3000 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Belvarafenib, a novel pan-RAF inhibitor, in solid tumor patients harboring BRAF, KRAS, or NRAS mutations: Phase I study.

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Background: Belvarafenib (HM95573/GDC-5573) is an oral type II pan-RAF kinase inhibitor which demonstrates selective anti-tumor activity in several non-clinical cancer models and in cancer patients with RAS- or RAF- mutation. Here we present overall safety and efficacy findings of two phase 1 studies, consisting of dose escalation and dose expansion stages. **Methods:** Patients with advanced solid cancers harboring documented RAS- or RAF- mutation were enrolled. In the dose escalation study, patients were treated with Belvarafenib at a starting dose of 50 mg once daily (QD) to 800 mg BID to assess safety and tolerability and identify the recommended dose (RD). Dose escalation was guided based on pharmacokinetic data and used a traditional 3+3 design. The dose expansion study was comprised of 6 cohorts (according to the type of tumor and RAS- or RAF gene mutation) and patients received the RD of Belvarafenib. The primary objective was to explore anti-tumor activity (per RECIST 1.1) and pharmacodynamic effects. **Results:** The dose escalation study included 72 patients in 9 dose cohorts (cut-off date of 18 Jan 2017). Dose dependent increase in exposures observed up to 650 mg BID. The most common treatment-emergent adverse events that occurred in more than 20% of patients were rash, dermatitis acneiform and pyrexia. A total of 4 DLTs (different kinds of rashes) were reported and included 2 DLTs at the 800 mg BID level. Therefore, 650 mg BID was considered the MTD and 450 mg BID was identified as the RD for Belvarafenib. There were 7 partial responses (3 confirmed PRs) from 200 mg QD to 800 mg BID in NRAS-mutant melanoma, BRAF-mutant melanoma, KRAS-mutant sarcoma, and BRAF-mutant GIST. Four of nine patients with NRAS-mutant melanoma had a PR (ORR 44%). The dose expansion study included 63 patients in 5 indication-specific and basket cohorts administered with 450 mg BID Belvarafenib (cut-off date of 6 Oct 2018). No new safety signal was detected. There were two PRs each in patients with NRAS-mutant melanoma (2/9), BRAF-mutant melanoma (2/6) and BRAF-mutant CRC (2/7), respectively. **Conclusions:** Belvarafenib was well tolerated and exhibited anti-tumor activity in patients with advanced solid tumors harboring RAS or RAF mutations. Belvarafenib is being further investigated in combination with the MEK inhibitor cobimetinib. Clinical trial information: NCT02405065, NCT03118817.

3001 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

A phase I dose escalation (DE) study of ERK inhibitor, LY3214996, in advanced (adv) cancer (CA) patients (pts).

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Background: LY3214996 is a selective and potent ERK1/2 inhibitor that has demonstrated tumor growth inhibition in several pre-clinical tumor models with *BRAF*, *RAS*, or *MAP2K1* mutations. This is the first-in-human Phase 1 Study of LY3214996 in adv CA pts. **Methods:** The goals of this DE study were to determine a recommended Phase 2 dose (RP2D), safety, pharmacokinetic (PK), and preliminary efficacy of LY3214996 (NCT02857270; I8S-MC-JUAB; Eli Lilly & Co.). Pts with adv CA, $\geq$18 yrs of age, ECOG $\leq$1, and with adequate organ function were eligible. Pharmacodynamic (PD) biomarkers including pRSK were evaluated in blood and paired tumor tissue. The DE phase evaluated PO doses using the Bayesian model-based toxicity band method. **Results:** A total of 51 pts with median age of 62 yrs (range: 21-81) received at least 1 dose of LY3214996 with a median of 3 cycles (range: 1-12). Most pts had a mutation in *RAS* (N = 33) or *BRAF* (N = 16) and had a median of 4 prior lines of treatment. The DLTs observed in the study include grade (G) 3 cough and fatigue, G3 dehydration, increased creatinine (Cr), G3 increased CPK, G3 rash $>$ 7 days, and 1 pt with renal failure. TRAEs to LY3214996 occurring in $\geq$10% of pts included nausea, vomiting, diarrhea, dermatitis acneiform, fatigue, pruritus, and blurred vision. LY3214996 exposures increased with dose. Tumor regression was observed in 7 pts with *BRAF*/non-*BRAF* mutant CA including 5 pts who failed prior IO/MAPK inhibitors. Four pts achieved stable disease (2 *BRAF*, 1 *RAS* and 1 *CRAF* mutation) that lasted $>$ 4 mos. Up to 100% pRSK decrease from baseline in tumor was observed. **Conclusions:** LY3214996 had an acceptable safety profile, favorable PK, and potent tumor PD inhibition at RP2D. This supports further exploration of LY3214996 as monotherapy and in combination in CA pts with activating MAPK pathway alterations. Clinical trial information: NCT02857270.

