, not treatment-related). PK parameters for PEMI in the PEMI + PEMBRO combination were comparable with those for PEMI monotherapy. Five pts had partial response (3 had *FGFR* rearrangements or mutations); 5 pts had stable disease. **Conclusions:** PEMI + PEMBRO combination therapy was tolerable with no new safety signals, and demonstrated preliminary antitumor activity in pts with advanced malignancies including those with *FGF/FGFR* alterations. Clinical trial information: NCT02393248. Research Sponsor: Incyte Corporation.

3607 Poster Session (Board #337), Fri, 8:00 AM-11:00 AM

Results of a completed first-in-human phase Ib dose-escalation study of oral CBL0137 in patients with advanced solid tumors. *First Author: Mikhail Fedyanin, Federal State Budgetary Institution N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russian Federation*

Background: Curaxin CBL0137 is a novel compound with broad anticancer activity in animal models. The drug is a non-genotoxic DNA intercalator that interferes with histone/DNA binding causing decondensation of chromatin in tumor cells, functional inactivation of histone chaperone FACT, activation of p53 and IFN responses, and inhibition of pro-cancer transcriptional factors, MYC, NF-kB, HSF1, and HIF1a. **Methods:** The study enrolled adults with advanced chemorefractory solid tumors, ECOG PS ≤2, and adequate organ function. The primary objective was to find the maximum tolerated dose (MTD) and recommended dosing regimen (RDR). Secondary objectives were to evaluate CBL0137 safety, pharmacokinetics, and efficacy. CBL1037 was given orally once daily (QD) for the first 14 days of repeated 28-day cycles. A 3+3 dose escalation determined the MTD, defined as the highest dose at which ≤1 of 6 pts had Cycle 1 dose-limiting toxicity (DLT). Pharmacokinetics were assessed on Days 1 and 13. Efficacy was evaluated every 8 weeks. **Results:** 60 pts were enrolled (females/males [n]: 42/18; median [range] age 56 [25-76] years; ECOG PS [n] 0/1/2: 8/49/3); cancer types [n]: ovarian cancer [15], colorectal cancer [14], breast cancer [11], others [20]) over 16 dose levels ranging from 4 mg to 200 mg QD. Durations of therapy ranged from 6 to 342 days. Three DLTs were observed: prolongation of QTc Gr 3 (88 mg QD), neutropenia/thrombocytopenia Gr 4 (200 mg QD), and LV dysfunction Gr 3 (200 mg QD). Dose-dependent nausea/vomiting was observed and was Gr 2-4 at 200 mg QD. Gr 1/2 photosensitization occurred in 11 subjects across doses from 48 to 200 mg QD but was successfully managed with sun protection and resulted in no dose modifications or discontinuations. On Day 1, mean (range) plasma CBL0137 T_{max} values were 5.1 (1-10) hrs. Generally linear increases in AUC occurred with increasing CBL0137 dose. Mean (range) $t_{1/2}$ values were 25.6 (0.3-166) hrs, with minor dose dependency. Mean (range) Day 13/Day 1 C_{trough} ratios showed 3.6 (1.7-7.2)-fold accumulations. Disease control was registered in 11 pts who had stable disease (SD). Target lesion regressions up to 21% were documented in 4 patients with breast cancer (2), sarcoma (1), and ovarian cancer (1). Pts with breast cancer (1) and sarcoma (1) had SD for > 36 weeks. **Conclusions:** The Phase 2 RDR for oral CBL0137 was established as 180 mg QD x 14 days in 28-day cycles based on bone marrow and gastrointestinal DLTs at 200 mg QD. CBL0137 showed a manageable safety profile with efficacy signals. Further study as a component of combinations is planned. Clinical trial information: 847. Research Sponsor: Incuron.

3609 Poster Session (Board #339), Fri, 8:00 AM-11:00 AM

CTEP 9557: A dose-escalation trial of combination dabrafenib, trametinib, and AT13387 in patients with BRAF mutant solid tumors. *First Author: Meghan Mooradian, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Combination BRAF and MEK inhibitor therapy is associated with response in patients (pts) with BRAF mutant (mut) solid tumors; however critical limitations for the durable activity of these agents remains. Preclinically, the addition of heat shock protein 90 (HSP90) inhibitors improves the efficacy of BRAF inhibitor (BRAFi) therapy in both BRAFi-sensitive and resistant mutant cell lines. **Methods:** CTEP study 9557 (NCT02097225) is a phase I study designed to determine the safety and efficacy of the small molecule HSP90inhibitor, AT13387, in combination with dabrafenib (dab) and trametinib (tram) in patients with $BRAF^{V600E/K}$ mut solid tumors. Prior chemotherapy, immunotherapy, BRAF and/or MEK exposure was permitted. The primary objective was to determine the maximum tolerated dose (MTD). **Results:** From July 2015 to June 2018, 22 patients with previously treated, metastatic $BRAF^{V600E/K}$ mut solid tumors were enrolled using a 3 + 3 design at four dose levels (DL) (Table). Pts were predominantly female (59%) with a median age of 57.5yrs (37 -75). The most common tumor type was $BRAF^{V600E}$mut colon cancer (N=12). Dose limiting toxicities (DLTs) occurred in one patient in DL3 and one in DL4, specifically grade 3 myelosuppression and fatigue, respectively. The MTD was Dab 150mg [BID/PO], Tram 2mg [QD/PO] and AT1187 260mg/m2 [D1,8,15/IV]. Twenty-one of 22 pts were eligible for efficacy assessment. Best response, per RECIST 1.1, was partial response (PR) in 2 pts – one with colon ca (TKI-naïve), one with melanoma (TKI-resistant) - stable disease (SD) in 8 pts, and disease progression (PD) in 11 with a disease control rate (PR + SD) of 47.6% (90% CI: 29% - 67%). Median time to progression was significantly longer in DL3 (3.9 mths; 1.8-9.2) compared to DL1 (1.6mths; 0.9-1.7) or DL2 (1.5; 0.6-3.6). Median PFS and OS were 1.8mths (90% CI: 1.6 – 3.7mths) and 5.1 mths (90% CI: 2.5 -10.6mths), respectively. Median OS was not reached in DL3/4. Correlative data on the expression of the key signaling proteins relating to response will be presented at the meeting. **Conclusions:** HSP90 inhibition combined with BRAF/MEK inhibition was determined to be safe with evidence of disease control in a heavily pre-treated population of pts with $BRAF^{V600E/K}$ mut solid tumors. Clinical trial information: NCT02097225.Research Sponsor: U.S. National Institutes of Health.

Dose level cohorts.

DOSE LEVEL	DABRAFENIB [BID/PO]	TRAMETINIB [QD/PO]	AT13387 [D1,8,15/IV]
-1	75 mg	1 mg	180 mg/m2
1	150 mg	1 mg	180 mg/m2
2	150 mg	2 mg	180 mg/m2
3	150 mg	2 mg	220 mg/m2
4	150 mg	2 mg	260 mg/m2

3610 Poster Session (Board #340), Fri, 8:00 AM-11:00 AM

Activity and safety of larotrectinib in adult patients with TRK fusion cancer: An expanded data set. *First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The highly selective TRK inhibitor larotrectinib is approved for the treatment of adult and pediatric cancers that harbor *NTRK* gene fusions; it achieves a 79% overall response rate (ORR) in this population (Hong et al., *Lancet Oncol*, 2020). The activity of larotrectinib in adults alone was further characterized in this update with a larger series of patients and more mature durability data. **Methods:** Adults (aged ≥18 y) with TRK fusion cancer treated in three larotrectinib clinical trials (NCT02122913, NCT02576431, and NCT02637687) were analyzed. Larotrectinib was administered 100 mg BID until disease progression, withdrawal, or unacceptable toxicity. ORR was investigator-assessed (RECIST v1.1). Compared to previously presented data on 74 patients, this expanded data set includes an additional 42 patients (data cutoff: July 15, 2019). **Results:** 116 adults (median age: 56 y, range 19–84 y; 53% female) with TRK fusion cancer were treated. Tumor types included thyroid cancer (22%), salivary gland cancer (19%), soft tissue sarcoma (16%), lung cancer (12%), colon cancer (7%), melanoma (5%), breast cancer (5%), GIST (3%), and 9 other types (≤2% each). *NTRK* fusions involved *NTRK1* (43%), *NTRK2* (3%), and *NTRK3* (54%). 78% of patients had received prior systemic therapy (with 68% of those receiving ≥2 prior therapies). The ORR was 71% (95% CI 62–79): 10% complete response, 60% partial response (2% pending confirmation), 16% stable disease, 9% progressive disease, 3% not determined. In patients with brain metastases, the ORR was 71% (95% CI 42–92; 10 of 14 patients, all partial responses). Median duration of response for the overall data set (n = 116) was 35.2 mo (95% CI 21.6–not estimable [NE]). Median progression-free survival was 25.8 mo (95% CI 15.2–NE). Median overall survival was not reached (range 0.5+ to 51.6+ mo) at a median follow-up of 15.8 mo. Duration of treatment ranged from 0.10 to 51.6+ mo. 12% of patients had dose reductions. One patient (1%) discontinued due to a larotrectinib-related adverse event (AE). AEs were mostly grade 1–2; no new unexpected AEs were reported. **Conclusions:** In an expanded data set of adults with TRK fusion cancer, larotrectinib demonstrated robust and durable tumor-agnostic efficacy and favorable safety, supporting *NTRK* gene fusion testing in patients with solid tumors of any type. Clinical trial information: NTC02122913, NCT02576431, NCT02637687. Research Sponsor: Bayer and Loxo Oncology (a subsidiary of Lilly).

3611 Poster Session (Board #341), Fri, 8:00 AM-11:00 AM

A phase I, first-in-human, open-label, dose-escalation, safety, pharmacokinetic, and pharmacodynamic study of oral TP-1287 administered daily to patients with advanced solid tumors. *First Author: Ben George, Froedtert & The Medical College of Wisconsin, Milwaukee, WI*

Background: TP-1287 is a an orally bioavailable phosphate prodrug of alvocidib, a cyclin dependent kinase 9 (CDK9) inhibitor. TP-1287 exhibits potent inhibition of intracellular kinases including CDK9. Inhibition of CDK9 leads to downregulation of the BCL-2 family member, MCL-1, which in turn inhibits tumor growth in preclinical animal models of prostate, breast, and lung carcinomas. **Methods:** This is a multicenter, Phase 1, dose escalation study using a standard 3+3 design with a modified Fibonacci scheme to examine the safety and clinical activity of TP-1287 in patients with advanced solid tumors. Patients will be added at the maximum tolerated dose (i.e. expansion cohort) to test TP-1287 as a single agent in patients with castrate resistant prostate cancer. **Results:** Twenty-two patients who were enrolled between December 2018 and January 2020 received a range of doses from 1 mg QD to 11 mg BID over 7 cohorts. Data are available for 20 patients as of the data cutoff date. TP-1287 plasma PK C_{max} and AUC increased in near linear fashion over cohorts 1 thru 6, reaching 80 ng/mL and 499.3 ng*h/mL in cohort 6 for C_{max} and AUC, respectively. TP-1287 treatment resulted in dose-dependent reductions of phospho-RNA Pol II, consistent with CDK9 inhibition, as measured by a flow cytometric assay assessing pharmacodynamic changes in phosphorylation state in PBMCs. The most frequently observed Grade 3 AE was unrelated anemia in 2 patients. All other events of Grade 3 (9 events/7 patients) and Grade 4 (1 event/seizure with new CNS mets) were unlikely related or unrelated. Clinical benefit was seen in one sarcoma patient with PR (15+cycles), one RCC patient with SD (7+cycles) and 2 bladder cancer patients with SD (6 and 8 cycles). **Conclusions:** These findings suggest that TP-1287 is tolerated as a monotherapy in patients with heavily pretreated, relapsed, refractory solid tumors and further clinical development in selected indications is warranted. Clinical trial information: NCT03298984. Research Sponsor: Tolero Pharmaceuticals, Inc.

3612 Poster Session (Board #342), Fri, 8:00 AM-11:00 AM

Phase II trial of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886 Hydrogen Sulfate) in adults with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN). *First Author: Geraldine Helen O'Sullivan Coyne, Developmental Therapeutics Clinic/Early Clinical Trials Development Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD*

Background: NF1-related PN are locally invasive tumors characterized by increased activation of the RAS pathway causing significant morbidity including disfigurement, pain and functional limitations. Selumetinib has received breakthrough designation for NF1 PN based on phase I / II trials in children. We present results for the ongoing phase II study of selumetinib in adults with NF1 PN, which includes pharmacodynamic (PD) evaluation of serial tumor biopsies as well as functional/patient-reported outcomes (PROs). **Methods:** Open-label Simon 2-stage design. Eligibility: NF1 patients (pts) ≥18 years old with inoperable/symptomatic/progressive PN. First 2 pts received selumetinib 75 mg BID; subsequent pts received selumetinib 50 mg BID. Primary objective: response rate by volumetric MRI analysis (partial response [PR]; ≥20% volume decrease). Secondary objectives: PD studies on pre/on-treatment biopsies of PN and cutaneous neurofibromas, assessment of clinical benefit using PROs (Numeric Rating Scale-11, Pain Interference Index), and PN-specific functional assessments. Validated, fit-for-purpose, isozyme-specific measurements of pERK/ERK/pMEK/MEK performed using SOPs designed for labile phosphoproteins (PMID 27001313). **Results:** As of February 2020, 27 pts have enrolled. Outcomes are reported for 23 pts (74% male; median age 33 years, range 18-60). Most common PN-related morbidity: pain (19 pts). Sixteen pts achieved PR (69%), with 13/16 confirmed; no disease progression. Time to response: 11 months (range 5-25); median change in PN volume at best response: -22% (range -41% to +5.5%); median duration of treatment: 28 months (range 2-50). Selumetinib suppressed tumor pERK1,2/ERK1,2 but not pMEK1,2/MEK1,2 ratios from 1-10 hours following oral dosing (one $t_{1/2}$). Pt-reported target tumor pain intensity and pain interference scores significantly improved (both $p < 0.03$). Pts 1 and 2 were dose-reduced due to grade 3 intolerable rash (n = 2) and pain (n = 1). Grade ≥3 drug-related toxicities on 50 mg (21 pts) include transaminitis (5 pts), rash (1 pt) and pancreatic enzyme elevation (1 pt). Two pts were dose reduced (rash = 1 pt, transaminitis = 1 pt). Two pts discontinued by choice, 2 pts withdrawn by PI (best interest of patient), and 1 pt each removed for transaminitis, surgical resection, serious concurrent medical illness, and noncompliance. **Conclusions:** Selumetinib shrinks the majority of adult PN and results in molecular target suppression and clinical benefit. Clinical trial information: NCT02407405. Research Sponsor: U.S. National Institutes of Health.

3613 Poster Session (Board #343), Fri, 8:00 AM-11:00 AM

Phase I study of afatinib plus selumetinib in patients with KRAS mutation-positive colorectal, non-small cell lung and pancreatic cancer. *First Author: Sanne Huijberts, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Mutations in the *KRAS* gene result in a constitutively activated RAS-RAF-MEK-ERK (MAPK) pathway. In KRAS mutant tumors, the antitumor activity of MEK inhibitors is limited due to intrinsic resistance caused by feedback activation of upstream epidermal growth factor receptors (HER). This upstream activation not only reactivates MAPK, but also the phosphoinositide 3-kinase (PI3K)-AKT pathway in preclinical research. Based on these data, a phase I clinical trial was initiated with the combination of the orally administered pan-HER inhibitor afatinib and the MEK inhibitor selumetinib in patients with *KRAS* mutant and *PIK3CA* wildtype colorectal cancer (CRC), non-small cell lung cancer (NSCLC), or pancreatic cancer to determine the recommended phase 2 regimen (RP2R). **Methods:** In this multicentre study, patients received escalating doses of afatinib and selumetinib according to a 3+3 design starting with 20 mg afatinib once daily (QD) continuously and 25 mg selumetinib twice daily (BID) in a 21 days on/7 days off schedule. Continuous and intermittent dosing were explored to assess optimal exposure and tolerability. The primary aim was determining the RP2R. Secondary objectives included assessment of anti-tumor activity and the analyses of pharmacokinetic and pharmacodynamic parameters for target inhibition. Clinicaltrials.gov identifier: NCT2450656. **Results:** In total, 26 mostly heavily pretreated patients with CRC (n=19), NSCLC (n=6) and pancreatic cancer (n=1) were enrolled among 5 dose-levels. Dose-limiting toxicities (DLTs) occurred in 6 patients and consisted of grade 3 diarrhea (n=3), decreased appetite (n=1), nausea/vomiting (n=1), dehydration (n=2) and mucositis (n=1). Clinical efficacy was limited with no responses according to RECIST v1.1 and stable disease for 221 days in a patient with NSCLC as best response. **Conclusions:** The RP2R was determined at 20 mg afatinib QD continuously and 25 mg selumetinib BID 21 days on/7 days off for continuous dosing. The 3 patients treated in the escalation cohort of the ongoing intermittent dose-level with 20 mg afatinib QD and 25 mg selumetinib BID 5 days on/2 days off, experienced no DLTs. Pending the latest safety results of the expansion cohort for this ongoing dose-level, the RP2R of intermittent dosing has not been established at the moment. Clinical trial information: NCT2450656. Research Sponsor: Boehringer Ingelheim Inc., AstraZeneca Inc.

3614 Poster Session (Board #344), Fri, 8:00 AM-11:00 AM

Quality of life of adults and children with TRK fusion cancer treated with larotrectinib compared to the general population. *First Author: Shivaani Kummar, Stanford Cancer Institute, Stanford University, Palo Alto, CA*

Background: *NTRK* gene fusions occur in diverse tumor types in adults and children. The selective TRK inhibitor, larotrectinib, has shown high response rates, durable disease control, and a favorable safety profile in patients (pts) with TRK fusion cancer. We report an expanded quality of life (QoL) analysis for pts treated with larotrectinib. **Methods:** QoL data were collected in two trials of larotrectinib in pts with TRK fusion cancer using EORTC QLQ-C30 (adults) and PedsQL (children) questionnaires, and were analyzed descriptively and longitudinally. EORTC QLQ-C30 global health scores (GHS) and PedsQL total scores range from 0 to 100, with higher scores indicating better QoL. We calculated the proportion of pts with normal/above and below normal QoL scores compared to values in the literature for the US general population. **Results:** By July 2019, 126 pts with TRK fusion cancer (74 adults, 24 children ≥2 yrs, and 28 infants <2 yrs) had received larotrectinib and completed baseline (BL) and ≥1 post-BL questionnaire. Most pts had clinically meaningful QoL improvements that reached or exceeded the minimally important difference (Table); a positive change from BL was also seen in infants: mean best change of 12.0 (SD 13.8). Of 52 adults with BL EORTC QLQ-C30 GHS at or above the population norm, 51 remained in this category on treatment and 1 moved into the below normal category. Of 22 adults with BL scores below the population norm, 20 moved into the normal/above normal category. All 9 children aged ≥2 yrs with BL PedsQL scores at or above the population norm remained in this category on treatment. Of 15 children with BL scores below the population norm, 10 moved into the normal/above normal category. Sustained QoL improvements (change from BL ≥0) occurred by 2 months of treatment in 69% of adults and 75% of children. Median duration of sustained improvement in EORTC QLQ-C30 GHS and PedsQL total score was 12.0 months (range 1.7–20.3) and not estimable (range 1.1–23.0), respectively. **Conclusions:** Adults and children with TRK fusion cancer treated with larotrectinib had rapid, clinically meaningful, and sustained improvements in QoL. Clinical trial information: NCT02576431, NCT02637687.Research Sponsor: Bayer HealthCare and Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly.

	EORTC QLQ-C30 GHS	PedsQL total score (≥2 yrs old)
BL and ≥1 post-BL measurement, n	74	24
Best change in total score from BL, mean (SD)	17.5 (20.0)	20.7 (17.2)
Best post-BL score above BL score, % (n)	69 (51)	88 (21)
MID* improvement, % (n)	59 (44)	79 (19)
BL and ≥2 post-BL measurements, n	64	24
Sustained improvement for ≥2 consecutive cycles, % (n)	47 (30)	75 (18)

*Minimally important difference: ≥10 points for EORTC QLQ-C30; ≥4.5 points for PedsQL

3615 Poster Session (Board #345), Fri, 8:00 AM-11:00 AM

Single-agent ONC201 in recurrent H3 K27M-mutant diffuse midline glioma. *First Author: Isabel Arrillaga-Romany, Massachusetts General Hospital, Boston, MA*

Background: Recurrent H3 K27M-mutant diffuse midline glioma is a lethal brain tumor that predominantly affects children and young adults and has no effective therapy. ONC201 is a first-in-class orally administered, anti-cancer small molecule that selectively antagonizes the dopamine receptors DRD2/DRD3 and agonizes ClpP, a mitochondrial protease. Prior studies have indicated dysregulated dopamine receptor expression and enhanced ONC201 sensitivity among H3 K27M-mutant gliomas. **Methods:** Adults with midline H3 K27M-mutant glioma patients were enrolled to a dedicated Phase II clinical trial (NCT03295396), a multi-arm Phase II clinical trial (NCT02525692), and expanded access protocols under the Sponsor's IND. Results were pooled among patients treated with ONC201 monotherapy through any of these trial with H3 K27M confirmed glioma, progressive and measurable disease by RANO, > 90 days from completion of prior radiation, no evidence of leptomeningeal dissemination, midline location other than primarily pons or spinal cord, and baseline KPS > 60. Using an enrollment cutoff of February 15, 2019 and data cutoff of July 31, 2019, there were 20 patients (NCT03295396, 12; NCT02525692, 7; expanded access, 1). Dosage was 625 mg weekly in 19 and once every 3 weeks in 1. **Results:** No DLTs or treatment discontinuations due to toxicity occurred. Midline gliomas can exhibit minimal contrast enhancement or exhibit a mixture of contrast-enhancing and non-contrast enhancing regions in the tumor. As a result, blinded independent central review (BICR) of tumor response by MRI was assessed by RANO-HGG and RANO-LGG for each patient to capture contrast-enhancing lesions by T1 post-contrast and non-contrast-enhancing assessments by T2/FLAIR, respectively, in the object response rate. The best response by RANO-HGG or RANO-LGG is 30% (95% CI, 11.9-54.3%). Duration of response by RANO-HGG is median 52.7 weeks (range 15.9-138.3). One patient with stable disease as of this data cutoff has continued on treatment beyond 12 months and recently underwent an investigator-reported PR by RANO-HGG that is pending confirmation. **Conclusions:** Single agent ONC201 is well tolerated and clinically active in recurrent H3 K27M-mutant diffuse midline glioma patients. Clinical trial information: NCT03295396, NCT02525692. Research Sponsor: U.S. National Institutes of Health.

3616 Poster Session (Board #346), Fri, 8:00 AM-11:00 AM

The next-generation RET inhibitor TPX-0046 is active in drug-resistant and naïve RET-driven cancer models. *First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *RET* fusions/mutations drive oncogenesis in lung and thyroid cancers, and several other malignancies. Selective RET inhibitors (selpercatinib/pralsetinib) are active in patients with these cancers; unfortunately, resistance often occurs. On-target resistance includes the acquisition of solvent front mutations (SFMs i.e. *RET* G810 substitutions). TPX-0046 is a structurally differentiated RET inhibitor that is potent against a range of RET fusions and mutations including SFMs. **Methods:** The rationally-designed, compact, macrocyclic RET/SRC inhibitor TPX-0046 was characterized in RET-driven *in vitro* and *in vivo* tumor models. **Results:** In enzymatic assays, TPX-0046 showed low nanomolar potency against wild-type RET and 18 *RET* mutations/fusions. It was potent against SRC and spared VEGFR2/KDR. TPX-0046 inhibited RET phosphorylation ($IC_{50} < 10$ nM) in tumor cell lines (LC2/ad, *CCDC6-RET*; TT, *RET* C634W) and Ba/F3 engineered RET models (WT, G810R). In cell proliferation assays, TPX-0046 inhibited *KIF5B-RET* Ba/F3, LC2/ad, and TT cells with IC_{50} values ~1 nM. Ba/F3 RET engineered cells with SFMs (e.g. G810C/R/S) were potently inhibited by TPX-0046 (mean proliferation IC_{50} 1–17 nM). TPX-0046 demonstrated marked *in vivo* anti-tumor efficacy in RET-driven cell-derived and patient-derived xenograft tumor models. In a Ba/F3 *KIF5B-RET* xenograft model, a single dose of 5 mg/kg TPX-0046 inhibited > 80% of RET phosphorylation (corresponding mean free plasma concentration: 51 nM). At 5 mg/kg BID, tumor regression was observed in RET-dependent xenograft models, including those that harbor RET SFMs: TT, CTG-0838 PDX (NSCLC, *KIF5B-RET)*, CR1520 PDX (CRC, *NCOA4-RET*), Ba/F3 *KIF5B-RET*, and Ba/F3 *KIF5B-RET* G810R. **Conclusions:** TPX-0046 is a unique next-generation RET inhibitor that possesses potent *in vitro* and *in vivo* activity against a diverse range of *RET* alterations, including SFM-mediated resistance. A phase 1/2 trial for RET inhibitor-resistant and naïve RET-driven cancers is on-going (NCT04161391). Research Sponsor: Turning Point Therapeutics.

3617 Poster Session (Board #347), Fri, 8:00 AM-11:00 AM

Clinical efficacy of ONC201 in thalamic H3 K27M-mutant glioma. *First Author: Abed Rahman Kawakibi, Michigan Medicine, Ann Arbor, MI*

Background: Diffuse midline gliomas, H3 K27M-mutant are associated with a poor prognosis compared to H3 wild-type gliomas and have no effective therapy following first-line radiation. ONC201 is a bitopic DRD2 antagonist and allosteric ClpP agonist that has shown encouraging single agent efficacy in recurrent H3 K27M-mutant gliomas located in various midline structures of the brain. In addition to tumor and immune cells, the pharmacodynamics of ONC201 extend to stromal cells that can mediate a bystander antitumor response in preclinical models. Given this observation and that the thalamus has the highest extrastriatal expression of DRD2, we report the clinical experience of ONC201 in a subgroup of H3 K27M-mutant glioma patients with primary tumors located in the thalamus. **Methods:** We analyzed 29 thalamic H3 K27M-mutant glioma patients treated with ONC201 in clinical trials enrolled as of 5/22/19. Nineteen enrolled with recurrent disease whereas 10 enrolled following radiation prior to recurrence. Twelve patients enrolled on NCT03295396, 10 NCT03416530, 4 NCT02525692, and 3 expanded access. Median age was 22 years old (range: 5-70) and baseline KPS was 80 (range: 60-90). Median time from radiation to start of ONC201 was 1.8 months (range: 0.2-8.7) for non-recurrent patients and 7.2 months (range: 1.4-102.0) for recurrent patients. **Results:** As of 12/18/2019, PFS6 and OS12 measured relative to initiation of ONC201 are 26.3% and 36.8%, respectively, in the recurrent group. For patients initiating ONC201 post-radiation prior to recurrence, median PFS or OS have not been reached with a median follow up of 21.9 months (8.6-26.6) from diagnosis, which surpass historical OS of 13.5 months. Best response for evaluable recurrent patients by RANO: 1 CR, 3 PR, 4 SD, 8 PD, 3 not reported; for non-recurrent patients: 2 PR, 4 SD, 1 PD, 3 not reported. Median duration of response for recurrent patients is 14.0 months (2.0-33.1). ONC201 was well tolerated and no dose-limiting toxicities or treatment discontinuations due to toxicity occurred. Furthermore, H3 K27M cell-free tumor DNA in plasma and CSF correlated with MRI response. **Conclusions:** In summary, single agent ONC201 administered at recurrence or following radiation, demonstrates promising clinical efficacy in thalamic H3 K27M-mutant glioma patients. Investigations are ongoing to assess whether micro-environmental DRD2 expression correlates with responses of thalamic H3 K27M-mutant glioma to ONC201. Clinical trial information: NCT03295396, NCT03416530, NCT02525692. Research Sponsor: None.

3618 Poster Session (Board #348), Fri, 8:00 AM-11:00 AM

BET inhibitor molibresib for the treatment of advanced solid tumors: Final results from an open-label phase I/II study. *First Author: Sophie Cousin, Medical Oncology, Institute Bergonié, Bordeaux, France*

Background: Molibresib is an orally available, small molecule bromodomain and extra-terminal domain (BET) protein inhibitor under investigation for treatment of advanced solid tumors. **Methods:** This was an open-label, single- and repeat-dose, 2-part, Phase 1/2 study including patients (aged ≥16 years) with advanced solid tumors. Part 1: patients received different oral doses of molibresib (2–100mg QD; amorphous free-base formulation) to determine recommended Phase 2 dose. Part 2 (expansion cohort): patients with various tumor types received the bioequivalent besylate formulation (75mg) to explore clinical activity at recommended dose. Safety and efficacy (response rate [RR] based on RECIST 1.1 criteria, progression-free survival [PFS], and overall survival [OS]) were evaluated for the total cohort (patients from Part 1 and 2). Safety, pharmacokinetic, pharmacodynamic, and efficacy per tumor type were evaluated in Part 2. **Results:** Part 1 only data have previously been reported. Overall, 196 patients were included in the total cohort (1 patient in Part 1 was counted twice). In the all treated population, 195 patients (median age 58 years; 46% male) received ≥1 dose of molibresib (Part 1: n = 93; Part 2: n = 102). Adverse events (AEs) were experienced by 193/196 (98%) patients; 180/196 (92%) had a treatment-related AE (TRAE). AEs led to permanent treatment discontinuation in 38/196 (19%) patients. Of different tumor types in Part 2, NUT carcinoma (NC) had the lowest frequency of TRAEs (10/12 [83%]) and AEs leading to permanent treatment discontinuation (1/12 [8%]). In total cohort, 3/31 NC patients and 1/35 with castration-resistant prostate cancer (CRPC) achieved a confirmed partial response. A further 67/196 (34%) achieved stable disease (SD). In Part 2, RR in 12 NC patients was 8% (CI: 0.2–38.5); 50% had SD and median PFS was 4.8 months with median OS of 5.0 months. In CRPC patients, RR was 4% (CI: 0.1–21.9); 22% had SD; median PFS was 8.0 months with median OS of 9.1 months. Plasma concentrations for molibresib and active metabolites were similar between different tumor types. Gene expression analysis from pre- and post-dose biopsy samples collected from 10 mCRPC patients showed transcriptional downregulation of Myc target genes upon treatment with molibresib. **Conclusions:** Molibresib demonstrated a manageable safety and tolerability profile with single agent activity observed in selected patients with NC and CRPC. Clinical trial information: NCT01587703. Research Sponsor: GSK, Other Foundation.

3619 Poster Session (Board #349), Fri, 8:00 AM-11:00 AM

ONC201 in previously irradiated pediatric H3 K27M-mutant glioma or newly diagnosed DIPG. *First Author: Sharon L. Gardner, New York University School of Medicine, New York, NY*

Background: ONC201 is a first-in-class DRD2 antagonist and ClpP agonist that has demonstrated promising activity in high-grade glioma preclinical models and radiographic regressions with single agent ONC201 in recurrent H3 K27M-mutant glioma patients . The recommended phase 2 dose (RP2D) of 625mg ONC201 orally once a week has been established in adult patients as well tolerated and biologically active. ONC201 efficacy has been shown in high-grade glioma preclinical models and radiographic regressions with single agent ONC201 have been reported in adult recurrent H3 K27M-mutant glioma patients. We report results from the first Phase I pediatric clinical trial of ONC201. **Methods:** This open-label, multi-center trial for pediatric H3 K27M-mutant glioma or non-biopsied DIPG employed a 3+3 dose-escalation and dose-expansion design with 6 arms. Arms A and E, which have completed accrual, determined the RP2D of ONC201 using oral capsule and liquid formulations in post-radiation pediatric H3 K27M-mutant glioma patients ONC201, respectively. Arm B aims to determine the RP2D for ONC201 in combination with radiotherapy in patients with newly diagnosed DIPG. Arms C and D aim to measure intratumoral ONC201 concentrations in midline glioma patients and the impact of ONC201 on H3 K27M DNA levels in CSF, respectively. Arm F was recently opened to study ONC201 as a single agent in patients with progressive H3 K27M-mutant tumors (excluding DIPG and spinal cord tumors) following radiotherapy. After determining the RP2D, a dose-expansion cohort will evaluate the safety, radiographic response, and activity of ONC201. **Results:** An RP2D of weekly 625mg ONC201 scaled by body weight as a capsule or in liquid formulation was established in the primary endpoints of arms A, B and E alone or in combination with radiation, without incidence of dose-limiting toxicity (DLT). Pharmacokinetic profiles were similar to those observed in adults ($T_{1/2}$: 8.4h; T_{max}: 2.1h; C_{max}: 2.3ug/mL; $AUC_{0\text{-tlast}}$: 16.4ug/mL), with similar exposure across body weights. **Conclusions:** ONC201 was well tolerated without DLTs at the same adult RP2D scaled by body weight as monotherapy or in combination with radiotherapy in pediatric H3 K27M-mutant glioma patients. Further investigation of ONC201 to treat H3 K27M-mutant glioma and DIPG is warranted. Clinical trial information: NCT03416530. Research Sponsor: U.S. National Institutes of Health.

3620 Poster Session (Board #350), Fri, 8:00 AM-11:00 AM

Pan-cancer analysis of FGFR1-3 genomic alterations to reveal a complex molecular landscape. *First Author: Melanie A. Krook, The Ohio State University Comprehensive Cancer Center, Ohio State University, Columbus, OH*

Background: Activating genomic alterations (GAs) in the fibroblast growth factor receptor (FGFR) gene family occur in many tumor types. *FGFR1-3* mutations and rearrangements are of particular interest given evidence of clinical activity of selective FGFR inhibitors in patients (pts) with susceptible alterations. We queried *FGFR1-3* GAs in patient tumor samples analyzed using comprehensive genomic profiling (CGP) and performed *in vitro* characterization of select novel alterations. **Methods:** Tumor samples were assayed by hybrid capture based CGP on 0.8-1.2 Mb of the genome to identify GAs in exons and select introns in up to 404 genes (Foundation Medicine, Inc, Cambridge MA). Cell lines were stably transduced with alterations of interest and transformation assays and drug sensitivity assays were performed to determine oncogenic potential and sensitivity to FGFR inhibition by pemigatinib. **Results:** GAs in *FGFR1-3* were present in 6314 of 274,694 pt specimens (2.3%), of which 4091 (64.8%) were short variants and 2269 (35.9%) were rearrangements. Tumor types with the highest frequency of *FGFR1-3* alterations were bladder cancer (17.9%), cholangiocarcinoma (11.1%), endometrial cancer (7.9%), and glioma (5.5%) (Table). We identified 270 unique *FGFR1-3* short-variants, including 144 missense mutations and 94 truncating alterations. Of short variants, the most frequent were *FGFR3* p.S249C (18.3%), *FGFR2* p.S252W (9.9%) and *FGFR1* p.N546K (6.9%). Truncating alterations were largely identified in exon 18, downstream of the kinase domain. We identified 476 unique *FGFR1-3* rearrangement pairs (*FGFR1*; n=77, *FGFR2*; n=338, *FGFR3*; n=61). *FGFR3-TACC3* was the most prevalent *FGFR* rearrangement (29.0%), followed by *FGFR2-BICC1* and *FGFR2*-N/A (both 9.7%). *In vitro* analysis of the transforming potential and drug sensitivity for select alterations will be reported. **Conclusions:** *FGFR1-3* mutations and rearrangements are highly diverse and present at low to moderate frequencies across many cancers. Therefore, cataloging and characterizing these diverse alterations has the potential to facilitate precision medicine. Tumor-specific and -agnostic trials of selective FGFR inhibitors in pts with susceptible alterations are ongoing. Research Sponsor: Incyte Corporation.