3002 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Dabrafenib and trametinib in patients with tumors with BRAF V600E/K mutations: Results from the molecular analysis for therapy choice (MATCH) Arm H.

April K.S. Salama, Shuli Li, Erin Renee Macrae, Jong-In Park, Edith P. Mitchell, James A. Zwiebel, Helen X. Chen, Robert James Gray, Lisa McShane, Lawrence Rubinstein, David Patton, Paul M. Williams, Stanley R. Hamilton, Deborah Kay Armstrong, Barbara A. Conley, Carlos L. Arteaga, Lyndsay Harris, Peter J. O'Dwyer, Alice P. Chen, Keith Flaherty; Duke University, Durham, NC; E-A Biostatistical Center-Boston, Boston, MA; Columbus Oncology and Hematology Associates Inc, Columbus, OH; Medical College of Wisconsin, Milwaukee, WI; Thomas Jefferson Univ Hosp, Philadelphia, PA; Cancer Therapy Evaluation Program, Bethesda, MD; CTEP National Cancer Institute, Rockville, MD; Dana-Farber Cancer Institute-ECOG-ACRIN Biostatistics Center, Boston, MA; Biometric Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD; National Cancer Institute/Center for Biomedical Informatics & Information Technology, Rockville, MD; Molecular Characterization Laboratory, Frederick National Laboratory for Cancer Research, Frederick, MD; The University of Texas MD Anderson Cancer Center, Houston, TX; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Cancer Diagnosis Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD; Simmons Cancer Center, UT Southwestern Medical Center, Dallas, TX; Cancer Diagnosis Program, National Cancer Institute, Rockville, MD; University of Pennsylvania Abramson Cancer Center, Division of Medical Oncology, Philadelphia, PA; Division of Cancer Treatment and Diagnosis, NCI, NIH, Bethesda, MD; Dana-Farber Cancer Institute/Harvard Medical School and Massachusetts General Hospital, Boston, MA

Background: The NCI-MATCH precision medicine trial assigns patients (pts) with solid tumors, lymphomas, or multiple myeloma with progression on prior treatment to a targeted therapy based on genetic alterations identified in pre-treatment biopsies. Arm H (EAY131-H) evaluated the combination of the BRAF inhibitor (inh) dabrafenib (DAB), and the MEK inh, trametinib (TRM), in pts with BRAF V600E/K mutations. **Methods:** Pts with melanoma, thyroid, or colorectal cancer were excluded. Pts with NSCLC were excluded after the U.S. Food and Drug Administration (FDA) approved DAB/TRM for this indication. Pts received DAB 150 mg po BID and TRM 2 mg PO daily on 28 day cycles until disease progression or intolerable toxicity; restaging was performed every 2 cycles. The primary endpoint was objective response rate (ORR); secondary endpoints included progression-free survival (PFS), 6-month PFS, and overall survival (OS). **Results:** A total of 35 pts were enrolled from 1/2016-2/2018; 2 were ineligible (CrCl below criteria; labs out of window). Over 17 distinct tumor histologies were represented. 58% of pts were female, median age was 63 (range 21-85), 94% were Caucasian, and 48% of pts had received at least 3 prior therapies (range 1- 8). The confirmed ORR was 33.3% (90% CI 19.9%, 49.1%), with a median duration of response (DoR) of 12 months (mon). Varied histologies had a DoR of $>$ 12 mon: histiocytic sarcoma, cholangiocarcinoma and mixed adenoneuroendocrine carcinoma of unknown primary, among others. Median PFS was 9.4 mon; the 6 mon PFS rate was 70.6% (90% CI 58.2%-85.5%), and an additional 10 pts had a PFS $>$ 5.5 mon. Median OS has not been reached. At the time of data cutoff (12/2018) 11 pts continue on treatment. Adverse events (AE) were comparable to previously reported profiles of DAB/TRM; no new AEs were identified. The most frequent grade 3 AEs were fatigue, neutropenia, hyponatremia, hypophosphatemia, and urinary tract infection; there was 1 grade 4 sepsis; no grade 5 AEs. **Conclusions:** In this pre-treated, mixed histology cohort, DAB and TRM showed promising activity outside of currently approved FDA indications warranting further investigations. Correlative analyses are planned. Clinical trial information: NCT02465060.

3003 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Phase 1 study evaluating the safety, tolerability, pharmacokinetics (PK), and efficacy of AMG 510, a novel small molecule *KRAS^{G12C}* inhibitor, in advanced solid tumors.