Disease Group	Pts, n	Short Variant, %	Rearrangement, %	Total, %
Bladder	4338	14.6	3.6	17.9
Cholangiocarcinoma	4826	1.9	9.4	11.1
Endometrial	7055	7.4	0.5	7.9
Glioma	10072	2.7	2.8	5.5
Cancer of unknown primary	13989	2.2	2.2	4.4
Kidney	4687	3.2	0.8	3.9
Cervix	2008	2.4	1.7	3.9
Head and neck	4210	2.3	0.7	3.0
Melanoma	7097	2.2	0.1	2.3
Plasma cell neoplasm	2530	1.9	0.2	2.1

3621 Poster Session (Board #351), Fri, 8:00 AM-11:00 AM

Identifying pan-cancer transcriptomic determinants of perineural and lymphovascular invasion using machine learning. *First Author: Jimmy Guo, Broad Institute, Cambridge, MA*

Background: Tumor invasion of nerves, blood vessels, and lymphatics are a primary means of local recurrence and escape from the local microenvironment, resulting in metastases and poor clinical outcomes. However, the genetic drivers that are most pertinent to these malignant processes are not well understood, and few therapeutics successfully target perineural invasion (PNI) and lympho-vascular invasion (LVI). Identifying genetic drivers and biomarkers can be valuable for therapeutic targeting and prognostication. **Methods:** We analyzed surgical pathology reports and bulk RNA-seq data of 1,624 patients across 12 cancer types from The Cancer Genome Atlas (TCGA). Differential gene expression analysis between patients with and without PNI/LVI was performed using DEseq2 in Python while adjusting for age, sex, race, and cancer type. Genes with an adjusted p-value < 0.001 were then used to derive parsimonious signatures using random forest classifier and recursive feature selection algorithms. **Results:** To assess whether these invasive histological phenotypes have clinical ramifications, we examined outcomes data and found that patients with PNI or LVI have reduced overall (OS) and disease-free survival (DFS) ($p < 0.05$) relative to those without. In addition, patients with both PNI and LVI have the lowest DFS from our pan-cancer analysis, suggesting that each may have non-redundant contributions to poor outcomes. From the differential gene expression analysis, we identified a set of 621 and 606 genes that were highly associated with PNI and LVI, respectively ($p_{adj} < 0.001$). Many of these genes such as TEKT5 ($p_{adj} = 3.18 \times 10^{-64}$), which is canonically associated with ciliary and flagellar microtubules, and SCRIB ($p_{adj} = 1.60 \times 10^{-21}$), which helps establish apico-basal cell polarity, have not been described previously in relevance to PNI and LVI, and warrant further scientific and clinical investigation. These genes were ultimately condensed into a signature that optimizes for both model simplicity and goodness of fit with up to 90% accuracy as determined by trials on both a logistic regression and neural network model. **Conclusions:** We concluded from a pan-cancer analysis that PNI and LVI are associated with poor outcomes, and we were able to robustly identify sets of genes that characterize each invasive mechanism for further functional investigation. Research Sponsor: None.

3622 Poster Session (Board #352), Fri, 8:00 AM-11:00 AM

Increased tumor purity and improved biomarker detection using precision needle punch enrichment of pathology specimen paraffin blocks: Method validation and implementation in a prospective clinical trial. *First Author: Jonathan Keith Killian, Foundation Medicine, Cambridge, MA*

Background: While many sequencing assays may be geared for short variants (SV), more complex biomarkers such as genomic loss of heterozygosity (gLOH) score, also referred to as homologous recombination deficiency (HRD) score, require higher tumor purity for confident detection. Practical methods to increase tumor nuclei percentage (TN%) from pathology specimens are needed to achieve biomarker results to maximize patient matching to approved therapies and/or clinical trial enrollment. **Methods:** Tumor purity of specimens was determined by the computational analysis pipeline component of the FDA-approved NGS assay, FoundationOneCDx. In the validation study, specimen purities for each tissue block were compared following either no enrichment (UnE, n=46), pathologist-directed enrichment by straight razor blade (RBE, n=30) or precision needle punch (NPE, n=47). Post-enrichment H&E slides confirmed target region sampled for the NPE arm. Based upon validation data, the needle punch process was implemented for the Lung-MAP prospective clinical trial (LM-NPE). TN% was compared between the first 55 tested LM-NPE specimens and the validation study to assess performance on real-world samples outside of a controlled validation experiment. **Results:** The mean computational TN% in the 4 groups were: UnE: 33%; RBE: 30%; NPE: 52%; and LM-NPE: 48%. In the validation study, NPE had significantly higher purity than both UnE and RBE ($p<0.001$); in the trial arm, LM-NPE performed equivalently to NPE ($p=0.344$). Based upon a 30% tumor purity cutoff, gLOH could be determined for 52% UnE, 50% RBE, 89% NPE and 71% LM-NPE. Comparing NPE and LM-NPE groups reveals no statistical difference in Pass/Fail rates for gLOH determination ($p=0.883$; Fisher's Test). **Conclusions:** Precision needle punch cores from tissue blocks have elevated tumor purity, and consequently, a greater number of successful gLOH determinations. Moreover, this process is rapid and inexpensive. Precision punches may constitute best practice with respect to enriching tumor cells from low-purity specimens for biomarker detection in a routine laboratory specimen-processing setting. Research Sponsor: Foundation Medicine Inc.

Comparison	p-value Abs tumor purity	p-value gLOH Pass rate	Abs Diff in mean tumor purity	Abs Diff in gLOH Pass Rate
UnE (n=46) vs RBE (n=30)	0.491	0.853	3%	2%
UnE (n=46) vs NPE (n=47)	<0.001	<0.001	19%	37%
RBE (n=30) vs NPE (n=47)	<0.001	<0.001	22%	39%
LM-NPE (n=55) vs NPE (n=47)	0.344	0.883	4%	18%

3623 Poster Session (Board #353), Fri, 8:00 AM-11:00 AM

Targeting G1-S phase cell-cycle alterations with CDK4/6 inhibitor-based genomically matched personalized therapy approach. *First Author: Jacob J. Adashek, University of South Florida, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Although CDK4/6 inhibitors are established as a standard treatment option for hormone receptor-positive, HER2-negative metastatic breast cancer patients, its benefit in other solid tumors is unclear. Moreover, no clear biomarker exists that predicts the response to CDK4/6 inhibitors. Herein, we investigated the factors associated with clinical outcomes from CDK4/6 inhibitor-based therapy, used alone or in combination with other therapies targeting genomic co-alterations, among diverse cancer patients with potentially sensitizing alterations in G1-S phase cell-cycle alterations (defined as *CDK4/6* amplifications, *CCND1/2/3* amplifications or *CDKN2A/B* alterations). **Methods:** We interrogated molecular profiles of 2,457 patients with diverse solid tumors for G1-S phase cell-cycle alterations and co-altered genes using clinical-grade next generation sequencing (182-465 genes). **Results:** G1-S phase cell-cycle alterations occurred in 20.6% (507/2,457) of patients with 99% of those with cell cycle alterations (N = 501/507) harboring at least one characterized co-alteration (median, 4; range, 0-24). Significant improvement in median PFS was observed when CDK4/6 inhibitor-based therapies matched a larger proportion of tumor alterations, often by being given together with other drugs that were matched to genomic co-alterations, hence achieving a high Matching Score (high Matching Score [≥50%] vs. low Matching Score [< 50%]: all cohorts including breast cancer [N = 58]: PFS: 6.2 vs. 3.2 months, P = 0.001; non-breast cancer cohort [N = 40]: PFS 6.2 vs. 2.0 months, P < 0.001 [multivariate]). (Matching Score roughly equivalent to number of alterations targeted divided by total number of characterized alterations). In contrast, targeting CDK4/6 alone in patients harboring cell-cycle pathway alterations along with other co-alterations, without targeting the genomic co-alterations, did not improve PFS even in patients who received matched CDK4/6 inhibitors as part of a combination regimen. Representative cases that were successfully treated with a matched combination strategy will also be presented. **Conclusions:** Most patients with G1-S phase cell-cycle alterations harbored co-genomic alterations. Our current study suggests that targeting co-alterations along with cell cycle molecular alterations may be necessary to achieve better clinical outcome. Further clinical investigation with larger numbers of patients are required. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

3624 Poster Session (Board #354), Fri, 8:00 AM-11:00 AM

Tumor genomic analysis for biomarker identification in a phase I trial of the Wee 1 inhibitor adavosertib (AZD1775). *First Author: Abdul Rafeh Naqash, Developmental Therapeutics Clinic/Early Clinical Trials Development Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD*

Background: Adavosertib, a first-in-class Wee1 kinase inhibitor, abrogates G2/M cell cycle arrest causing premature mitosis and DNA replication stress, yielding enhanced DNA damage. Here we report on potential biomarkers of response from tumor genomic analysis in patients (pts) with solid tumors treated with adavosertib. **Methods:** Adavosertib was administered once daily on days 1-5 and 8-12 of a 21-day cycle. RECIST 1.1 was used to evaluate clinical response. Paired tumor biopsies were obtained for RNASeq gene expression profiling (GEP) and for whole-exome sequencing (WES) to evaluate gene mutation and copy number amplification (CNA). Fold change (FC) was calculated to define gene overexpression. To identify the frequency of CNA and mRNA overexpression for the genomic biomarkers of interest, cBioPortal analysis using TCGA and MSK-IMPACT datasets was performed. Differential GEP analysis of tumor and paired normal tissue was performed using the gene expression profiling interactive analysis (GEPIA) interface (Tang et al. 2017). **Results:** Out of 35 pts evaluable for response, 6 (17%) had partial response (PR; 4 ovarian carcinoma [OVC], 2 endometrial carcinoma [EC]). The median duration of response was 5.2 months (range 4.0-23.1). Eighteen pts (51.4%) had stable disease. Genomic analysis of tumor biopsies was available for 9 pts; 7 of these pts were evaluable for response, and 3 had PR (2 OVC, 1 EC). WES revealed TP53 mutations in 6 pts (66.6%; 3 pts with PR, 2 with progressive disease,1 not evaluable). On WES, tumor Cyclin E1 (*CCNE1*) CNA was present in 1 of 3 PR pts while tumors from all 3 PR samples showed relatively high *CCNE1* expression by RNAseq (FC = 4.07). In the MSK-IMPACT 2017 dataset, *CCNE1* CNA was identified in 1.8% of pts (194 of 10336); of which, OVC (10.3%) and EC (8.7%) had the highest incidence of *CCNE1* CNAs. In separate tumor-specific (OVC, EC) TCGA datasets having *CCNE1* overexpression and/or CNA, overlap in *CCNE1* overexpression with *CCNE1* CNA was 35.5% (OVC) and 25.2% (EC). Compared to normal ovarian/ endometrial tissues, GEPIA analysis revealed significantly higher *CCNE1* mRNA expression in OVC (FC = 3.5) and EC (FC = 3.8). **Conclusions:** *CCNE1*alterations (overexpression and/or CNA) tend to be enriched in OVC and EC with a limited fraction showing both overexpression and CNA. Tumor genomic analysis of additional OVC and EC pts treated with adavosertib is required to determine whether *CCNE1* mRNA overexpression, regardless of *CCNE1* CNA, is a potential biomarker of response to this drug in these tumor types. Funded by NCI contract No. HHSN261200800001E. Clinical trial information: NCT01748825. Research Sponsor: U.S. National Institutes of Health, Funded by NCI contract No. HHSN261200800001E.

3625 Poster Session (Board #355), Fri, 8:00 AM-11:00 AM

Therapeutic vulnerabilities among KRAS G12C mutant (mut) advanced cancers based on co-alteration (co-alt) patterns. *First Author: Maliha Nusrat, Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Oncogenic *KRAS* mut drive cancers and confer therapeutic resistance by activating MAPK signaling. Inhibiting *KRAS* has been elusive until the recent promising phase I trials with KRAS G12C inhibitors (i). We characterized frequencies of *KRAS* G12C mut and gene co-alt among advanced cancer patients (pts) to identify therapeutic vulnerabilities for combination development. **Methods:** We analyzed next generation sequencing datasets from MD Anderson Cancer Center (MDACC, n = 42,316) and AACR GENIE (n = 56,970). Genes and individual alterations were annotated for potential actionability with approved or investigational drugs and grouped into 12 oncogenic pathways. Frequencies of potential drug combinations with KRAS G12Ci were estimated per tumor type based on co-occurrence of potentially actionable alterations. **Results:** *KRAS* G12C was present in 850/34,801 (2.4%) advanced solid tumor and 22/7698 (0.3%) hematologic malignancy pts in MDACC dataset; and 1422 (2.5%) pts in AACR GENIE. Among solid tumor pts, 798 had histology data and 640 had ≥46 gene profiling. Most common cancers were non-small cell lung (NSCLC, 67%), colorectal (CRC, 24%), other gastrointestinal (oGI, 4%) and gynecologic (gyn, 2%). KRAS G12C prevalence was 19.5% (441/2265) in NSCLC and 4.2% (146/3469) in CRC. Genes most commonly co-altered were *TP53* (42%), *STK11* (17%) and *MET* (11%) in NSCLC; *TP53* (58%), *APC* (54%) and *PIK3CA* (24%) in CRC; *TP53* (42%), *APC* (21%) and *ATM* (21%) in oGI; *TP53* (56%), *PIK3CA* (25%), and *PTEN* (19%) in gyn cancers. These co-alt did not impact overall survival. In both datasets, as compared to *KRAS* wild, *KRAS* G12C was significantly co-altered with *STK11* in NSCLC; *PIK3CA* and *SMAD4* in CRC ($P < 0.05$ for all). *EGFR* mut in NSCLC and *BRAF* mut in CRC rarely co-occurred with *KRAS* G12C ($P < 0.01$). Most frequently co-altered oncogenic pathways in NSCLC, CRC, oGI and gyn cancers respectively included PI3K (27, 32, 33, 44 %), receptor tyrosine kinases (13, 16, 42, 13 %) and DNA damage repair (12, 10, 38, 19 %). Potentially actionable co-alt frequencies suggest that combining KRAS G12Ci with mTORi or PI3Ki would be indicated most frequently, in 24% and 13% of all pts respectively. **Conclusions:** KRAS G12Ci development is most relevant for NSCLC, gastrointestinal and gyn cancers. The co-alt patterns highlight relevant oncogenic pathways and candidate drugs for future combination therapies. Co-inhibition of PI3K-mTOR and MAPK pathways has shown synergism in prior pre-clinical studies but had poor tolerance in pts. There is opportunity to revisit this approach with the new KRAS G12Ci. Research Sponsor: Cancer Prevention Research Institutive of Texas (CPRIT) Precision Oncology Decision Support Core RP150535.

3626 Poster Session (Board #356), Fri, 8:00 AM-11:00 AM

The landscape of predictive biomarkers for ATR inhibition in Chinese solid-tumor patients. *First Author: Rong Shen, Department of Chemotherapy, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China*

Background: Ataxia Telangiectasia and Rad3-related (ATR) is one of the core regulators participating in DNA damage response as a sensor of replication stress. Besides, ATR also plays a role in cell cycle checkpoint activation and DNA replication regulation. Several ATR inhibitors (ATRi) have been demonstrated in anti-cancer clinical trials. Herein, we describe the distribution of selected biomarkers, which have been shown to predict a higher sensitivity to ATRi according to preclinical data, in Chinese cancer population. **Methods:** FFPE tumor tissues and matched blood samples from 10,194 Chinese patients with 25 different types of solid tumors were collected. NGS based 450 cancer genes panel assay were performed to detect genomic alterations, including SNV, short and long insertions/deletions, CNV and rearrangements/fusions. The testing was carried out by a CAP accredited and CLIA certified laboratory. **Results:** The prevalence of *ARID1A* mutations, *ATM* mutations, *BRCA1/BRCA2* mutations, *MYC* amplification, and *CCNE1* amplification accounted for 9.5%, 4.7%, 6.0%, 3.5% and 3.3% of this cohort respectively. The most common tumors with *ARID1A* mutations were endometrial carcinoma (EC, 34.4%), gastric carcinoma (GC, 19.4%), small bowel carcinoma (SBC, 19.3%), intrahepatic cholangiocarcinoma (19.3%), extrahepatic cholangiocarcinoma (17.7%) and urothelial carcinoma (UC, 16.7%). For *ATM* mutations, the prevalence was colorectal carcinoma (CRC, 8.9%), SBC (8.8%), pancreatic cancer (7.8%), UC (7.3%), gallbladder carcinoma (GBC, 7.1%) and GC (6.8%). For *BRCA1/BRCA2* mutations, the prevalence was ovarian carcinoma (29.5%, Germline 23%), breast carcinoma (13.3%, Germline 7.1%), EC (11.5%, Germline 3.3%), UC (10.4%), melanoma (8.5%) and CRC (7.9%). For *MYC* amplification, the prevalence was breast carcinoma (10.2%), ovarian carcinoma (9.2%), esophageal carcinoma (7.2%), thymic tumor (6.1%), cancer of unknown primary (CUP, 5.8%) and gastrointestinal neuroendocrine tumor (GI-NET, 5.4%). For *CCNE1* amplification, the prevalence was GC (11.9%), GBC (8.8%), bone sarcoma (7.7%), ovarian carcinoma (6.9%), CUP (4.2%) and GI-NET (4.1%). **Conclusions:** Our study reported the prevalence of gene mutations of ATRi sensitivity determinants in a large cohort of Chinese cancer patients. The results revealed the high prevalence and different distribution of these biomarkers across a wide spectrum of cancers. The genomic profile study also provided information for ATRi sensitivity assessment and the drug combinations with ATR inhibition. Research Sponsor: None.

3627 Poster Session (Board #357), Fri, 8:00 AM-11:00 AM

Modeling differentially expressed genes in patient tumors to guide expression-based biomarker development. *First Author: Derek Liu, Dana–Farber Cancer Institute, Boston, MA*

Background: Differential gene expression (DGE) methods, initially developed for analyzing bulk RNA changes in pure tumor cell lines under experimental settings, are commonly used to identify biomarkers in and infer biological differences between patient tumor samples, which are admixtures of tumor and non-tumor components. Methods to sensitively and accurately detect cell type-specific expression differences in admixed patient samples are not well characterized but may greatly affect emerging targeted and immunotherapy biomarker strategies. To address this issue, we developed a simulation framework to benchmark our ability to detect changes in tumor-intrinsic gene expression. **Methods:** Pseudobulk RNAseq melanoma cohorts were simulated by sampling from melanoma single cell RNAseq data. Simulation parameters were optimized to maximize concordance of gene expression means and variances (Spearman r = 0.81, 0.68, respectively) between the TCGA SKCM cohort (n = 462) and matched simulated cohort, and then validated in two independent melanoma cohorts (n = 42, 129; means Spearman r = 0.80, 0.78; variances Spearman r = 0.68, 0.63). Using this simulation framework, we benchmarked the effect of sample size, magnitude of differential expression, and differences in cell type proportions on the sensitivity and positive predictive value (PPV) of detecting true differentially expressed genes in the tumor-intrinsic compartment. **Results:** Reference cohorts of 50 total tumors (n = 10) were simulated to contain a 2 standard deviation tumor-intrinsic expression change in 50 randomly selected genes and a 11% difference in mean purity between two equally sized 25-tumor subgroups. DGE analysis using DESeq2 with an FDR q-value threshold of 0.1 yielded a sensitivity of 0.37 and PPV of 0.29. DGE analysis of the same simulated cohorts using a non-parametric Mann-Whitney U test with an FDR q-value threshold of 0.1 yielded a sensitivity of 0.13 and PPV of 0.76. **Conclusions:** Commonly used DGE methods for existing expression-based biomarker strategies have poor sensitivity and PPV in admixed tumor samples, limiting our ability to find meaningful transcriptional biomarkers in clinical cohorts. We are currently developing methods to more accurately detect true differentially expressed genes in admixed bulk RNAseq samples and applying these approaches for biomarker discovery in immunotherapy-treated patient cohorts and other clinical tumor cohorts. Research Sponsor: U.S. National Institutes of Health.