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Background: The *KRAS^{G12C}* mutation is found in approximately 13% of lung adenocarcinomas and 1–3% of other solid tumors, but there is no approved therapy that targets this mutation. AMG 510 is a novel small molecule that specifically and irreversibly inhibits *KRAS^{G12C}* by locking it in an inactive GDP-bound state. **Methods:** This phase 1, first-in-human, open-label, multicenter study (NCT03600883) is evaluating the safety, tolerability, PK, and efficacy of AMG 510 in adult patients (pts) with locally-advanced or metastatic *KRAS^{G12C}* mutant solid tumors. The primary endpoint is safety; key secondary endpoints include PK, ORR (assessed every 6 weeks [wks]), DOR, and PFS. Key inclusion criteria: *KRAS^{G12C}* mutation identified through DNA sequencing, measurable or evaluable disease, ECOG PS $\leq$2, life expectancy $>$3 months (mo). Key exclusion criteria: active brain metastases, myocardial infarction within 6 mo. A dose exploration will determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D). A dose expansion will enroll pts with NSCLC, CRC, and other advanced solid tumors carrying the *KRAS^{G12C}* mutation. AMG 510 will be given PO until disease progression, intolerance, or withdrawal of consent. **Results:** 22 pts (8 men, 14 women; median age 55.5 y) were enrolled in the first 3 dose cohorts. Tumor types: 6 NSCLC, 15 CRC, 1 other. Most pts (n=17) had $\geq$3 prior lines of treatment (tx). Median tx duration was 28 d (range: 8–134). 5 pts reported 10 treatment-related AEs (grade 1, n=9; grade 2, n=1); there were no DLTs. Tumor response was evaluated in 9 pts (4 with $\geq$2 assessments); 13 pts have not reached their first assessment.1 pt had a PR (NSCLC at wks 6 and 12, tx ongoing), 6 pts had SD (4 CRC and 2 NSCLC; median tx duration 9.7 wks [range: 6.3–19.1], tx ongoing), 2 pts had PD. 20 pts are continuing to receive AMG 510. A second PR (NSCLC at wk 6, tx ongoing) was reported after data cutoff. **Conclusions:** AMG 510 has been well tolerated at the dose levels tested and has shown antitumor activity when administered as monotherapy to patients with advanced KRAS^{G12C} mutant solid tumors. MTD has not been determined, and enrollment into the dose exploration is ongoing. Clinical trial information: NCT03600883.

3004 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

First-in-human phase 1 study of ABBV-085, an antibody-drug conjugate (ADC) targeting LRRC15, in sarcomas and other advanced solid tumors.

George D. Demetri, Jason J. Luke, Antoine Hollebecque, John D. Powderly, Alexander I. Spira, Vivek Subbiah, Dominic W. Lai, Huibin Yue, Sreeneeranj Kasichayanula, Scott Gulbranson, James Purcell, Melinda Myzak, Randy Robinson, Victor Manuel Villalobos, Anthony W. Tolcher; Dana-Farber Cancer Institute and Ludwig Center at Harvard Medical School, Boston, MA; The University of Chicago Medicine, Chicago, IL; Gustave Roussy, Villejuif, France; Carolina BioOncology Institute, Huntersville, NC; Virginia Cancer Specialists, Fairfax, VA; The University of Texas MD Anderson Cancer Center, Houston, TX; Oncology Early Development, AbbVie Inc., Redwood City, CA; University of Colorado, Denver, CO; South Texas Accelerated Research Therapeutics, San Antonio, TX

Background: ABBV-085 is an ADC (conjugated to monomethyl auristatin E, drug:antibody ratio of 2:1) directed against leucine-rich repeat containing 15 (LRRC15), a type 1 transmembrane protein highly expressed on the surface of sarcomas and cancer-associated fibroblasts in stroma of many other cancers. ABBV-085 induced antitumor activity in both *in vitro* and xenograft models of sarcoma. This phase 1, first-in-human, 2-part study assessed the safety/tolerability of ABBV-085 in patients (pts) with advanced solid tumors (NCT02565758). **Methods:** Eligible pts (≥18 yr; advanced solid tumors) received ABBV-085 intravenously in a 3+3 dose-escalation (DE) design; 0.3- to 4.8-mg/kg doses every 2 wk (8 cohorts). Pharmacokinetics (PK) were assessed in cycle 1 and cycle 3. **Results:** As of Dec 2018, 78 pts were enrolled in monotherapy DE and dose-expansion (EXP) cohorts (≤2.7 mg/kg, n = 21; 3.6 mg/kg, n = 45; 4.2 mg/kg, n = 6; 4.8 mg/kg, n = 6); median age: 58 yr (range 21–84); median treatment (Tx) duration: 6.2 wk (range 0.3–54.4). Overall, 77 (98.7%) pts reported ≥1 Tx-emergent adverse events (TEAEs). Fatigue (48.7%) was most common; 19 (24.4%) pts reported grade 1/2 blurred vision (reversible on study discontinuation). Grade ≥3 TEAEs were reported in 56 (71.8%) pts; anemia (14.1%) was the most common. Dose-limiting toxicities occurred at 3.6 mg/kg (n = 1; anemia), 4.2 mg/kg (n = 1; hypertriglyceridemia), and 4.8 mg/kg (n = 2; ileus and nausea); 3.6 mg/kg was chosen as the recommended phase 1b dose (RP1bD). PK exhibited dose-proportional increase in the area under the curve after single-dose administration; half-life was 2.84 days at the RP1bD. Of the 27 sarcoma pts (DE [n = 8]/EXP [n = 19] cohorts; undifferentiated pleomorphic sarcoma [n = 10], osteosarcoma [n = 10], and other sarcomas [n = 7]) treated at the RP1bD, 4 (14.8%) had confirmed partial response (PR; 2 [7.4%] unconfirmed), 8 (29.6%) had stable disease, 11 (40.7%) had progressive disease; 2 (7.4%) were not evaluable. The median duration of response (confirmed responders) was 7.6 mo (95% CI: 5.6–9.2). Updated safety and efficacy data will be reported. **Conclusions:** ABBV-085 was well tolerated with durable PR observed in pts with advanced sarcomas. Clinical trial information: NCT02565758.

3005 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Single agent ONC201 in adult recurrent H3 K27M-mutant glioma.

Isabel Arrillaga, Sylvia Kurz, Ashley Sumrall, Nicholas A. Butowski, Rebecca A. Harrison, John Frederick De Groot, Nicole A. Shonka, Frank S. Lieberman, Yazmin Odia, Rohinton Tarapore, Krystal Merdinger, Joshua E. Allen, Wolfgang Oster, Minesh P. Mehta, Timothy Francis Cloughesy, Andrew S. Chi, Andrew B. Lassman, Tracy Batchelor, Patrick Y. Wen; Massachusetts General Hospital, Boston, MA; NYU Langone Medical Center and School of Medicine, New York, NY; Levine Cancer Institute, Charlotte, NC; University of California, San Francisco, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Nebraska Medical Center, Omaha, NE; University of Pittsburgh Medical Center, Pittsburgh, PA; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; Oncoceutics, Philadelphia, PA; University of California Los Angeles, Los Angeles, CA; Columbia University Irving Medical Center, New York, NY; Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA

Background: H3 K27M-mutant glioma is associated with a poor prognosis and there is no effective therapy following radiation. We report the clinical experience with single agent ONC201, the first small molecule DRD2 antagonist in oncology, in adults with recurrent H3 K27M-mutant glioma. **Methods:** Twenty-nine adult patients with recurrent H3 K27M-mutant glioma have been treated with single agent ONC201 as of January 20, 2019: 19 patients on NCT03295396; 8 patients on NCT02525692; 2 patients on compassionate use protocols under the Sponsor's IND. Median age was 57 years old (range: 17-74), median prior lines of therapy was 2 (range: 1-4) and all patients received prior radiation (median 8.5 months from radiation completion to ONC201 initiation). ONC201 was orally administered at 625 mg weekly, except for one patient dosed once every 3 weeks. **Results:** As of February 5, 2019, 13 of 29 patients remain on-trial within median follow up of 6.5 months (range: 0.6-33.6), 8 patients are alive but off-trial with median follow up of 2.4 months (range: 0.2-9), and 8 patients have expired. Nine of 29 patients (31%) remain progression-free on ONC201 with a median follow up of 6.5 months (range 0.6-33.6). No dose-limiting toxicities or treatment discontinuations due to toxicity occurred. Three patients have experienced durable partial responses by RANO (4.3-28.5 months). In addition, one patient experienced complete regression that continues for $>$ 14 months of all $<$ 1 cm tumor lesions that are not measurable by RANO. Furthermore, 10 patients had a best response of stable disease by RANO, 12 patients experienced progressive disease, and 3 patients are not yet evaluable. Among the patients with a best response of stable disease by RANO, one patient had $>$ 50% tumor regression in the basal ganglia that did not qualify as a partial response by RANO due to a new lesion on a confirmatory scan. Another patient with stable disease by RANO has had 37% tumor regression so far in the brainstem and remains on-treatment for 6 months. All tumor regressions remain durable to date and some were associated with improvements in disease-associated neurological symptoms. **Conclusions:** Single agent ONC201 is well tolerated and clinically active in adult recurrent H3 K27M-mutant glioma patients. Clinical trial information: NCT03295396; NCT02525692.

3006 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Talazoparib beyond BRCA: A phase II trial of talazoparib monotherapy in *BRCA1* and *BRCA2* wild-type patients with advanced HER2-negative breast cancer or other solid tumors with a mutation in homologous recombination (HR) pathway genes.