3628 Poster Session (Board #358), Fri, 8:00 AM-11:00 AM

Employing RNA sequencing to enhance treatment options for cancer patients. *First Author: Gargi D. Basu, Ashion Analytics, Phoenix, AZ*

Background: Fusions and translocations account for 20% of cancer mortality globally. Maximizing their detection enhances the utility of precision medicine for various solid and hematologic cancers. Practice guidelines stress the importance of RNA sequencing. Novel assay techniques employing a comprehensive genomic profiling approach, including RNA sequencing, yield information beyond conventional DNA next generation sequencing (NGS) alone. **Methods:** Tumor samples (N = 1517) were assayed combining whole transcriptome (RNA) sequencing, whole exome (DNA) sequencing, and comparison of tumor sequence vs. paired normal DNA. Results were analyzed to determine the frequency of rare and common RNA fusion and variant detection. Findings were mapped to a knowledge-base of targeted treatment options. **Results:** Analysis detected 79 (5.2%) actionable fusions and 15 (1%) transcript variants across major solid and heme-based malignancies. Notably, we observed actionable transcript variants that are not detectable at the DNA level including: EGFRvIII, EGFRvIVa and EGFRvIVb in GBM; ARv7 in prostate, and METe14 in TNBC. Many fusion cases (42%, n = 33) had no other actionable molecular abnormalities. Novel fusions included: SLC12A/ROS1 in low-grade spindle cell neoplasm with myogenic differentiation, KANK1/NTRK2 in ganglioneuroblastoma, ETV6/NTRK3 in metastatic mammary analogue secretory carcinoma, FGFR1/SCT in germ cell tumor, ZNF33B/RET fusion in GBM, SH3BP4/ERBB4 and EML4/ALK in RCC, VTCN1/NRG1 in pancreatic cancer, and AGRN/NRG1 in cholangiocarcinoma. More common actionable fusion events included: EML4/ALK in NSCLC, KIAA1549/BRAF in pilocytic astrocytoma, FGFR2 and FGFR3 in cholangiocarcinoma and urothelial cancers and ESR1 in endocrine therapy-resistant breast cancers. The fusion events detected in heme-based malignancies included MLLT10 and MLLT4 in AML, BCR/ABL in leukemias, TCF3/PBX1 in B cell ALL, NPM1/ALK in ALCL, and novel fusion CIITA/CD274 in DLBCL. All RNA fusions and transcript variants found were matched to FDA-approved or investigational treatment options. **Conclusions:** Maximizing the rate of variant detection for targeted therapy relies on precise identification of common and rare fusion events. Without the addition of RNA sequencing, 15 transcript variants in our cohort would have been missed and 33 of the fusions may have gone undetected by conventional DNA NGS testing, resulting in zero targeted treatment options for this vulnerable population. Further use of comprehensive genomic profiling is vital to optimizing cancer care. Research Sponsor: None.

3629 Poster Session (Board #359), Fri, 8:00 AM-11:00 AM

Identifying functional loss of *ATM* gene in patients with advanced cancer. *First Author: Patrick Glen Pilie, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: *ATM* is frequently mutated in cancer, and defects may serve as a putative predictive biomarker. However, the functional impact of most *ATM* variants is not well known. In this study, we examined the relationship between *ATM* variants and ATM protein expression to better discern ATM functional defects in patients (pts) with advanced cancer. **Methods:** We retrospectively identified pts seen at MD Anderson Cancer Center who had *ATM* variants detected on CLIA-certified next generation sequencing (NGS) assays. ATM immunohistochemistry (IHC) was performed on available tumors. We then prospectively assessed ATM IHC on tumors from pts who were referred for DNA damage repair inhibitor (DDRi) trials. Functional classification of the variants was performed via published in silico tools and/or precision oncology decision support (PODS). An IHC cut-off of 100% loss in tumor cell nuclei defined ATM loss of protein (LOP). **Results:** Of 1394 *ATM*-mutant tumors identified retrospectively, *ATM* alterations were classified as 16% (N = 216) inactivating, 12% (N = 163) potentially inactivating, 71% (N = 993) variant of unknown significance (VUS), and 2% (N = 22) benign. Coding variants were seen across the *ATM* exonic structure/splice sites, and 20 individual variants were shared in > 10 pts. 263/297 available retrospective tumor samples had interpretable IHC results; 27% (N = 72) had ATM LOP. LOP was most prevalent in tumors with inactivating *ATM* variants (39/100, 39%); but, importantly, LOP was seen in 20% (N = 33/162) of potentially inactivating/VUS, thus better clarifying their functional impact. In the prospective cohort of 217 pt tumors, 17% (N = 37) had ATM LOP. 29% (N = 62/217) of this cohort also had *ATM* variants. ATM LOP was seen in 48% of tumors with inactivating variants (N = 14/29), 25% of tumors with potentially/VUS(N = 9/36), and 9% (N = 14/156) of tumors without *ATM* variants identified. ATM LOP was detected most commonly in colorectal (24%; N = 8/34), cholangiocarcinoma (20%; N = 6/30), prostate (16%; N = 16/104) and pancreatic (9%; N = 1/11) cancers among this cohort of pts referred for DDRi trials. **Conclusions:** *ATM* coding variants occurred across the gene, with certain variants shared across tumor types. The functional impact of most *ATM* variants was VUS, and ATM LOP can help clarify function in up to 25% of these VUS. Also, ATM LOP can be seen even in tumors without *ATM* variants identified, suggesting epigenetic or post-translational loss. Future prospective studies assessing predictive capability of paired DNA and protein-level profiling of ATM are warranted. Research Sponsor: MD Anderson internal departmental funding.

3630 Poster Session (Board #360), Fri, 8:00 AM-11:00 AM

Predictive value of a CLIA-approved organoid based drug sensitivity test. *First Author: Astrid Margossian, Sengine Precision Medicine, Seattle, WA*

Background: Precision medicine integrates genetic, molecular, and clinical information to optimize therapy selection for cancer patients. *Ex vivo* drug testing has the potential to match the right drug to the right patient. We developed a CLIA-certified functional drug assay for all solid tumors which provides an actionable report of organoid sensitivity to targeted, endocrine and chemotherapy agents as a tool for therapeutic decisions. Objectives: To establish the predictive power of the test in relation to well-known genomic biomarkers as well as prior treatments to identify drug sensitivity. To demonstrate that functional drug testing increases the actionability of genomic reports. **Methods:** From 2016 to 2019, 240 organoids from cancer patients were subjected to functional testing at SEngine Precision Medicine. Patients with advanced primary or metastatic cancer (solid tumors) who were treatment naïve or had previous therapies fail. Fresh samples of tumor cells from core biopsies, surgical excisions, or fluids arrived <48 hrs following collection and were cultured as 3D organoids. They were evaluated using a multi-dose response format with a library of up to 130 compounds. Drug sensitivity was quantified using a score that combines sensitivity and personalization of each patient's response relative to a reference population. Known genomic actionability from levels of evidence 1-2 from MSKCC OncoKB were queried against results for correlation. **Results:** Organoids were derived from breast (18.7%), ovarian (18.3%), colorectal (17.9%), pancreatic (6.7%), and others solid tumors (38,3%). Median age of patients was 53 (r5-83). 68 drugs on average were tested per patient with a mean turnaround time of 18 days (r9 -37). A mean of 7 drugs per patient were identified as top scoring drugs. In 75 patients with genomic data, we found high concordance of drug sensitivity with known genomic anchors (e.g., inhibitors of BRCA1/ PARP, ERBB2/HER2, FGFR1-2/FGFR, KRAS, PIK3CA/PI3K), measured as sensitivity to drugs among this targeted groups. However, several patient samples demonstrated sensitivity to targeted agents in the absence of known genomic biomarkers. Most important, analysis of previous treatments indicated >90% of retrospective concordance. **Conclusions:** Organoid based drug testing exhibits strong concordance with genomic and retrospective clinical evidence. In addition, functional testing identifies candidate therapies in patients with no known biomarkers and can identify the significance of variants currently not validated. Research Sponsor: Sengine Precision Medicine.

3631 Poster Session (Board #361), Fri, 8:00 AM-11:00 AM

Comprehensive molecular analysis of microsatellite-stable (MSS) tumors with high mutational burden in gastrointestinal (GI) cancers. *First Author: Jingyuan Wang, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: Mutational signatures contributing to high tumor mutation burden (TMB-H) independent from microsatellite instability-high (MSI-H) status are not well-studied. We aimed to characterize specific molecular features of a large cohort of GI tumors with TMB-H & MSS. **Methods:** We sequenced23392 GI tumors, including 2707 gastroesophageal (GE), 11616 colorectal (CRC), and 9069 others. Samples were analyzed using Next-generation sequencing (NGS) and immunohistochemistry (IHC) (Caris Life Sciences, Phoenix, AZ). MMR/MSI status was evaluated by a combination of IHC, Fragment Analysis and NGS. Tumors with TMB ≥ 17 mutations/Mb were defined as TMB-H. PD-L1 was tested by IHC [22C3 (CPS score, positivity: CPS ≥ 1%) in GE tumors and SP142 (Positivity: TPS ≥ 5%) in other cancers]. Findings were compared in four groups (TMB-H/L & MSI-H/MSS) using Fisher-Exact or Chi-square and adjusted for multiple comparison by Benjamini-Hochberg. Significance was determined by adjusted (adj) $p < .05$. **Results:** Overall, TMB-H & MSS was observed in 1% of patients (pts) (n = 237, including 45 GE, 124 CRC, 68 others), while TMB-H & MSI-H, TMB-L & MSS, TMB-L & MSI-H were observed in 4% (n = 936), 94.4% (n = 22089) and 0.6% (n = 130) respectively. Compared to other groups, TMB-H & MSS showed the most prevalent amplifications (AMPs), including *CCND1* (5.6%), *FGF3/4/19* (4.9%, 4.3%, 4.4%), *MYC* (4.3%) (Top 5, adj $p < .05$), and the highest mutation rates in *POLE* (21.6%), *RB1* (13.1%), *CDC73* (10.3%), *RUNX1* (6.5%), and genes involved in PI3K & MAPK (*PIK3R1* 17%, *mTOR* 3.4%, *MAP2K1* 3.8%, *MAP2K4* 5.6%) and Wnt (*APC* 48.5%, *SMAD2* 6.5%, *TCF7L2* 3.8%) pathways (adj $p < .05$). The rates of HER2 AMP and high-expression (IHC) were the highest in TMB-H & MSS, followed by TMB-L & MSS, TMB-H & MSI-H, TMB-L & MSI-H (adj $p < .0001$); PD-L1 positive rate was similar between TMB-H & MSS and TMB-L & MSI-H, while the highest and lowest in TMB-H & MSI-H and TMB-L & MSS respectively in GE and other GI cancers (adj $p < .01$) (Table). **Conclusions:** This is the largest study to investigate the special molecular landscape of pts with TMB-H & MSS in GI cancers. Our data may provide novel insights for pt selection and more effective targeted combination immunotherapies (e.g. HER2, PI3K inhibitors) in GI cancers. Research Sponsor: National Cancer Institute (grant number P30CA014089), The Gloria Borges WunderGlo Foundation-The Wunder Project, Dhont Family Foundation, San Pedro Peninsula Cancer Guild, Daniel Butler Research Fund and Call to Cure Fund, Fong research project.

The status of HER2 and PD-L1 among four groups (TMB-H/L & MSI-H/MSS).

Moleculars	TMB-H & MSS (%)	TMB-L & MSS (%)	TMB-H & MSI-H (%)	TMB-L & MSI-H (%)	Adj *p*
HER2					
High expression (IHC)	**9.9**	4.5	0.3	0	< .0001
AMP	**3.4**	2.9	0.1	0	< .0001
PD-L1 positivity					
GE cancers (22C3)	73.9	71.4	**87.9**	73.9	< .01
Other GI cancers (SP142)	16.8	7.1	**22.9**	14.9	< .0001

3632 Poster Session (Board #362), Fri, 8:00 AM-11:00 AM

Comprehensive analysis of HER2 status through genomic, transcription, and translation among 5,305 patients with diverse malignancies. *First Author: Akram Mesleh Shayeb, University of California San Diego, Moores Cancer Center, La Jolla, CA*

Background: HER2 alterations is a predictive biomarker for anti-HER2 regimen. Success in breast and gastric cancers with anti-HER2 therapies translated to explore their efficacy in other tumors. Currently, measurement of HER2 can be done by assessing the expression of protein [e.g. immunohistochemistry (IHC)] or gene amplification of copy number variation (CNV) [e.g. fluorescence in situ hybridization or next-generation sequencing (NGS)]. But little is known about the transcription level (mRNA) of HER2. Herein, we investigated HER2 mRNA expression and its association with gene and protein expressions among diverse cancer types. **Methods:** Between 2015-2019, HER2 status was evaluated using IHC, qRT-PCR and NGS by Paradigm Diagnostics (CLIA-certified laboratory). All tumors in the database were included for analysis. Correlations between all 3 tests were done. An illustrative patient who was treated with anti-HER2 therapy base on the mRNA testing is presented. **Results:** HER2 testing was performed on 5305 patients (pts) with diverse cancers including NSCLC (n=1175), breast (n=1040) and colon (n=566); 4.1% (161/3926) had amplification through NGS, 33.3% (615/1848) had mRNA overexpression and 9.3% (236/2533) had overexpression by IHC. Of 723 pts who had all three tests performed, we found 7.5% (54/723) of pts with all three HER2 markers being positive (CNV [+]/mRNA [+]/ IHC [+]). Meanwhile, variety of amplification/ expression patterns were seen (see Table). CNV positivity translated to protein expression in 95% of cases. While only 4% of pts were IHC positive when CNV and mRNA were negative. 20% (144/723) of pts had mRNA overexpression alone among diverse cancer types. Representative case of 70yo female with metastatic cholangiocarcinoma harboring mRNA overexpression (but negative for CNV, IHC unclear due to sample insufficiency) who had near complete response to anti-HER2 therapy with progression-free survival of 24+ months is presented. **Conclusions:** HER2 status can be discordant with different assays but NGS positivity has excellent correlation with mRNA and protein expression. Of importance, HER2 mRNA can be overexpressed in 20% of pts even when gene amplification and protein expression are negative. Further studies are warranted to determine the clinical utility of mRNA as a biomarker for HER2 and potential use for anti-HER2 targeted therapies. Research Sponsor: None.

HER2 status signaling in a diverse cohort of cancers (n=723).

DNA	mRNA	Protein	Cases	%
+	+	+	54	7.5
+	+	-	1	0.1
+	-	+	1	0.1
+	-	-	1	0.1
-	+	+	41	5.7
-	+	-	144	19.9
-	-	+	26	3.6

3633 Poster Session (Board #363), Fri, 8:00 AM-11:00 AM

Olaparib monotherapy in pretreated patients with *BRCA1/2* alterations: Results of a DRUP trial cohort. *First Author: Hanneke van der Wijngaart, Department of Medical Oncology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands*

Background: Extensive molecular profiling in cancer regularly reveals targets for which approved drugs are available in tumor types outside the registered label. Efficacy of off-label use of these drugs is unavailable. Access to these drugs for pts is challenging. In the Drug Rediscovery Protocol (DRUP, Van der Velden et al, Nature 2019), pts are treated based on their tumor molecular profile. Here, we present the results of the successful cohort "Olaparib for tumors with *BRCA1/2* alterations". **Methods:** Twenty five adult cancer patients (pts) who exhausted all treatment options and had *BRCA1/2* loss of function (LoF) mutations (found in routine diagnostics) were included. No pts were eligible for on-label treatment with PARP inhibitors. Pts were treated with olaparib until disease progression or unacceptable toxicity. The primary endpoint was clinical benefit (CB: objective response or stable disease (SD) $\geq$ 16 weeks). Pts were enrolled using a Simon-like two-stage model, with 8 pts in stage 1 and up to 24 pts in stage 2 if at least 1 pt had CB in stage 1. A fresh frozen biopsy was obtained from each pt for whole genome sequencing (WGS) and target confirmation. **Results:** Fourteen pts (56%) had CB. The objective response rate was 32%. Nine different cancer types were included: prostate (n=11), breast (n=4), ovarian (n=2), pancreatic (n=3), colorectal (n=2), biliary tract (n=2), kidney (n=1), adrenal gland (n=1) and endometrial (n=1). WGS could be performed on 58% of baseline tumor biopsies, confirming the original *BRCA1/2* mutations in 86%. CB was observed in pts with both somatic and germline *BRCA* alterations and across tumor types. CB was only observed in cases with biallelic loss of *BRCA1/2* in the tumor and when classified as HRD by a pan-cancer homologous recombination deficiency classifier (CHORD), which relies on genome-wide SNV, indel, and SV mutational footprints for HRD detection. No evidence of complete *BRCA* loss and HRD was observed in 5 pts with PD, while 4 patients with effective *BRCA* complete loss and HRD also had PD. WGS analysis of these pts suggested resistance mechanisms due to other oncogenic drivers (e.g FGFR1 amplification, CTNNB1 stabilization, KEAP1 inactivation). **Conclusions:** Olaparib seems to be an effective treatment option for pts with *BRCA1/2* LoF mutated malignancies, regardless of histology, for both germline and somatic alterations, which needs confirmation in an independent cohort. CB of olaparib was observed in malignancies showing biallelic loss of *BRCA1/2* and when classified as HRD, indicating the importance of the *BRCA*/HRD signature status. Clinical trial information: NCT02925234. Research Sponsor: KWF Cancer Society, Pharmaceutical/ Biotech Company.

3634 Poster Session (Board #364), Fri, 8:00 AM-11:00 AM

A randomized, controlled trial of structured palliative care versus standard supportive care for patients enrolled on phase I clinical trials. *First Author: Michelle Elizabeth Treasure, Cleveland Clinic Foundation, Cleveland, OH*

Background: Phase 1 clinical trials are the first step in developing new cancer therapeutics. Patients enrolled in these studies have typically exhausted standard therapies and are at a point in their disease trajectory where they often are choosing between a phase 1 clinical trial and hospice care. These patients may have significant symptom burden, which can result in early trial discontinuation and confound phase 1 trial outcomes, including toxicity profiles, which may influence further drug development. This study aimed to determine the palliative care needs of patients enrolled on phase 1 clinical trials and their caregivers (CGs), along with differences in study duration, adverse event (AE) and symptom profiles, and quality of life (QOL) between those receiving structured palliative care vs usual supportive care. **Methods:** 68 patients enrolled on phase 1 clinical trials were randomly assigned to receive structured palliative care or usual supportive care. 39 of their CGs were enrolled and assigned to the same arm as the patient. Quality of life metrics were obtained monthly: the Functional Assessment of Cancer Therapy-General and Memorial Symptom Assessment Scale -Short Form for patients, and The Quality of Life in Life Threatening Illness - Family Carer Version and Caregiver Reaction Assessment for CGs. Palliative care resources utilized were assessed for those in the palliative care arm, and referrals to supportive care services assessed in those in the usual care arm. AEs recorded on the Phase 1 trials were evaluated & compared between arms. **Results:** Mean duration on phase 1 study was 132 days in the palliative care arm vs 114 days in the usual care arm ($p = 0.55$). Total weighted AE rate (# of AE [x] AE grade per month) was 26.9 in the palliative care arm vs 34.0 in the usual care arm ($p = 0.53$). Patients in the palliative care arm experienced better QOL and lower symptom burden, as did their CGs, compared to those in the usual care arm. While the differences in outcomes were not statistically significant, all results favored structured palliative care. **Conclusions:** Phase 1 patients and their CGs have physical and psychosocial needs which warrant palliative care services. Preliminary results suggest structured palliative care is associated with increased duration on study (by nearly 3 weeks), improved patient and CG QOL, and reduced patient symptom and CG burden. A larger study is warranted to confirm these results and further develop the ideal palliative care intervention in these populations. Clinical trial information: NCT02543541. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

3635 Poster Session (Board #365), Fri, 8:00 AM-11:00 AM

Pooled safety analysis of single-agent lurbinectedin versus topotecan (Results from a randomized phase III trial CORAIL and a phase II basket trial). *First Author: Alexandra Leary, Institut de Cancérologie Gustave Roussy, Villejuif, France*

Background: Lurbinectedin (L), an inhibitor of active transcription, has shown activity in second-line (2L) small cell lung cancer (SCLC) (ASCO 2019). Topotecan (T) is the only approved drug in 2L SCLC and is also used in platinum resistant ovarian cancer (PROC). **Methods:** This pooled safety analysis includes data from 554 patients (pts) treated with L at 3.2 mg/m^2 Day 1 q3wk 1-h (no primary prophylaxis with G-CSF required): 335 with selected solid tumors (9 indications, including 105 pts with SCLC) from a phase II Basket study and 219 with PROC in the phase III CORAIL study. An indirect exploratory comparison (pooled data from CORAIL + Basket) and a direct comparison (data from CORAIL) of L *vs.* T are presented. **Results:** Most common adverse events with L were grade 1/2 fatigue, nausea and vomiting. Treatment-related (L/T): dose reductions: 22.9/48.3%, delays: 25.8/52.9%, grade $\geq$3 serious adverse events (SAEs): 15.0/32.2%, discontinuations: 3.2/5.7%, deaths: 1.3/1.5%, G-CSF use: 23.8/70.1%, and transfusions: 15.9/52.9%. **Conclusions:** Lurbinectedin has a predictable and manageable safety profile. A significant safety advantage was observed when lurbinectedin was compared with topotecan in the CORAIL trial in terms of hematological toxicities. With the limitations of indirect comparisons, in the pooled safety analysis, fewer lurbinectedin-treated pts had severe hematological toxicities, SAEs, dose adjustments, treatment discontinuations and use of supportive treatments than topotecan-treated pts. Clinical trial information: NCT02421588 and NCT02454972. Research Sponsor: PharmaMar SA.

Safety profile (L *vs.* T): grade 3/4 adverse events (related or unknown) and laboratory abnormalities (regardless of relationship).

	Lurbinectedin 3.2 mg/m^2 1-h iv q3wk		Topotecan 1.5 mg/m^2 D1-D5 iv q3wk	P-value
	L Pool (n=554)	L CORAIL (n=219)	T CORAIL (n=87)	CORAIL (L *vs.* T)
Neutropenia	40.6	32.0	78.2 [a]	<.0001
Leukopenia	29.6	23.7	57.5 [a]	<.0001
Anemia	17.1	17.8	56.3	<.0001
Thrombocytopenia	9.9	9.1	33.3	<.0001
ALT increase	6.9	6.8	3.6	0.42
Fatigue	6.7	7.3	13.8	0.08
FN	6.3	5.5	11.5 [a]	0.08
Nausea	3.2	5.9	4.6	0.79
Vomiting	2.9	5.5	3.4	0.57
Diarrhea	0.9	0.9	4.6	0.06

[a] Primary G-CSF prophylaxis allowed.

3637 Poster Session (Board #367), Fri, 8:00 AM-11:00 AM

The skin types closely related to development of the facial acneiform rash and the therapeutic effects of EGFR inhibitors in RAS wild-type metastatic colorectal cancer: Ancillary analysis of FAEISS study. *First Author: Syusuke Yoshikawa, Shizuoka Cancer Center, Shizuoka, Japan*

Background: At ESMO2019, we reported the primary results of a randomized controlled trial (FAEISS study) investigating the efficacy of topical corticosteroid treatment to facial acneiform rash (AR) by EGFR inhibitors comparing groups starting with a very strong topical corticosteroid and the standard weak topical corticosteroid. As an ancillary analysis, we investigated the association between AR and the pre-treatment skin types, as well as between the skin types and therapeutic effects of EGFR inhibitors on the primary disease. **Methods:** Utilizing pre-treatment clinical photos of the face taken according to the method determined by FAEISS study protocol, we divided the skin types into categories including enlarged pore, oiliness, xerosis, wrinkles, skin color/redness, and allocated the score (1-3) by central review. The severity of AR occurred during the study was graded and was evaluated the association with the specific skin type by Fisher's exact test. We also investigated the association between the skin types and the best overall response (RECISTv1.1) to EGFR inhibitor therapy on the primary disease using the Cochran-Armitage trend test. **Results:** Of the registered 172 cases of RAS wild-type metastatic colorectal cancer [104 men and 68 women, median age = 68 (26-79)], omitting the cases with unevaluable data, finally we analyzed 146 cases for associations between the skin types and AR and 147 cases for best overall response. Interestingly, AR developed 13.6% of enlarged pore score 1, 29% of score 2 and 45.8% of score 3, and patients with enlarged pore tended to have more AR ($p = 0.058$). Surprisingly, the response(CR/PR/SD) of the primary disease were 59.1% of the enlarged pore score 1, 70.6% of score 2 and 87.0% of score 3, and showed statistically significant trend($p < 0.038$). **Conclusions:** This study suggested that a skin type (enlarged pore) is a possible marker predicting AR risk in EGFR inhibitor therapy for RAS wild-type metastatic colorectal cancer, and better therapeutic effects of EGFR inhibitors. Research Sponsor: None.

3638 Poster Session (Board #368), Fri, 8:00 AM-11:00 AM

Safety, tolerability, and preliminary pharmacokinetic/pharmacodynamic profile of JMT103 in patients with bone metastases from solid tumors: A multicenter, open-label, dose-escalation, phase I clinical study. *First Author: Jin Li, Department of Medical Oncology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China*

Background: Bone is one of the most common metastatic sites of malignancies. The metastatic tumor cells activate osteoclast activity and promote bone resorption via RANKL/RANK signaling pathway, and lead to osteolytic destruction. JMT103 is an innovative fully human IgG4 monoclonal antibody targeting RANKL. It can block RANKL/RANK signaling pathway, inhibit bone resorption, and protect bones from tumor metastasis. This study aimed to evaluate the safety and tolerability of JMT103 in patients with bone metastasis. **Methods:** This is a multicenter, open label, dose escalation, phase I clinical trial. The patients (ECOG score: 0-1) with bone metastasis from solid tumor who had not received bisphosphonates within 6 weeks before enrollment and were naïve to denosumab were enrolled. The initial dose was 0.5 mg/kg, sequentially escalated to 1.0, 2.0, and 3.0 mg/kg. JMT103 was injected subcutaneously by accelerated titration in 0.5 and 1.0 mg/kg dose groups, but via traditional "3+3" dose-escalation design in 2.0 and 3.0 mg/kg dose groups. Expansion study was conducted for subjects in 1.0, 2.0, and 3.0 mg/kg dose groups. Specifically, 3 additional doses (q4w) were injected after the end of 12-week single-dose study. The primary endpoints were maximum tolerated dose and safety. The secondary outcome measures included PK profile, preliminary efficacy biomarkers, immunogenicity, and bone mineral density (BMD). **Results:** From May 2018 to January 2020, 56 patients (13 males, 43 females, mean (SD) age: 55.57 (11.42) years) were enrolled, including bone metastasis from breast cancer (n = 36), gastric cancer (n = 5), lung cancer (n = 4), rectal cancer (n = 3), colorectal cancer (n = 2), or other solid tumors (n = 6). Nineteen patients participated in the dose-escalating study and 37 patients participated in the expansion study. JMT103 showed overall good safety. There were 74 drug-related AEs in all, including grade 3 (DLT hypocalcemia, n = 1; hypophosphatemia, n = 3), grade 2 (n = 15), and grade 1 (n = 55) AEs. The most common drug-related AEs were hypophosphatemia (n = 15), hypocalcemia (n = 12), and hypermagnesemia (n = 6). Median uNTx/Cr decrease from baseline was 76.6% (n = 20). **Conclusions:** JMT103 shows good safety and tolerability in patients with bone metastasis. Clinical trial information: NCT03550508. Research Sponsor: JMT-Bio Technology Co., Ltd.

3639 Poster Session (Board #369), Fri, 8:00 AM-11:00 AM

BXQ-350 to target to the lysosome and kill glioblastoma (GBM) cells via activation of apoptotic caspases in vitro. *First Author: Laura Felix, Student, Covington, KY*

Background: Apoptosis is a programmed cell death mechanism where cells respond to internal or external stimuli by initiating a cascade of events and enzymes leading to cell death. One of the hallmarks of cancer is the ability of tumor cells to resist these apoptotic stimuli. This allows tumor cells to have aberrant metabolisms, such as sphingolipid metabolism in tumor cell lysosomes, or mutations which would normally commit cells to death. Saposin C, the protein component of BXQ-350, Bexion Pharmaceuticals' proprietary biotherapeutic, is involved in normal lysosomal sphingolipid metabolism. Removing resistance, shortcutting steps leading to apoptosis, or correcting sphingolipid metabolism can result in the death of these tumor cells. **Methods:** The GBM cell line Gli36ΔEGFR was plated in 96 well plates at a density of $1x10^4$ cells per well in Dulbecco's Modified Eagle Media with 10% FBS overnight at 37°C for caspase and cytotoxicity assays. Cells were treated with 9uM to 30uM BXQ-350 in triplicate and incubated for 24 hours at 37°C. Promega's Caspase-Glo 9 or Caspase-Glo 3/7 reagent was added to appropriate wells and the plates were incubated at room temperature in the dark for 3 hours then luminescence was read. The parallel cytotoxic assay was run under the same conditions except Roche's MTT labeling reagent was added to the appropriate wells after 24 hours and incubated at 37°C for 4 hours. Solubilization solution was added to each well and the plate was incubated at 37°C overnight then absorbance was read. The GBM cell line U87 MG was used to determine lysosomal targeting. U87 MG cells were treated with 10uM BXQ-350 and incubated at 37°C overnight. They were stained with anti-SapC (RFP) and anti-LAMP1 (GFP) antibodies and images were taken. **Results:** BXQ-350 mediated cell death is correlated with a rise in Caspase 3, Caspase 7 and Caspase 9 activity. The caspase activity levels did not rise until after BXQ-350 passed its IC50 and stayed elevated. Caspases 3/7 levels showed higher activity compared to untreated than Caspase 9. In addition to this, BXQ-350 was seen to colocalize to LAMP1, a lysosomal membrane protein. **Conclusions:** BXQ-350 tracks to the lysosomal membrane where it initiates the cascade of enzymes necessary to cause apoptosis. Caspases 3/7 are the effector caspases and are necessary for the completion of the apoptotic pathway. The higher activity levels of these caspases show the cells are committed to cell death not allowing these cells to subvert apoptosis. This removes one of the major barriers to fighting cancer. Research Sponsor: Bexion Pharmaceuticals.

3640 Poster Session (Board #370), Fri, 8:00 AM-11:00 AM

Phase I dose-finding study of oral ERK1/2 inhibitor LTT462 in patients (pts) with advanced solid tumors harboring MAPK pathway alterations. *First Author: Filip Janku, Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX*

Background: LTT462 is an investigational small molecule inhibitor of ERK1/2, which has demonstrated preclinical activity in multiple MAPK activated cancer cells and xenograft models. This first-in-human study was designed to evaluate the safety and tolerability of LTT462 in advanced solid tumors harboring MAPK pathway alterations (NCT02711345). **Methods:** The dose-escalation part of this Phase I, open-label study, enrolled adult and adolescent pts with advanced solid tumors harboring ≥1 documented MAPK pathway alteration with progressive disease (PD) despite standard therapy, or for whom there is no effective standard treatment. Oral LTT462 was given once daily (QD) at 45–600 mg or twice daily (BID) at 150 mg or 200 mg. Objectives were to determine the maximum tolerated dose (MTD) using a Bayesian hierarchical logistic regression model guided by escalation with overdose control, and characterize safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of LTT462. **Results:** Sixty-five pts (median age 60 years) including 1 pt aged 15 were enrolled in the dose-escalation; most pts (22%) had 3 prior therapies. Most common primary sites for cancer were in the colon (n = 21; 32%), ovary (n = 9; 14%), and pancreas (n = 7; 11%). All pts discontinued, the majority due to PD (n = 44; 68%). Eleven pts experienced DLTs; 6 pts experienced Grade 3 eye disorder DLTs (4 pts retinopathy, 2 pts chorioretinopathy). Treatment-related adverse events (TRAEs) were reported for 89% of pts, most commonly (> 30%) diarrhea (n = 25; 38%) and nausea (n = 22; 34%). Grade 3/4 TRAEs were reported in 29% of pts; most common was retinopathy (n = 4; 6%). MTD of LTT462 was 400 mg QD and 150 mg BID. Overall, 8 pts (12%) had stable disease (SD) and 35 pts (54%) had PD. An unconfirmed partial response was reported in a pt with cholangiocarcinoma with *BRAF* mutation; best change in sum of target lesions per RECIST 1.1 was -33.9%. LTT462 increased plasma peak drug concentration and drug exposure at increasing doses between 45–450 mg QD. Exposure at LTT462 600 mg QD was lower than anticipated, indicating potential saturation of absorption at this dose. LTT462 inhibited ERK1/2 and reduced *DUSP6* expression relative to baseline in most pts evaluated. **Conclusions:** LTT462 is well tolerated. Limited clinical activity was reported with single agent LTT462; best overall response was SD. An ongoing study is investigating LTT462 in combination with the RAF inhibitor, LXH254, in NSCLC and melanoma. Clinical trial information: NCT02711345. Research Sponsor: Novartis.

3641 Poster Session (Board #371), Fri, 8:00 AM-11:00 AM

The incidence of myelodysplastic syndrome in patients receiving poly-ADP ribose polymerase inhibitors for treatment of solid tumors: A meta-analysis. *First Author: Roni Nitecki, MD Anderson Cancer Center, Houston, TX*

Background: Clinical trials have reported improved outcomes with PARPi (poly [adenosine diphosphate–ribose]-ADP polymerase inhibitor) therapy in ovarian, breast, pancreatic and lung cancers. There is concern that PARPi therapy may cause myelodysplastic syndrome (MDS). In this meta-analysis we seek to quantify the risk of MDS among patients treated with PARPi for solid tumor malignancies. **Methods:** We searched Medline, Embase, and Cochrane databases (up to January 6, 2020) to abstract randomized controlled trials that include a PARPi in the experimental arm in solid tumors. Combinations included PARPi versus (vs.) placebo, PARPi vs. cytotoxic treatment, and PARPi with cytotoxic treatment vs. cytotoxic treatment. We used to time-to-event curves to estimate person-time and calculated the incidence of MDS among all studies. We used random-effects Poisson regression models to estimate pooled incidence risk ratio (RR) for developing MDS. **Results:** We identified 14 studies, 10 in ovarian, 3 in breast, and 1 in pancreatic cancer patients. Of 5,646 patients, 62.3% received a PARPi alone or in combination with chemotherapy or bevacizumab, and 37.8% received treatment consisting of placebo alone or with chemotherapy or bevacizumab. PARPi were investigated as an upfront treatment in 2,827 patients, and as treatment for recurrence in 2,819 patients. The incidence of MDS was 6.73 cases vs. 3.85 per 1000 person-years in patients receiving PARPi as compared to control corresponding to a 3-year cumulative incidence of 2.0% and 1.1%. Accounting for intra-study clustering, PARPi use was associated with a 60% increase in risk (incidence RR 1.60, 95% Confidence Interval [CI] 0.89-2.87) of MDS compared to control. In the upfront setting, patients randomized to PARPi were twice as likely to develop MDS (RR 2.08, 95%, CI 1.39-3.64). Among patients treated for recurrence, the risk of MDS appeared to be similar among patient randomized to PARPi or control treatment (RR 1.13, 95% CI 0.35-3.64). In studies that compared PARPi in combination with other cytotoxic treatment vs. cytotoxic treatment alone, PARPi was associated with a large risk of MDS (RR 5.08, 95% CI 1.36-19.03). **Conclusions:** In pooled estimates from randomized controlled trials in solid tumors PARPi treatment appears to be associated with an increased incidence of MDS particularly in the upfront setting and when combined with cytotoxic treatment. Despite pooling 14 randomized trials our estimates remain imprecise due to the rarity of MDS. Research Sponsor: U.S. National Institutes of Health.