Joshua James Gruber, Anosheh Afghahi, Alyssa Hatton, Danika Scott, Alex McMillan, James M. Ford, Melinda L. Telli; Stanford University School of Medicine, Stanford, CA; University of Colorado School of Medicine, Aurora, CO; Stanford University School of Medicine, Palo Alto, CA

Background: Talazoparib, a PARP inhibitor, is active in germline *BRCA1/2* mutant advanced HER2-negative breast cancer, but its activity beyond *BRCA1/2* is unknown. We conducted a single institution phase II trial to evaluate talazoparib in patients (pts) with advanced HER2-negative breast cancer or other solid tumors with a germline (g) or somatic (s) alteration in HR pathway genes not including *BRCA1/2*. **Methods:** Eligible pts had measurable disease, lacked a germline or somatic mutation in *BRCA1/2*, received at least one prior therapy for advanced HER2-negative breast cancer or other solid tumor and had a HR pathway gene mutation: *PALB2, CHEK2, ATM, NBN, BARD1, BRIP1, RAD50, RAD51C, RAD51D, MRE11, ATR, PTEN, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL*. Pts with no progression on or within 8 weeks of their last platinum dose were eligible. Pts were treated with talazoparib 1 mg po daily until disease progression. Response was assessed every 8 +/- 1 weeks. If 2 or more responses were observed in 10 pts in stage I, the study would proceed to stage II and enroll 10 additional pts. The null hypothesis of a $\leq$ 5% objective response rate would be rejected if at least 3 of 20 respond. **Results:** Twenty pts were enrolled; 13 breast cancer (12 HR+/HER2-, 1 TNBC) and 7 non-breast cancer (pancreas, colon, uterine, testicular, parotid salivary). Median age was 54 years. Of 12 response evaluable pts with breast cancer, 3 had a RECIST response (ORR = 25%, 2 g*PALB2*, 1 g*CHEK2*/g*FANCA/sPTEN*) and 3 additional pts (g*PALB2*, s*ATR*, s*PTEN*) had SD $\geq$ 6 months (CBR = 50%). No responses were seen in non-breast tumors; 2 (g*CHEK2* testicular, g*ATM* colon) had SD $\geq$ 6 months. Talazoparib was well tolerated; 5 patients required dose reduction for hematologic toxicity. Results of tumor HR deficiency status assessment from metastatic biopsies and serial ctDNA profiling will be presented. **Conclusions:** In this proof-of-concept phase II study, single agent talazoparib demonstrated activity in HER2-negative advanced breast cancer pts with a HR pathway mutation beyond *BRCA1/2*. Further evaluation of talazoparib in this population is warranted. Clinical trial information: NCT02401347.

3007 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

First-in-human trial of the oral ataxia telangiectasia and Rad3-related (ATR) inhibitor BAY 1895344 in patients (pts) with advanced solid tumors.

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Background: The ATR kinase is a key regulator of the DNA damage response (DDR) machinery, activated by DNA damage and replication stress. BAY 1895344 is a novel, potent, and selective ATR inhibitor with anti-tumor activity in preclinical models with DDR defects. **Methods:** Pts with advanced metastatic solid tumors resistant or refractory to standard treatment, with and without DDR defects, received BAY 1895344 BID, 3 days (d) on/4 d off continuously in 3-weekly cycles. **Results:** As of December 20, 2018, 18 pts with colorectal (4), breast (3), prostate (2), and ovarian (2) cancers were enrolled across 6 cohorts (5 mg, 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg BID). Median prior lines of treatment was 5. No dose-limiting toxicities (DLTs) were reported in the 5-40 mg cohorts. 2/3 pts had DLTs in the 80 mg cohort (grade [G] 4 neutropenia, G4 neutropenia and G4 thrombocytopenia) and 2/7 had DLTs in the 60 mg cohort (G4 neutropenia, G2 fatigue). 40 mg BID 3 on/4 off was defined as the maximum tolerated dose. Most common treatment-emergent adverse events included anemia, neutropenia, nausea, and fatigue. Pharmacokinetics appeared dose proportional. Pharmacodynamic analyses showed modulation of pH2AX and/or pKAP1 in paired tumor biopsies at exposures associated with preclinical anti-tumor activity. In 13 pts with and without DDR defects treated at dose levels $\geq$40 mg BID, the objective response rate was 30.7%, including 2/2 pts at 40 mg (appendix and urothelial cancer), 1/8 pts at 60 mg (breast), and 1/3 pts at 80 mg (endometrial). All responders had ATM protein loss of expression and/or *ATM* mutation; median treatment duration was 347 d (range 293-364 d). A *BRCA1*-mutant, olaparib-resistant ovarian cancer pt (60 mg) had a CA125 response and stable disease $>$10 months. 41 additional pts have been enrolled in ongoing expansion cohorts in cancers with DDR defects (prostate, breast, gynecologic, colorectal) or ATM protein loss (all comers) with responses observed. **Conclusions:** The ATR inhibitor BAY 1895344 is tolerated at biologically active doses with anti-tumor activity against cancers with certain DDR defects, including ATM protein loss. Clinical trial information: NCT03188965.