3642 Poster Session (Board #372), Fri, 8:00 AM-11:00 AM

Evaluation of a computational decision support system for molecularly targeted treatment planning by the clinical outcome data of the randomized trial SHIVA01. *First Author: Anna Dirner, Oncompass Medicine Hungary Ltd, Budapest, Hungary*

Background: Precision oncology requires the identification of individual molecular pathomechanisms to find optimal personalized treatment strategies for every cancer patient. Incorporation of complex molecular information into routine clinical practice remains a significant challenge due to the lack of a reproducible, standardized process of clinical decision making. **Methods:** To provide a standardized process for molecular interpretation, we develop a precision oncology decision support system, the Realtime Oncology Molecular Treatment Calculator (MTC). MTC is a rule-based medical knowledge engine that dynamically aggregates and ranks relevant scientific and clinical evidence using currently 26,000 evidence-based associations and reproducible algorithm scoring of drivers, molecular targets to match molecular alterations to efficient therapies. To validate this novel method and system, we used data of the SHIVA01 trial of molecularly targeted therapy (Lancet Oncol 2015 16:1324-34). Molecular profiles of participants were uploaded to MTC and aggregated evidence level (AEL) values of associated targeted treatments were calculated, including those used in the SHIVA01 trial. **Results:** The MTC output provided a prioritized list of drugs associated with the driver alterations in the patient molecular profile, where ranking is based on AEL values. Of 113 patients who received targeted therapy with available clinical best response data, disease control was experienced in 63 cases (PR: 5, SD: 58), while disease progression occurred in 50 cases. The average AEL score for the therapies applied was significantly higher in the responsive group than in the non-responsive group (1512 and 614, respectively ($p = 0.049$)). In 94 cases, drugs other than those used for therapy were ranked higher by the MTC. The average AEL difference between the top-ranked and the used drugs was in an inverse correlation with clinical response, i.e. smaller differences associated with a better outcome. **Conclusions:** Results indicate that the aggregation of evidence-based tumor-driver-target-drug associations using standardized mathematical algorithms of this computational tool is a promising novel approach to improve clinical decisions in precision oncology. Further validation based on the results of other targeted clinical trials and real-life data using more detailed molecular profiles is warranted to explore the full clinical potential of this novel medical solution. Research Sponsor: ERA PerMed, Hungarian Innovation Agency, Agence Nationale de le Recherche, Site de Recherche Intégrée contre le Cancer (SiRIC) ERA PerMed (ERAPERMED2018-078), Hungarian Innovation Agency (NVKP_16-1-2016-0005).

3643 Poster Session (Board #373), Fri, 8:00 AM-11:00 AM

Survival associated with mutations in SWI/SNF chromatin remodeling complex genes. *First Author: Michael J. Hassett, Dana-Farber Cancer Institute, Boston, MA*

Background: The SWI/SNF (SWitch/Sucrose NonFermentable) chromatin remodeling complex (CRC) - a combinatorial assembly of products from multiple genes - alters histone/DNA interactions and thereby impacts transcription, DNA replication/repair, and cell division. Studies suggest that over 20% of human cancers contain mutations in at least one SWI/SNF gene, implying that it is the most highly mutated CRC in human cancer. To address existing knowledge gaps, we sought to evaluate the association between SWI/SNF mutations and overall survival (OS). **Methods:** We identified adult cancer patients who consented to have OncoPanel testing (Dana-Farber/Brigham & Women's Hospital's next generation sequencing platform) from June 2013-August 2019. These data were merged with institutional electronic health records and National Death Index vital status. We determined mutation frequency and co-occurrence for the nine SWI/SNF genes included in OncoPanel (ARID1A, ARID1B, ARID2, BCL11B, PBRM1, SMARCA4, SMARCB1, SMARCE1, and SS18). We assessed the association between mutation and OS (from time of OncoPanel testing) for cancers with at least 500 analyzed and 20 mutated cases, controlling for age and TP53 status. Exploratory analyses were conducted using cBioPortal and SAS (no multiple comparison adjustment). **Results:** Among 25,434 samples from 24,648 patients, a mutation in at least one evaluated SWI/SNF gene was identified in 26% of cases (ARID1A 10.5%, ARID1B 7.2%, SMARCA4 5.5%, PBRM1 4.9%, ARID2 4.8%, BCL11B 3.5%, SMARCE1 1.1%, SMARCB1 1.0%, and SS18 0.7%). The most frequently mutated cancers included small bowel (52%), endometrial (49%), ampullary (48%) and bladder (45%). Co-occurrence was common (30 of 36 potential gene-pairs), with the largest associations (odds ratio; all $P < .05$) seen for SMARCB1:BCL11B (4.19), ARID1B:BCL11B (3.87), ARID2:BCL11B (3.85), and SMARCA4:BCL11B (3.78). Associations between having a mutation and OS were seen for the following cancers/genes (odds ratio; all $P < .05$): ARID1A (colorectal 0.72, pancreatic 1.46), ARID1B (melanoma 0.32), SMARCA4 (esophagogastric 1.48, non-small cell lung 1.89, ovarian 0.43), SMARCB1 (non-small cell lung 2.04), and SS18 (soft tissue sarcoma 2.06). **Conclusions:** Mutations in SWI/SNF genes are widespread, with mutation rates varying by cancer type. Co-occurrence was common, especially with BCL11B. Associations with OS were both favorable and unfavorable, with variability seen by gene and cancer type. Future research should explore the mechanisms by which mutations in SWI/SNF genes influence treatment response/OS. Research Sponsor: Institutional.

TPS3645 Poster Session (Board #375), Fri, 8:00 AM-11:00 AM

A phase I trial of aerosol gemcitabine for the treatment of patients with solid tumors and lung metastases. *First Author: Nancy Beatriz Gordon, UT MD Anderson Cancer Ctr, Houston, TX*

Background: Pre-clinical studies of aerosol gemcitabine (GCB) in mice and dogs with osteosarcoma (OS) lung metastases demonstrated therapeutic efficacy. Aerosol GCB administered once weekly proved to be safe in adults with lung cancer. Direct delivery of GCB to the lungs via inhalation may offer higher drug concentration in the tumor with fewer side effects. We initiated a Phase I study to evaluate the feasibility and safety of aerosol GCB treatment in patients>12 years with solid tumors and lung metastases (2015-0720- NCT03093909). **Methods:** Eligibility criteria: 1) Diagnosis of solid tumor with lung metastases, 2) willing to comply with protocol therapy, 3) adequate organ function, 4) patient age > 12 and < 50 years, 5) good performance status, 6) resolution of all acute toxic effects of any prior anti-cancer therapy, and 7) no radiotherapy within 2 weeks. Patients who previously received systemic GCB are eligible. Objectives: To determine the maximum tolerated dose (MTD) and toxicities of aerosol GCB, to evaluate for drug spillover into the circulation, and to preliminarily assess the anti-tumor activity. Correlative studies include effect of aerosol GCB on immune cell infiltration in the lung, autophagy, apoptosis, heat shock protein 27, evidence of DNA strand breaks (gH2AX) and expression of human equilibrative nucleoside transporter-1.Aerosol GCB is administered via a breath-induced nebulizer twice a week in 28-day cycles. A maximum of 6 dose levels will be studied; the starting dose is 0.75 mg/kg twice weekly. If no progressive disease or unacceptable treatment-related toxicity, patients may continue for 12 cycles. The study uses the accelerated titration method for the first 2 dose levels then the 3+3 design for the remaining dose levels. After determining the MTD, we will evaluate the defined MTD in an expansion cohort of 14 patients with relapsed OS. Symptoms, pulse oximetry, and pulmonary function are assessed prior to each nebulized dose using remote spirometry that allows raw numbers and flow-volume curves to be uploaded and transmitted via bluetooth to an android tablet provided to patients. Data is transmitted to a web portal and captured in a HIPAA-compliant web-based database (REDCap) that is accessible to the research team. **Results:** To date, the study enrolled 4 patients and accrual is ongoing at dose level 3. **Conclusions:** This study will provide information on the feasibility and safety of aerosol GCB. If proven to be feasible and safe, it can potentially offer a novel approach to treat metastatic OS to the lungs while minimizing systemic toxicity. Clinical trial information: NCT03093909. Research Sponsor: The Gateway for Cancer Research and Archer Charitable Foundation.

TPS3646 Poster Session (Board #376), Fri, 8:00 AM-11:00 AM

A phase I/II, two-part, multicenter, first-in-human study of DS-7300a in patients with advanced solid malignant tumors. *First Author: Johanna C. Bendell, Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN*

Background: B7 homologue 3 (B7-H3) is a protein that is overexpressed in various cancer types, including lung, head and neck squamous cell carcinoma, prostate, esophageal, and breast. B7-H3 overexpression is associated with poor prognosis because it promotes increased invasive and metastatic potential of cancer cells (Dong P, et al. *Front Oncol.* 2018;8:264). Currently, no B7-H3–targeted cancer therapies are approved. DS-7300a is an antibody-drug conjugate composed of a humanized anti–B7-H3 IgG1 monoclonal antibody (MABX-9001a) conjugated to a drug linker that releases its payload upon internalization by cancer cells. The payload, DXd, is an exatecan derivative that inhibits topoisomerase I, an enzyme that relaxes supercoiled DNA for replication and transcription. DS-7300a induced apoptosis in cancer cells in vitro and showed potent antitumor activity in xenograft models of various types of solid tumors in vivo. **Methods:** This phase 1/2, multicenter, nonrandomized, open-label, first-in-human study of DS-7300a is ongoing in the United States and Japan in patients with selected advanced solid tumors (NCT04145622). This study has 2 parts: dose escalation (part 1) and dose expansion (part 2). Primary objectives are to evaluate the safety, tolerability, and antitumor activity of DS-7300a and to determine the maximum tolerated dose or recommended dose for the expansion part. Secondary objectives include the pharmacokinetic characterization of DS-7300a, determination of the total levels of anti–B7-H3 antibody and the drug component (DXd), and assessment of the incidence of anti-drug antibodies against DS-7300a. Key inclusion criteria are age $\geq$ 18 years (United States) or $\geq$ 20 years (Japan), an ECOG performance status of 0 or 1, $\geq$ 1 measurable lesion according to RECIST 1.1 as assessed by the investigator, and consent to provide pre- and on-treatment tissue samples (mandatory if clinically allowed and not contraindicated). Key exclusion criteria include prior treatment with orlotamab, enoblituzumab, other B7-H3–targeted agents, or an antibody-drug conjugate that is conjugated with a topoisomerase I inhibitor. Dose expansion will start with 3 cohorts, including patients with selected advanced solid tumors. In both parts, DS-7300a will be administered intravenously on day 1 of each 21-day cycle. During dose escalation, the starting dose of DS-7300a is 0.8 mg/kg. This trial is currently in the dose-escalation part. Clinical trial information: NCT04145622. Research Sponsor: Daiichi Sankyo Co., Ltd.

TPS3647 Poster Session (Board #377), Fri, 8:00 AM-11:00 AM

EV-202: A phase II study of enfortumab vedotin in patients with select previously treated locally advanced or metastatic solid tumors. *First Author: Justine Yang Bruce, Carbone Cancer Center, University of Wisconsin, Madison, WI*

Background: Nectin-4, a transmembrane cell adhesion protein, is highly expressed in urothelial carcinoma (UC), breast cancer (BC), non-small cell lung cancer (NSCLC), and gastroesophageal cancers (GEC); targeting Nectin-4 on these tumors may provide a novel treatment approach. Enfortumab vedotin (EV), an investigational human monoclonal antibody-drug conjugate, binds to Nectin-4 and upon internalization releases MMAE resulting in cell cycle arrest and cell death. Recently, EV received accelerated approval by the FDA for the treatment of adults with locally advanced/metastatic UC who previously received a PD-1 or PD-L1 inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting. Use of EV in this study is investigational. **Methods:** This open-label phase 2 study (NCT04225117) will assess the efficacy and safety/tolerability of EV in patients (pts) with previously treated locally advanced/metastatic malignant solid tumors. Adult pts (~240) with histologically or cytologically confirmed disease and an ECOG $\leq$1 will be enrolled into 1 of 6 tumor-specific cohorts (Table), with ~40 pts each. While Nectin-4 expression is not required for enrollment, it is being tested retrospectively. Patients with active CNS metastases, grade $\geq$2 preexisting sensory or motor neuropathy, grade $\geq$3 immunotherapy-related hypothyroidism or panhypopituitarism, ongoing grade $>$3 immunotherapy-related AEs requiring high-dose steroids, or a history of uncontrolled diabetes mellitus within 3 months of the study will be excluded. All pts will receive EV 1.25 mg/kg IV on Days 1, 8, and 15 of each 28-day cycle until treatment discontinuation criteria are met; dose reductions/interruptions will be permitted. For all cohorts, the primary endpoint is investigator-assessed confirmed objective response rate (RECIST v1.1); secondary endpoints include duration of response, disease control rate, progression-free and overall survival, and safety/tolerability of EV. This study is recruiting as of February 2020. Clinical trial information: NCT04225117.Research Sponsor: Astellas Pharma, Inc.

Cohort	Tumor Type
1	Hormone receptor–positive/human epidermal growth factor receptor 2–negative BC
2	Triple-negative BC
3	Squamous NSCLC
4	Nonsquamous NSCLC
5	Head and neck cancer
6	GEC, including gastroesophageal junction adenocarcinoma

TPS3648 Poster Session (Board #378), Fri, 8:00 AM-11:00 AM

TROPiCS–03: A phase II open-label study of sacituzumab govitecan (SG) in patients with metastatic solid tumors. *First Author: Ashish Saxena, Weill Cornell Medicine, New York-Presbyterian Hospital, New York, NY*

Background: Trophoblast cell surface antigen (Trop-2) is highly expressed in many epithelial cancers (non–small-cell lung cancer [NSCLC], endometrial cancer, urothelial carcinoma [UC], and triple-negative breast cancer [TNBC]) and has been linked to aggressive disease and poor prognosis. SG is a Trop-2–directed antibody drug conjugate containing SN-38 (active metabolite of irinotecan) with a 7.5:1 drug-to-antibody ratio and unique hydrolyzable linker that allows for extracellular bystander effect. The phase 1/2 IMMU-132-01 basket study reported clinical activity with SG in patients with multiple tumor types not selected for Trop-2 expression including NSCLC (objective response rate [ORR]: 17%), TNBC (ORR: 33%), and UC (ORR: 31%).1-3 Results from the overall safety population (N=420) from this study found that SG was tolerable, with a predictable and manageable safety profile, and low discontinuation rates due to AEs. **Methods:** To test a biomarker-enrichment strategy with Trop-2, the TROPiCS-03 (TROP-2 Investigations in Cancer with SG) study was initiated. TROPiCS-03 (NCT03964727) is a multi-cohort, open-label, phase 2 study in patients with metastatic solid tumors - presently NSCLC (adenocarcinoma and squamous cell carcinoma), head and neck squamous cell carcinoma, and endometrial cancer - selected based on elevated Trop-2 expression by a validated IHC assay. Patients receive SG (10 mg/kg IV, days 1 and 8 every 21 days) and continue treatment until lack of clinical benefit or unacceptable toxicity. The primary endpoint is objective response rate (local assessment) and additional endpoints include clinical benefit rate, duration of response, progression-free survival, and safety. Females or males $\geq$18 years old who are histologically documented to have locally advanced or metastatic (M1, stage 4) solid tumors of the above types are eligible. Patients must have ECOG 0 or 1 and adequate clinical laboratory results to be enrolled. All subjects will have progressed after prior platinum-based chemotherapy and programmed death-ligand 1 (PD-L1) or programmed cell death protein 1 (PD-1) directed therapy. Patients who have previously received topoisomerase I inhibitors and those with known active CNS metastases are excluded. Approximately 160 patients will be enrolled in the trial overall; enrollment in the NSCLC cohort is currently in progress. References: Heist RS et al. *J Clin Oncol.* 2017;35:2790-7, Bardia A et al., *NEJM.* 2019;380:741-51.,Tagawa ST et al., Oral presentation; ASCO-GU 2019, San Francisco, CA. Clinical trial information: NCT03964727. Research Sponsor: Immunomedics, Inc.

TPS3649 Poster Session (Board #379), Fri, 8:00 AM-11:00 AM

Phase I study of the antibody-drug conjugate ABBV-321 in patients with non-small cell lung cancer and squamous head and neck cancer with overexpression of the epidermal growth factor receptor. *First Author: Benedito A. Carneiro, The Warren Alpert Medical School, Brown University, Providence, RI*

Background: ABBV-321 (serclutamab talirine) is an epidermal growth factor receptor (EGFR)-targeted antibody-drug conjugate that consists of a humanized immunoglobulin G1 anti-EGFR monoclonal antibody conjugated to a pyrrolobenzodiazepine (PBD) dimer via a maleimidocaproyl-valine-alanine linker. Once bound, ABBV-321 is internalized, the maleimidocaproyl-valine-alanine linker undergoes proteolytic cleavage, and the cytotoxic PBD is released, causing DNA cross-links and cell death. Preclinical studies have shown cytotoxicity in numerous human xenograft and patient (pt)-derived tumor models. This first-in-human trial is assessing the safety, pharmacokinetic (PK), and preliminary antitumor activity of ABBV-321 in pts with advanced solid tumor types likely to exhibit elevated levels of EGFR. **Methods:** This is a 2-part, multicenter phase 1 study (NCT03234712) of ABBV-321 monotherapy in pts ($\geq$18 years; Eastern Cooperative Oncology Group performance status 0–1) with advanced solid tumors associated with overexpression of EGFR. EGFR overexpression will be determined by centralized testing using an RNA-based assay. Primary objectives of the completed part 1 (dose escalation) were to determine the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of ABBV-321 and assess the PK and toxicity and safety profile; part 2 (dose expansion) will evaluate safety and PK profile at the RP2D in specific cohorts (NSCLC and HNSCC). Secondary objectives include assessment of preliminary antitumor activity. Pts will receive escalating doses of ABBV-321 until the MTD/RP2D is determined. Dose-limiting toxicities will be assessed during the first cycle of dosing. Adverse events (AEs) will be evaluated per National Cancer Institute Common Terminology Criteria for AEs (version 4.03). Blood samples for PK analysis (ABBV-321, total antibody, unconjugated PBD) will be collected at designated time points throughout the study. The multinational trial is active, with the first pt screened on 1 Feb 2018. The dose-escalation phase has been completed; screening and enrollment for the expansion phase of the study in NSCLC and HNSCC is underway. Clinical trial information: NCT03234712. Research Sponsor: AbbVie, Inc.

TPS3650 Poster Session (Board #380), Fri, 8:00 AM-11:00 AM

A basket trial of trastuzumab deruxtecan, a HER2-targeted antibody-drug conjugate, for HER2-amplified solid tumors identified by circulating tumor DNA analysis (HERALD trial). *First Author: Masataka Yagisawa, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Trastuzumab deruxtecan, a new HER2-targeting antibody-drug conjugate, has been approved for unresectable or metastatic HER2-positive breast cancer by the Food and Drug Administration. In a phase I/II trial, trastuzumab deruxtecan showed a manageable safety profile and antitumor activity in HER2-positive various cancer types. In addition, a tissue-based HER2 test occasionally cannot identify accurate HER2 status due to spatial and temporal intratumoral heterogeneity, leading to potentially missing an opportunity for responders to receive benefit from anti-HER2-targeted therapy. Circulating tumor DNA (ctDNA) analysis can detect comprehensive somatic genome alterations by assessment of spatial and temporal intratumoral heterogeneity with minimal invasiveness. **Methods:** We designed an investigator-initiated multicenter phase II basket trial to evaluate efficacy and safety of trastuzumab deruxtecan in advanced solid tumor malignancies with *HER2* amplification identified by Guardant360, a 74-gene sequencing ctDNA panel, as a part of the Nationwide Cancer Genome Screening Project (GOZILA study, UMIN000029315). The key eligibility criteria are as follows: 1) Histopathologically confirmed advanced solid tumor malignancy; 2) Identified *HER2* amplification by Guardant360; 3) Failed prior standard therapy. The participants will receive intravenously 5.4 mg/kg of trastuzumab deruxtecan every 3 weeks. The primary endpoint is objective response rate (ORR). The planned sample size is 55-65. A Bayesian model considering the potential heterogeneity across cancer types will be applied to detect ORR of 5% versus 25% to a certain level while maintaining the false-positive error rate in each cancer type at 10%. Furthermore, tumor tissue, ctDNA and circulating tumor cells are serially collected and analyzed to investigate the predictive biomarkers and resistance mechanisms. The trial was activated in late 2019. At the time of the abstract submission, 2 patients have been enrolled. This trial is granted by AMED under Grant Number JP18lk0201084. Clinical trial information: JapicCTI-194707. Research Sponsor: Japan Agency for Medical Research and Development.

TPS3651 Poster Session (Board #381), Fri, 8:00 AM-11:00 AM

A phase I, open-label, dose-escalation trial of BI 1701963 as monotherapy and in combination with trametinib in patients with KRAS mutated advanced or metastatic solid tumors. *First Author: Eelke Gort, University Medical Center Utrecht, Utrecht, Netherlands*

Background: Activating mutations of *KRAS* drive many types of cancer. Activation of KRAS relies on guanine nucleotide exchange factors, such as SOS1, to mediate exchange of GDP for GTP. BI 1701963 is a small-molecule protein–protein interaction inhibitor that prevents the interaction between KRAS and SOS. Binding of BI 1701963 to the catalytic site of SOS1 inhibits binding of SOS1 to RAS–GDP, thereby hindering the exchange from RAS–GDP (inactive form) to RAS–GTP (active form). In preclinical studies this has been shown to lead to cytostasis in cancer cells addicted to KRAS signaling. **Methods:** NCT04111458 is a first-in-human trial of BI 1701963 in patients aged ≥18 years with tumors harboring *KRAS* mutations. Primary objectives are to determine the maximum tolerated dose (MTD) and recommended Phase II dose of BI 1701963 as monotherapy and in combination with trametinib, based on dose-limiting toxicities (DLTs). Secondary objectives are to evaluate safety, tolerability, pharmacokinetics/-dynamics and preliminary efficacy. The study will have two arms (mono- and combination therapy), and be divided into dose escalation (Part A), confirmation (Part B) and expansion (Part C, combination only) phases. Inclusion criteria include activating *KRAS* mutation, ≥1 evaluable lesion (RECIST 1.1), ECOG PS ≤1 and adequate organ function. Exclusion criteria include history of: RAS, MAPK or SOS1 targeting therapies; retinal vein occlusion; retinal pigment epithelial detachment; and decreased cardiac function. Parts B and C will be conducted in patients with advanced NSCLC. Treatment will continue until confirmed clinical benefit, defined toxicities, or withdrawal of consent. The primary endpoints are: Part A, the MTD, and the number of patients with DLTs during Cycle 1; Part B (monotherapy), the number of patients with DLTs; Part C, objective response (OR, RECIST 1.1). Starting doses of BI 1701963 in Part A will be 50 mg once daily (QD) orally (monotherapy) and 100 mg QD (combination, once proved safe as monotherapy) and will be escalated until the MTD is reached. The starting dose of trametinib will be 1 mg QD, escalated to the MTD or a max. of 2 mg QD. Dose cohorts will include ≥3 patients, with two therapeutic relevant doses (TRDs) established in each arm. In Part B, patients will be randomized to groups receiving one of the TRDs. If an OR is observed at a TRD in the combination arm, additional patients will be recruited into expansion cohorts receiving the relevant dose. As of Feb 11, 2020 three patients have been treated. Clinical trial information: NCT04111458. Research Sponsor: Boehringer Ingelheim.

TPS3652 Poster Session (Board #382), Fri, 8:00 AM-11:00 AM

SGN228-001: A phase I open-label dose-escalation, and expansion study of SGN-CD228A in select advanced solid tumors. *First Author: Amita Patnaik, START, San Antonio, TX*

Background: SGN-CD228A is an investigational antibody-drug conjugate (ADC) that targets CD228, a cell-surface oncofetal protein with prevalent expression in several types of cancer and limited expression on normal tissues. SGN-CD228A consists of a humanized IgG1 anti-CD228 monoclonal antibody conjugated to an average of 8 molecules of monomethyl auristatin E (MMAE) via a PEGylated β-glucuronidase cleavable linker. MMAE is a well-studied and highly active chemotype with an established safety profile. The proposed mechanism of action involves binding CD228 on cell surfaces, ADC internalization, and trafficking to lysosomes. MMAE is then released through β-glucuronidase cleavage of the glucuronide MMAE linker. MMAE then binds tubulin, which disrupts microtubule networks and causes cell cycle arrest and apoptosis. **Methods:** SGN228-001 (NCT04042480) is a phase 1, open label, multicenter, dose escalation, and expansion study enrolling up to 240 subjects to evaluate the safety, tolerability, PK, and antitumor activity of SGN-CD228A in select advanced solid tumors. Eligible subjects are ≥18 years of age and have metastatic cutaneous melanoma, malignant pleural mesothelioma, human epidermal growth factor receptor 2-negative metastatic breast cancer, advanced non-small cell lung cancer, metastatic colorectal cancer, or advanced pancreatic ductal adenocarcinoma. Subjects must have relapsed, refractory, or progressive disease, and should have no appropriate standard therapy available. Measurable disease per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), Eastern Cooperative Oncology Group (ECOG) performance status score of ≤1, and adequate renal, hepatic, and hematologic function are required. The study includes dose escalation and dose expansion, with multiple disease-specific dose expansion cohorts and a biology cohort. Dose escalation will be conducted using the modified toxicity probability interval method (Ji 2010) to evaluate the safety and identify the maximum tolerated dose of SGN-CD228A. Following dose escalation, disease-specific expansion cohorts and a biology cohort (to evaluate exploratory biomarkers) are planned. Response assessments will be conducted every 6 weeks per RECIST v1.1 and all subjects will be followed for safety. Pharmacokinetics and markers of pharmacodynamics will be assessed regularly. Key efficacy endpoints include objective response rate, progression-free survival, and duration of objective response. Enrollment is ongoing in the US and planned in Europe. Clinical trial information: NCT04042480. Research Sponsor: Seattle Genetics Inc.

TPS3653 Poster Session (Board #383), Fri, 8:00 AM-11:00 AM

Randomized phase II trial of topotecan plus M6620 (VX-970) versus topotecan alone in patients with relapsed small-cell neuroendocrine cancers including small cell lung cancer. *First Author: Nobuyuki Takahashi, National Cancer Institute, Bethesda, MD*

Background: Ataxia telangiectasia and Rad3-related (ATR) is an essential kinase that senses stressed replication forks and orchestrates the multifaceted replication stress response. Cancer cells under replication stress are particularly susceptible to ATR inhibition. Small-cell neuroendocrine cancers (SCNCs) are highly aggressive and arise in multiple tissues, most commonly lung (SCLC). We hypothesized that SCNCs are under replication stress and that exacerbating this stress could selectively kill SCNC by replicative damage. Based on promising data from a single-arm study, this study seeks to evaluate the improvement of progression free survival (PFS) by adding M6620 to topotecan in patients with SCNC. **Methods:** This study is an investigator-initiated, multicenter, open-label randomized phase 2 clinical trial. Key inclusion criterion are patients at age ≥18 with SCNCs that had relapsed after at least one prior chemotherapy, ECOG PS ≤ 2, and adequate organ function. Patents with asymptomatic brain metastasis, irrespective sensitivity with prior platinum-based chemotherapy, and previously treated with immune checkpoint inhibitors are eligible. The primary cohort consists of 54 patients with SCLC randomized 2:1 to receive either topotecan in combination with M6620 or topotecan alone. Topotecan is administered 1.25 mg/m^2 intravenously over 30 minutes every 23 hours on day 1 through 5, pegfilgrastim 6 mg subcutaneously on day 6 and M6620 is administered at 210 mg/m^2 intravenously over 60 minutes on day 2 and day 5 if the patient is randomized to the combination arm, in 21-day cycles. Patients randomized to the topotecan alone arm can cross-over to the combination arm at disease progression. An exploratory cohort will enroll 20 patients with SCNC. Primary endpoint is PFS improvement with the combination compared with topotecan alone. Secondary endpoints are ORR and overall survival. To evaluate the genomic features associated with clinical outcomes and to gain insight into the underlying mechanisms of ATR inhibitor response, we require mandatory biopsy before starting treatment. Clinical trial information: NCT03896503. Research Sponsor: U.S. National Institutes of Health.

TPS3654 **Poster Session (Board #384), Fri, 8:00 AM-11:00 AM**

A phase II basket study of MCLA-128, a bispecific antibody targeting the HER3 pathway, in NRG1 fusion-positive advanced solid tumors. *First Author: Alison M. Schram, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *NRG1* fusions are oncogenic drivers across various cancers. NRG1 fusion proteins bind to HER3, leading to HER2/HER3 heterodimerization, increased downstream signaling, and tumor growth. Clinical responses to anti-HER3 antibodies or HER2 tyrosine kinase inhibitors have been reported. In contrast to these agents, MCLA-128 is a HER2/HER3 bispecific antibody that blocks both NRG1 binding and HER2/3 dimerization. Two patients with chemotherapy-resistant *ATP1B1-NRG1*-positive pancreatic *KRAS*-wild-type adenocarcinomas who received MCLA-128 through FDA-approved single-patient Investigational New Drug (IND) applications showed significant tumor shrinkage and durable tumor marker (CA-19-9) response. These data support the evaluation of MCLA-128 in *NRG1* fusion-positive tumors using a basket approach. **Methods:** This is a global, open-label, multicenter phase 2 basket trial of MCLA-128 in patients with solid tumors harboring *NRG1* gene fusions. Main eligibility criteria are locally advanced unresectable or metastatic cancers harboring an *NRG1* fusion, and failure under prior standard therapy appropriate for the tumor type and disease stage. Genomic screening of tumor tissue is done at a local laboratory (with post-hoc central confirmation) or central laboratory (RNA sequencing). Three *NRG1* fusion-positive tumor cohorts are being evaluated: pancreatic cancer, NSCLC, and other solid tumors. The sample size for the first two cohorts is up to 25 patients; the basket group may enroll up to 40 patients. The primary endpoint for all cohorts is investigator-assessed objective response rate (RECIST v1.1). The key secondary endpoint is duration of response. Other secondary endpoints include progression-free and overall survival. Eligible patients receive a bi-weekly dosing regimen of 750 mg of MCLA-128 (2-hour infusion), every 2 weeks, in 4-week cycles. The study is actively accruing patients in North America, Europe, and Asia. *Previously presented at ESMO 2019, 685TiP, Schram et al.-Reused with permission.* Clinical trial information: NCT02912949. Research Sponsor: Merus NV.

TPS3655 **Poster Session (Board #385), Fri, 8:00 AM-11:00 AM**

BT5528-100 phase I/II study of the safety, pharmacokinetics, and preliminary clinical activity of BT5528 in patients with advanced malignancies associated with EphA2 expression. *First Author: Johanna C. Bendell, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

Background: BT5528 is a Bicycle Toxin Conjugate (BTC), comprising a bicyclic peptide targeting the tumor antigen EphA2, linked to a cytotoxin (monomethyl auristatin E [MMAE]) via a tumor microenvironment cleavable linker. *Bicycles* are a novel class of chemically synthesized constrained peptides, developed by Bicycle Therapeutics. EphA2 is reported to be overexpressed in a range of solid tumors, contributes to oncogenesis, tumor-associated angiogenesis and metastasis. Intracellular EphA2 signaling converges on pathways that are integral to cell growth, proliferation, migration and invasion. Increased EphA2 expression has been identified as a resistance mechanism to EGFR Tyrosine Kinase Inhibitor based therapy. BT5528 mechanism of action is dependent on tumor penetration, target binding and release of MMAE toxin payload. BTCs offer advantages over antibody-toxin conjugates exhibiting rapid penetration of dense tumors and decreased extra-tumor exposure. BT5528 exhibited a favorable preclinical profile supporting the initiation of a first-in-human study to investigate safety and efficacy of BT5528 in indications with evidence of EphA2 expression including non-small-cell lung cancer (NSCLC), ovarian cancer, triple-negative breast cancer (TNBC), gastric/upper gastrointestinal (GI), pancreatic and urothelial cancers. **Methods:** BT5528-100 (NCT04180371) is a Ph I/II study to evaluate safety and tolerability of weekly BT5528 alone and in combination with Q4W nivolumab. Each dose escalation utilizes a 3+3 design which converts to a Bayesian design to determine MTD or MAD and RP2D for BT5528 with and without nivolumab. Eligible patients must have advanced solid tumors associated with EphA2 expression which have recurred after exhausting standard treatment options. Patients must have available tumor tissue and acceptable hematologic and organ function, with exclusions for uncontrolled brain metastases, thromboembolic events, bleeding disorders, uncontrolled hypertension, CYP3A4 inhibitors/inducers or, for the nivolumab cohorts, autoimmune disease. On-study tumor and blood samples will be collected for biomarker evaluations including tumor EphA2 expression, ADA, and candidate response biomarkers for BT5528 alone and combination with nivolumab. Pharmacokinetic data will be reported for C1D1 and D15 for BT5528 and MMAE. The expansion phase will enroll specific tumor types to evaluate clinical activity of BT5528. Enrollment is ongoing. Clinical trial information: NCT04180371. Research Sponsor: Bicycle Tx Limited.

TPS3656 **Poster Session (Board #386), Fri, 8:00 AM-11:00 AM**

An open-label, first-in-human, phase I trial of the safety and efficacy of daily PCLX-001. *First Author: Randeep S. Sangha, Cross Cancer Institute, Edmonton, AB, Canada*

Background: Myristoylation regulates numerous membrane-bound signal transduction pathways important in cancer biology. This modification is catalyzed by N-myristoyltransferases 1 and 2 (NMT1 and NMT2). PCLX-001 is an oral small molecule with high affinity for both NMT proteins (IC50 of 5nM and 8nM, respectively) with high bioavailability and drug-like pharmacokinetic properties. In *ex vivo* sensitivity screening cell lines of hematologic cancer origin were exquisitely sensitive to PCLX-001, although high sensitivities and cell killing were also seen in some solid tumor lines derived from lung, pancreas, breast, colon, and bladder carcinomas. PCLX-001 demonstrated strong preclinical single-agent antitumor activity and tolerability *in vivo* in subcutaneous tumor xenograft models derived from lymphoma cell lines, lung cancer cell lines, a breast cancer cell line, as well as in a patient derived xenograft model from a patient with refractory DLBCL. The primary objective of this study is to determine the MTD and/or recommended phase II dose, safety, tolerability, and pharmacokinetics of PCLX-001 as a single agent, in patients with refractory lymphomas and advanced solid tumors. The secondary objective of the study is to evaluate the preliminary single agent antitumor activity of PCLX-001 in the patient populations studied. **Methods:** This is a multicenter, open-label, phase I dose-escalation study of oral PCLX-001 comprised of two parts (dose escalation and dose expansion). Eligible patients will have: histologically-confirmed advanced solid tumor or B-cell lymphomas who have failed prior therapy and/or are not eligible for therapies; ages $\geq$ 18 years; adequate organ function; life expectancy of at least 12 weeks; and measurable disease. Part A (dose-escalation) patients will be accrued in cohorts of 3 to 6 patients to each dose level, starting at 20 mg daily on a 28 day cycle. Dose escalation will follow a modified Fibonacci design such that the magnitude of escalation decreases as the dose level nears the human equivalent dose of the highest non-severely toxic dose in dogs and then escalate at 1.4 times the previous dose. Dose escalation and determination of the maximum tolerated dose will be based on the occurrence of dose limiting toxicities in cycle 1. Part B will have two single agent expansion cohorts (n = 20 each) in advanced solid malignancies and relapsed/refractory B-cell lymphoma, to determine the preliminary clinical activity of PCLX-001 to determine the recommended phase II dose. The first patient on study is planned for Q3 2020. Research Sponsor: Pacylex, Other Foundation.

TPS3657 **Poster Session (Board #387), Fri, 8:00 AM-11:00 AM**

A phase I/II, open-label, dose-escalation, and cohort-expansion study evaluating the safety, pharmacokinetics, and therapeutic activity of OBI-999 in patients with advanced solid tumors. *First Author: Apostolia Maria Tsimberidou, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Aberrant glycosylation is a hallmark of cancer. Glycosphingolipids (GSLs), glycans conjugated to a lipid (ceramide) core, are essential for the recruitment of immune-related proteins to specific membrane microdomains. Globo H (GH) is a GSL found on normal cells but highly overexpressed on various epithelial tumors playing a role in tumor development and progression. GH is a promising target for immunotherapy. OBI-999 is an ADC composed of a human recombinant immunoglobulin G (IgG) monoclonal antibody that selectively and specifically binds to GH, attached by a linker to the antimitotic agent monomethyl auristatin E (MMAE). Its mechanism of action is based on tumor-selective delivery of MMAE to GH-expressing tumors with subsequent tumor cell death. Preclinical studies demonstrated that OBI-999 antibody binds specifically to the GH antigen, and antitumor efficacy was noted in breast, gastric, pancreatic, and lung cancer xenograft models. The pharmacokinetics (PK) of OBI-999 were determined in normal and tumor-bearing mice, rats, and monkeys. Exposure of OBI-999 increased proportionally with dose. No sex difference or accumulation was seen. The primary objectives are to determine dose limiting toxicities (DLTs), the maximum tolerated dose (MTD), and the phase 2 recommended dose (P2RD). The secondary objectives are to assess the rates of objective response and clinical benefit, the duration of progression-free survival, the immunogenicity of OBI-999, and the PK and pharmacodynamics (PD) of OBI-999 and MMAE. **Methods:** In Part 1, a "3+3" dose-escalation part of the study, up to 30 patients with advanced solid tumors refractory to $\geq$1 line of systemic therapy, who cannot tolerate standard therapy, or for whom no standard treatment is available, regardless of GH status will be treated. OBI-999 will be administered as a 60-minute IV infusion using a dose range of 0.4, 0.8, 1.2, 1.6, and 2.0 mg/kg on day 1 of every 21-day cycle. In Part 2, the cohort-expansion portion of the study, patients will be treated at the MTD or at a lower RP2D as determined by cumulative toxicities and tolerability profile. The study will determine the preliminary clinical activity and safety of OBI-999 in up to 155 patients with advanced solid tumors, pancreatic, gastric, esophageal, and colorectal cancer according to a Simon two-stage phase 2 design. Patients must have GH overexpression defined as an H-score of $\geq$100 according to an FDA Investigational Device Exempt (IDE) validated IHC assay. Clinical trial information: NCT04084366. Research Sponsor: OBI Pharma Inc.