3008 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Phase 1/2 trial of FF-10502-01, a pyrimidine antimetabolite, in patients with advanced cholangiocarcinoma and solid tumors.

Filip Janku, Shiraj Sen, Shubham Pant, Lindsay Bramwell, Vivek Subbiah, Tracey Way, Milind M. Javle, Cassie Stone, Bhumika Prajapati, Shinji Hagiwara, Mary Johansen, Timothy Madden, Gary Maier, Ruth Ann Subach, Kazunori Saeki, Takeaki Suzuki, David S. Wages, Catherine A. Wheeler, Gerald Steven Falchook; The University of Texas MD Anderson Cancer Center, Houston, TX; Sarah Cannon Research Institute, Denver, CO; University of Texas MD Anderson Cancer Center, Houston, TX; FUJIFILM Corporation, Minato-Ku, Tokyo, Japan; FUJIFILM Pharmaceuticals, Cambridge, MA; FUJIFILM Pharmaceuticals U.S.A., Inc., Cambridge, MA; FUJIFILM Pharmaceuticals U.S.A., Inc, Cambridge, MA; FUJIFILM Pharmaceuticals U.S.A., Inc, Brookline, MA; Doc Wages LLC, Southborough, MA

Background: FF10502 is a synthetic pyrimidine nucleoside similar to gemcitabine (gem) with a sulfur in the pentose ring. FF10502 is a more potent inhibitor of DNA polymerase Beta than gem with activity in gem resistant patient (pt) derived xenograft models. FF10502 is avidly taken up into DNA and has greater activity against quiescent cells than gem. **Methods:** Pts $>$ 18 years old with advanced disease who had progressed on standard of care were enrolled into 9 dose levels to determine maximum tolerated dose (MTD) and dose limiting toxicities (DLTs) and subsequently into two expansion cohorts: biliary or solid tumors (ST). FF10502 at doses of 8 to 135 mg/m^2 was administered iv on days 1, 8, 15 of a 28-day cycle until progressive disease or toxicity. PK/PD evaluations were performed on all pts. Response was assessed by RECIST 1.1. **Results:** 76 pts were treated; 35 pts in dose escalation, including 7 cholangiocarcinoma pts. MTD was 90 mg/m2. DLTs included 2 pts with hypotension at 135mg/m^2 (G3 and G4) and 1 pt each with G3 fatigue and G2 rash at 100mg/m^2. In expansion, 19 cholangiocarcinoma, 3 gallbladder and 19 other pts (13 pancreatic, 2 urothelial, and 1 each ovarian, prostate, NSCLC, SCCHN each) were treated. 1 pt with prior rituximab for ITP developed PML. G3 treatment-related low platelets occurred in 3 pts at 90mg/m2 after cycle 1. There were 5 partial responses (PRs), including 4 pts who had progressed on prior gemcitabine: 3 of 26 pts with cholangiocarcinoma, 1 urothelial carcinoma and 1 chondroblastic osteosarcoma. 7 cholangiocarcinoma pts stayed on therapy for $\geq$6 months. FF10502 incorporation intoperipheral blood cellular DNA was seen, andbiomarkeranalysisdata to identify pts with higher potential for clinical response will be presented. **Conclusions:** FF10502 is well tolerated in pts with advanced cancers refractory to standard therapies. Early signals of efficacy warranting further exploration were seen in heavily pretreated cholangiocarcinoma pts (median: 4 prior therapies). Patient selection based on differential effects of FF10502 on DNA polymerases will be explored. Clinical trial information: NCT02661542.

3009 Poster Discussion Session; Displayed in Poster Session (Board #1), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

A phase I study of mirvetuximab soravtansine (IMGN853) and gemcitabine (G) in patients with FOLR1-positive recurrent epithelial ovarian (EOC), endometrial cancer (EC), or triple-negative breast cancer (TNBC).

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Background: IMGN853 is an antibody-drug conjugate targeting the folate receptor alpha (FOLR1), linked to maytansinoid, DM4. IMGN853 has promising single agent activity in FOLR1+ EOC. The recommended phase 2 dose (RP2D) is 6 mg/kg, based on adjusted ideal body weight (AIBW) IV every 3 wks. This study evaluates IMGN853 and G. **Methods:** Patients (pts) with FOLR1+ tumors including: platinum resistant EOC with ≤4 prior chemotherapy (CT) regimens, EC with ≤2 CT and TNBC ≤4 CT are eligible. FOLR1 + is defined as ≥25% of tumor staining (all tumors) ≥2+ intensity (EOC, EC) and ≥1+ (TNBC). A standard 3+3 design combines IMGN853 and G. EOC pts undergo one research biopsy to assess intratumoral vs. circulating DM4 level and biopsy vs. archival tissue FOLR1 expression. Dose-limiting toxicity (DLT) is assessed during cycle 1. Responses as per RECIST 1.1 are assessed at 12 wks. and adverse events (AEs) are evaluated by CTCAE v4.0. **Results:** From 10/2017 to 1/2019 a total of 15 pts. were treated (3 additional pts have consented on dose level [DL] 4):10 EOC, 3 EC and 2 TNBC. One pt. on DL1 had grade (G) 4 thrombocytopenia (PLT) DLT. Three pts were inevaluable for DLT and were replaced: 1 pt. at DL1 with G4 neutropenia without fever of unknown duration due to delayed follow up blood work, 1 pt. at DL2 and 1 pt. at DL3 due to incomplete cycle 1. No DLTs were observed on DL2-3. Day 8 cycle 1 dose modifications were required in 3 of 4 patients on DL3 (for mucositis [1 pt.], and PLT [2 pts]). We are now enrolling at the RP2D for both agents, and MTD will be determined prior to May 2019. **Conclusions:** IMGN853 in combination with G is achievable at clinically relevant doses and the recommended Phase 2 dose and MTD will be reported. Support: NCCN grant; with support from ImmunoGen Corp and Cancer Center Support Grant P30CA033572. Clinical trial information: NCT02996825.

DL	IMGN853 (mg/kg, AIBW) D1q3W)	Gemcitabine (mg/m2, D1D8q3W)	Evaluable/Treated	DLTs	Responses
1	5 mg/kg IV, day 1	600 mg/m^2 IV, d1,8	6/7	1 G4 PLT	3 PR (2 EOC+1 EC)
2	6 mg/kg IV, day 1	600 mg/m^2 IV, d1, 8	3/4	None	1 PR (1 TNBC)
3	6 mg/kg IV day 1	800 mg/m^2 IV, d1, 8	3/4	None	2 PR (2 EOC)
4	6 mg/kg IV, day 1	1000 mg/m^2 IV, d1,8 8	3 consented	-	-

3010 Poster Discussion Session; Displayed in Poster Session (Board #2), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

Phase 1 dose escalation study of XMT-1536, a novel NaPi2b-targeting antibody-drug conjugate (ADC), in patients (pts) with solid tumors likely to express NaPi2b.

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Background: XMT-1536 is a Dolaflexin ADC targeting the sodium-phosphate cotransporter NaPi2b, expressed in ovarian, non-squamous lung, papillary thyroid, endometrial, papillary renal and salivary duct cancers. **Methods:** In this ongoing Phase 1 study, pts with solid tumors likely to express NaPi2b, who progressed on standard therapy, are treated with intravenous XMT-1536 using a 3+3 design with a modified Fibonacci escalation. NaPi2b expression by IHC is being examined retrospectively in archived tumors. Primary objectives in dose escalation are safety and tolerability and determination of maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D). (ClinicalTrials.gov NCT03319628). **Results:** As of Jan. 28, 2019, 36 pts (22 ovarian, 7 endometrial, 4 NSCLC, 3 other) have received treatment with XMT-1536. Treatment was initially given every 3 weeks (q3w); 20 pts were treated in dose cohorts from 3 to 40 mg/m^2. There was one DLT of reversible AST elevation at 40 mg/m^2. The dosing interval was then changed to every 4 weeks (q4w), and dose escalation was restarted at 20 mg/m^2. There was one DLT of reversible AST elevation at 30 mg/m^2 on the q4w schedule. Further followup and dose escalation are ongoing. The most common ($\geq$10% of patients) treatment-related adverse events (TRAEs) have been nausea, fatigue, headache, increased AST, anorexia, increased alkaline phosphatase, fever, increased GGT, myalgia, and vomiting. Grade 3 TRAEs were reversible AST increases in 3 patients and increased GGT, decreased lymphocytes, and systolic congestive heart failure in 1 patient each. Treatment-related serious AEs of fever and systolic congestive heart failure occurred in 1 patient each. Among patients dosed at 20 mg/m^2 or higher who had restaging scans (n=20), there were 2 PR, in ovarian cancer pts at 30 mg/m^2 q3w and 20 mg/m^2 q4w, and 11 SD, with disease control maintained for up to 24 weeks. Patient-level results for NaPi2b expression will be presented. The systemic exposure of total payload showed approximately dose-proportional increase. Plasma concentration of free drug payload and its active metabolite were low. **Conclusions:** XMT-1536 has been well-tolerated up to the 30 mg/m^2 dose level with early signs of anti-tumor activity. Dose escalation continues in pts with advanced solid tumors likely to express NaPi2b. Clinical trial information: NCT03319628.

3011 Poster Discussion Session; Displayed in Poster Session (Board #3), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

Results of the phase 1b study of ABBV-399 (telisotuzumab vedotin; teliso-v) in combination with erlotinib in patients with c-Met+ non-small cell lung cancer by EGFR mutation status.