TPS3658 Poster Session (Board #388), Fri, 8:00 AM-11:00 AM

A first-in-man phase I/II study of OBI-3424, an AKR1C3-selective bis-alkylating agent prodrug, in subjects with advanced cancer, including hepatocellular carcinoma (HCC) and castrate-resistant prostate cancer (CRPC). *First Author: Apostolia Maria Tsimberidou, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Aldo-keto reductase family 1 member C3 (AKR1C3) modulates cellular differentiation and proliferation through indirect regulation of ligand access to hormone and nuclear receptor signaling. AKR1C3 is expressed at high levels in various human cancers, including HCC. In prostate cancer cells exposed to anti-androgen therapies, AKR1C3 is adaptively upregulated. CRPC is a potential indication for this targeted alkylating agent. AKR1C3 tumor expression is associated with poor patient survival and resistance to cancer therapies. OBI-3424 is a nitro-benzene prodrug of a nitrogen mustard that can be selectively cleaved in the presence of AKR1C3 enzyme into a bis-alkylating agent capable of forming intra- and inter-strand crosslinks with DNA, thereby resulting in cell death. The selectivity of OBI-3424 for AKR1C3 distinguishes it from traditional alkylating agents, which are nonselective. The primary objectives of the study are to evaluate the safety and tolerability of single-agent OBI-3424. The dose-escalation phase will determine the dose-limiting toxicities (DLT), maximum tolerable dose (MTD), and recommended Phase 2 dose (RP2D) of OBI-3424 through assessment of PK of OBI-3424 and OBI-2660 in plasma and urine. After determining the maximum tolerated dose (MTD), the study will enroll subjects with advanced HCC or CRPC, two tumor types with a high likelihood of over-expression of AKR1C3, into the dose expansion portion of the study according to a Simon two-stage phase 2 design. This phase is designed to assess the objective response rate, and progression-free survival in patients with HCC and CRPC. Immunohistochemistry assays are being developed to assess tumor expression of AKR1C3 for this study. The clinical safety and relationship of efficacy to AKR1C3 tumor expression will serve to guide further clinical development of OBI-3424 in these two unmet need settings. **Methods:** Based on the toxicology and PK results in cynomolgus monkeys, the starting dose is one sixth of the human equivalent dose of the highest non-severely toxic dose observed. Doses of 1, 2, 4, 6, 8, 12, and 14 mg/m^2 will be used. OBI-3424 is administered intravenously (IV) over 30 minutes on days 1 and 8 of each 21-day cycle. Subjects without clinically significant disease progression may continue on treatment for up to 2 years, if they do not experience a DLT or other significant toxicity. Clinical trial information: NCT03592264. Research Sponsor: OBI Pharma Inc.

TPS3659 Poster Session (Board #389), Fri, 8:00 AM-11:00 AM

SKB264 ADC: A first-in-human study of SKB264 in patients with locally advanced unresectable/metastatic solid tumors who are refractory to available standard therapies. *First Author: Yongheng Liu, Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., Chengdu, China*

Background: Elevated expression of trophoblast antigen 2 (TROP2) is often associated with invasion/aggression, progression, and metastasis of many different tumor types. Efficacies of anti-TROP2 ADC have been demonstrated both preclinically and in the clinical trials. SKB264 is being developed as a further optimized TROP2-targeting ADC with a proprietary cytotoxic, belotecan-derived payload and novel stable conjugation chemistry to achieve average DAR (Drug Antibody Ratio) of 7.4. Release of payload upon SKB264 internalization is in a TROP2 expression dependent manner. Extensive preclinical studies demonstrated antitumor activity of SKB264 in vitro, in xenograft and patient-derived xenograft (PDX) animal models. In addition, safety studies have demonstrated a good safety profile to allow SKB264 to be studied in clinical trials. **Methods:** SKB264-01 is a global open label multicenter study. The study is divided into 2 parts, the phase I is to determine the safety profile, define MTD and/or the RP2D, and characterize DLTs of SKB264. Dose escalation and MTD identification will be directed using a Bayesian logistic regression model (BLRM) with overdose control. The phase II is to evaluate efficacy and obtain clinical activity data of SKB264 as a monotherapeutic agent at the RP2D in each of the designated Phase II cohorts and overall (n = 16 per cohort; n = 48 for entire Phase II part). Objective response rate (ORR) will be continuously evaluated in each cohort using a Bayesian hierarchical model. TROP2 assessments will not be performed prior to enrollment but it will be assessed retrospectively. Confirmation of TROP2 expression by immunohistology or other methods is not required, but the Sponsor will request tissue specimens from archived materials for determination of TROP2 expression. The patient must have, in the judgment of the investigator, historically documented, incurable, locally advanced or metastatic cancer that are refractory to standard therapies of one of the following types: i. ovarian epithelial cancer, ii. gastric adenocarcinoma, iii. pancreatic adenocarcinoma, iv. triple negative breast cancer, v. bladder cancer. Patient will receive study drug as a single IV infusion at the prescribed dose level at each administration. Cycles will continue until disease progression or unacceptable toxicity. Adverse Events (AE) will be graded according to CTCAE V.5.0. Responses will be evaluated according to RECIST V1.1. The enrollment will began in Mar 2020 in USA sites. Clinical trial information: NCT04152499. Research Sponsor: KLUS Pharm Inc.

TPS3660 Poster Session (Board #390), Fri, 8:00 AM-11:00 AM

A phase Ia/Ib, dose-escalation/expansion study of BI 907828 in combination with BI 754091 and BI 754111 in patients (pts) with advanced solid tumors. *First Author: Anthony W. Tolcher, NEXT Oncology, San Antonio, TX*

Background: Preclinical data show that the combination of a murine double minute 2–tumor protein 53 (MDM2–TP53) antagonist with anti-PD-1 and anti-LAG3 antibodies produces an anti-tumor effect in multiple tumor types. This Phase Ia/Ib study aims to determine the safety, recommended dose for expansion (RDE), and preliminary efficacy of BI 907828, a MDM2–TP53 antagonist, with BI 754091, an anti-PD-1 antibody, and BI 754111, an anti-LAG-3 antibody, in a variety of *TP53* wild-type cancers. **Methods:** In Phase Ia (dose escalation), ~30 pts with a confirmed diagnosis of any unresectable, advanced/metastatic solid tumor, irrespective of *TP53* mutation status, will be enrolled. Pts will receive one dose of BI 907828 every 21 days (Q3W), at a starting dose of 10 mg orally, plus BI 754091 and BI 754111 (240 mg and 600 mg, respectively, Q3W, intravenously). Dose escalation will be guided by a Bayesian Logistic Regression Model with overdose control. The primary endpoint is the maximum-tolerated dose of BI 907828 based on dose-limiting toxicities (DLTs) during the first treatment cycle. Secondary endpoints include pharmacokinetics and DLTs in the treatment period (to determine the RDE). In Phase Ib (dose expansion), pts with previously treated, unresectable, advanced/metastatic *TP53* wild-type tumors with ≥1 measurable target lesion will be enrolled into four expansion cohorts (1: NSCLC; 2: melanoma; 3: well-differentiated/dedifferentiated liposarcoma or undifferentiated pleomorphic sarcoma; 4: hepatocellular carcinoma). The RDE of BI 907828 will be administered with fixed doses of BI754091 and BI 754111 (Q3W). In the NSCLC cohort only, pts will be randomized to one of three arms: RDE of BI 907828 + 240 mg BI 754091 + 600 mg BI 754111 (arm A, 32 pts); 240 mg BI 754091 + 600 mg BI 754111 (arm B, 32 pts); RDE of BI 907828 + 240 mg BI 754091 (arm C, 16 pts). The primary endpoint is objective response (OR, per RECIST 1.1). Secondary endpoints include OR (per iRECIST), disease control (per RECIST 1.1 and iRECIST), progression-free survival (PFS), PFS rate at 12 and 24 weeks (cohort 3), and safety. Phase Ib will include at least 140 evaluable pts (80 pts in cohort 1 and 20 pts each in cohorts 2–4). Clinical trial information: NCT03964233. Research Sponsor: Boehringer Ingelheim.

TPS3661 Poster Session (Board #391), Fri, 8:00 AM-11:00 AM

Trial in progress: A phase Ib study of AMG 510, a specific and irreversible KRAS^{G12C} inhibitor, in combination with other anticancer therapies in patients with advanced solid tumors harboring *KRAS* p.G12C mutation (CodeBreak 101). *First Author: Marwan Fakih, City of Hope National Medical Center, Duarte, CA*

Background: Kirsten rat sarcoma viral oncogene homolog *(KRAS)* p.G12C mutation has been identified as a driver oncogenic mutation in several solid tumors (eg, non-small cell lung cancer [NSCLC], colorectal cancer [CRC]). Development of therapies targeting KRAS^{G12C} has been unsuccessful. AMG 510 is a specific and irreversible small molecule inhibitor of KRAS^{G12C}. A first-in-human clinical trial of AMG 510 monotherapy in patients with *KRAS* p.G12C mutant solid tumors is currently ongoing. AMG 510 in combination with additional anticancer therapies may lead to enhanced antitumor efficacy. This study is a master protocol designed to evaluate multiple investigational regimens of AMG 510 in patients with *KRAS* p.G12C mutant solid tumors. Here, we present two combination cohorts of AMG 510 with a mitogen-activated protein kinase kinase (MEK) inhibitor and an investigational anti-programmed cell death protein-1 (PD-1) therapy, respectively. Additional combination cohorts will be presented at the meeting. **Methods:** This is a phase 1b, open-label study evaluating AMG 510 in combination with a MEK inhibitor or an investigational anti-PD-1 therapy in pts with *KRAS* p.G12C mutant solid tumors. The dose exploration phase (part 1; n=20) will evaluate the safety and tolerability of AMG 510 in combination with the MEK inhibitor or anti-PD-1 therapy; this will be followed by a dose expansion phase (part 2; n=40) to verify the safety and tolerability profile of AMG 510 combination therapies and assess antitumor efficacy. Key eligibility criteria include locally-advanced or metastatic malignancy with *KRAS* p.G12C mutation identified through molecular testing and at least one or multiple lines of prior systemic therapy (eg, ≥2 for advanced/metastatic colorectal cancer). Primary endpoints include dose-limiting toxicities, treatment-emergent or -related adverse events. Secondary endpoints include pharmacokinetic parameters of combination regimens, disease control rate, duration of response, progression-free survival, and duration of stable disease (measured by computed tomography or magnetic resonance imaging and assessed per RECIST 1.1). The study began enrolling pts in December 2019 and is ongoing. For more information, please contact Amgen Medical Information: medinfo@amgen.com. Clinical trial information: NCT04185883. Research Sponsor: Amgen Inc.

TPS3662 Poster Session (Board #392), Fri, 8:00 AM-11:00 AM

First-in-human phase I study of SY-5609, an oral, potent, and selective noncovalent CDK7 inhibitor, in adult patients with select advanced solid tumors. *First Author: Kyriakos P. Papadopoulos, South Texas Accelerated Research Therapeutics, LLC, San Antonio, TX*

Background: SY-5609 is an oral, noncovalent, highly selective and potent inhibitor of cyclin-dependent kinase 7 (CDK7), a key regulator of 2 biological processes that play critical roles in driving tumor development: transcription and cell cycle control. Evaluation of SY-5609 as a single agent in PDX models from a range of solid tumors, including breast, ovarian, lung and colorectal tumors, revealed robust antitumor activity including complete regressions, and activity in models known to be resistant to standard of care therapy. Models with genetic alterations in RB pathway genes demonstrated deep ($>$ 90% TGI) and sustained SY-5609-induced tumor regressions following treatment discontinuation, in contrast to models without genetic alteration in RB pathway genes, suggesting that tumor cells with aberrant cell-cycle control may be particularly sensitive to SY-5609 treatment. The study is designed to evaluate the safety, tolerability, and maximum tolerated dose (MTD) of SY-5609, to characterize the pharmacokinetic (PK), pharmacodynamic (PD), and preliminary antitumor activity of SY-5609, and to explore candidate biomarkers predictive of response to SY-5609. **Methods:** This is a multi-center, open-label Phase 1 trial expected to enroll approximately 60 adult patients with select advanced solid tumors for which standard treatment is no longer effective. The dose escalation phase of the trial is open to adult patients with ovarian, breast, colorectal, or lung cancer, and patients with any solid tumor histology with molecular evidence of deregulated RB cell cycle control. SY-5609 is being administered orally once daily, for each 4-week cycle. Initially, patients will be enrolled into single-patient accelerated titration cohorts; subsequent cohorts will transition to a 3 + 3 design. Following completion of DLT evaluation at a given dose level, additional patients may be enrolled at that dose to further characterize safety, PK, PD, and early clinical activity. Data from this trial will support dose selection for planned evaluations of antitumor activity of SY-5609 as a single agent and in combination. Clinical trial information: NCT04247126. Research Sponsor: Syros Pharmaceuticals.

TPS3663 Poster Session (Board #393), Fri, 8:00 AM-11:00 AM

A phase I, open-label, multicenter, first-in-human study of the safety, tolerability, pharmacokinetics, and antitumor activity of TPX-0022, a novel MET/CSF1R/SRC inhibitor, in patients with advanced solid tumors harboring genetic alterations in MET. *First Author: David S. Hong, Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Alterations in the MET gene, including amplifications, chromosomal translocations, and activating mutations (kinase domain [KD] or exon 14 [Δex14]), occur across various tumors and may function as oncogenic drivers. SRC family kinases function as a key downstream node for MET signaling. CSF1R is a receptor tyrosine kinase associated with tumor progression and suppression of the immune response in the tumor microenvironment. TPX-0022 is a type I kinase inhibitor with a novel macrocyclic structure that potently inhibits MET, CSF1R and SRC to simultaneously target oncogenic MET signaling, its key downstream mediators, and the tumor microenvironment. **Methods:** This is a multicenter phase 1 first-in-human, open-label study to determine the safety, tolerability, PK, and preliminary efficacy of TPX-0022 in adults with advanced solid tumors harboring genetic alterations in MET. TPX-0022 will be administered orally in continuous 28-day cycles. The primary endpoint is the incidence of DLTs and determination of recommended phase 2 dose (RP2D). Secondary endpoints include ORR by blinded independent central review, intra-cranial response rate, PFS and OS (dose expansion only). In the dose escalation portion, ~30 subjects age $\geq$18 with solid tumors harboring MET gene amplifications, Δex14, fusions or KD mutations as determined by local tissue-based or liquid biopsy will be enrolled in a 3+3 design. Intrasubject dose escalation will also be allowed. Once the RP2D has been determined, a food effect sub-study will be conducted and ~80 subjects will be enrolled in a dose expansion portion of the study into the following cohorts: I: non-small cell lung cancer (NSCLC) Δex14 (MET therapy naïve), II: NSCLC Δex14 (MET therapy pre-treated), III: MET amplified NSCLC, gastric, or hepatocellular carcinoma, IV: solid tumors with MET KD mutations or fusions. Correlative studies will include analysis of circulating cell-free DNA to identify genomic alterations that may predict activity of TPX-0022 as well as circulating protein biomarkers such as s-MET, HGF, CSF1 and serum cytokines. The study is open and enrolling in the dose escalation portion at the time of submission. Clinical trial information: NCT03993873. Research Sponsor: Turning Point Therapeutics.

TPS3665 Poster Session (Board #395), Fri, 8:00 AM-11:00 AM

Masterkey-01: Phase I/II, open-label multicenter study to assess safety, tolerability, pharmacokinetics, and antitumor activity of BDTX-189, an inhibitor of allosteric ErbB mutations, in patients with advanced solid malignancies. *First Author: Erika Paige Hamilton, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

Background: A significant unmet need exists for drugs targeting allosteric ErbB mutations (non-canonical mutations outside the ATP binding site). Current EGFR and HER2 tyrosine kinase inhibitors or mAbs have limited antitumor activity against allosteric mutations, resulting in toxicity before adequate drug exposure (Connell and Doherty, 2017). BDTX-189 is a potent and selective orally available irreversible inhibitor targeting unique oncogenic driver mutations of ErbB kinases in EGFR and HER2, while sparing WT EGFR. Preclinical studies demonstrated antitumor activity across a range of allosteric ErbB mutants, including extracellular domain allosteric mutations of HER2 as well as EGFR and HER2 kinase domain exon 20 insertions (Buck, 2019). This first-in-human trial (NCT04209465) is aimed to determine the recommended phase 2 dose (RP2) and schedule (Phase 1, P1), and evaluate the efficacy (Phase 2, P2) of BDTX-189. P1 primary objective is to determine the RP2 dose and schedule of monotherapy BDTX-189. Secondary objectives include assessment of safety, tolerability, pharmacokinetics (PK), pharmacodynamic (PD) effects in tumor, and preliminary efficacy. The P2 primary objective is to assess antitumor activity of monotherapy BDTX-189. **Methods:** The study will enroll patients (pts) $\geq$18 yrs with histologically or cytologically confirmed locally advanced or metastatic solid tumors with no standard therapy available or for whom standard therapy is unsuitable or intolerable. P1 dose-escalation will use a BOIN design (Yuan, 2016) and will enroll $\leq$ 88 pts with allosteric HER2 or HER3 mutation; EGFR or HER2 exon 20 insertion mutation; HER2 amplified or overexpressing tumor; or EGFR exon 19 deletion or L858R mutation. BDTX-189 will be dosed orally (PO) initially QD in 3 wk cycles. Regimen optimization will use PK, PD and safety data and may explore a BID schedule. An expansion cohort of $\leq$12 pts will further evaluate safety and preliminary efficacy of BDTX-189 prior to P2. P2, utilizing a Simon 2-stage design, will enroll $\leq$100 pts with NSCLC with EGFR or HER2 exon 20 insertion mutations (cohort 1); breast cancer with an allosteric ErbB mutation (cohort 2); tumors (except breast) with S310F/Y mutation (cohort 3); and other allosteric ErbB mutations not defined in cohorts 1-3 (cohort 4). Assessments include safety, tolerability, DLTs, evaluation of MTD, PK, PD, and preliminary antitumor activity. Enrollment began 1/2020. Clinical trial information: NCT04209465. Research Sponsor: Black Diamond Therapeutics.