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Background: Telisotuzumab vedotin (ABBV-399; teliso-v [T]) is a c-Met–targeted antibody and MMAE drug conjugate. Activity of T was shown in late-line c-Met+ non-small cell lung cancer (NSCLC) irrespective of EGFR mutation (M+) status. We present mature data from the T+ erlotinib (E) cohort of a phase 1b study (NCT02099058) by EGFR M+ status. **Methods:** T was administered at 2.4 mg/kg (dose-escalation phase) or 2.7 mg/kg IV Q3W, and E at 150 mg PO QD/prior tolerated dose in adult patients (pts) with advanced NSCLC. Efficacy-evaluable pts were c-Met+ (central lab IHC H-score ≥150 or local lab MET amplification/Ex 14 skipping) and had ≥1 postbaseline scan or discontinued study. EGFR M+ was defined as del19 or L858R by local lab. PK was assessed. **Results:** As of Dec 2018, 42 NSCLC pts received T+E; 37 were c-MET+ (36 evaluable; 35 H-score≥150, 1 MET amplified). Median age was 65 years, 25 pts (69%) had ECOG PS 1, 29 (81%) were EGFR M+ (97% had prior EGFR TKI, 55% 3rd-generation TKI, 69% TKI as last prior therapy, and 62% platinum doublet). All-grade (Gr; ≥20%) adverse events (AEs) were dermatitis acneiform (38%), diarrhea (36%), peripheral motor/sensory neuropathy (52%; 7% Gr 3), dyspnea, fatigue, hypoalbuminemia (31% each), decreased appetite, nausea (24% each), asthenia, vomiting (21% each). Gr ≥3 (≥10%) AE: pulmonary embolism (14%). PK of T+E was similar to single-agent T. The table presents efficacy data. **Conclusions:** These data suggest acceptable safety and promising activity of T+E and support further study in EGFR M+ c-Met+ NSCLC pts for whom frontline EGFR TKI failed. Clinical trial information: NCT02099058.

	EGFR M+ (n = 29)	EGFR non-M+ (n = 7)*
Objective response rate†, % (95% CI)	34.5 (17.9, 54.3)	28.6 (3.7, 71.0)
Complete response, n	1	0
Median duration of response, mo (95% CI)	Not reached (NR) (2.8, not estimable [NE])	NR (NR, NE)
Median progression-free survival (PFS), mo (95% CI)	NR (2.8, NE)	5.9 (1.2, NE)
Median follow-up, mo	4	6
6-mo PFS rate (95% CI)	0.51 (0.30, 0.69)	0.43 (0.10, 0.73)
Median treatment duration, wk (range)		
T	15.4 (3.1–45.1)	18.1 (3.1–39.1)
E	22.9 (3.1–110.4)	12.0 (4.6–42.0)

*EGFR wild-type, mutations other than del19 or L858R, and unknown mutation status.
†RECIST version 1.1.

3012 Poster Discussion Session; Displayed in Poster Session (Board #4), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

A phase 0 first-in-human study using NU-0129: A gold base spherical nucleic acid (SNA) nanoconjugate targeting BCL2L12 in recurrent glioblastoma patients.

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Background: Glioblastoma is a difficult to treat tumor with therapeutics limited by their ability to cross the blood brain barrier. SNAs, *i.e.*, gold nanoparticle cores covalently conjugated with a corona of densely packed, highly oriented siRNA oligonucleotides targeted to the GBM oncogene BCL2L12, represent a novel class of blood-brain and blood-tumor barrier-permeable nanomedicinal conjugates, for suppressing gene expression in the tumors of GBM patients. **Methods:** This is a single-arm, open-label, "window of opportunity" phase 0 first-in-human trial to determine the safety and bioavailability of a novel nano-therapeutic compound, NU-0129. Enrolled patients were treated with intravenous NU-0129 at the dose of 0.04mg/kg. This treatment dosing was considered microdosing defined as 1/50ththe NOAEL (no observed adverse event level) from non-human primate studies. Treatment was followed by tumor resection 8-48 hours later. Primary outcome patient safety and toxicity was monitored weekly for 3 weeks post-infusion. Secondary objectives included biodistribution of NU0129 in tissue, evaluation of pharmacokinetics of NU0129 and the feasibility of NU0129 administration. Exploratory objectives included Bcl2L12 expression and post treatment apoptotic markers as well as progression free survival and overall survival rates. **Results:** 8 patients were enrolled, treated and subsequently underwent surgical resection. No significant treatment related toxicities were seen. Severe ($>$ grade 3) adverse events were observed in two patients: hypophosphatemia (one grade 3, one grade 4) and one patient with grade 3 lymphopenia, all were considered as "possibly related" by treating oncologists. In 6 of the 8 patients sufficient tumor tissue was available for analysis of gold accumulation by ICP-MS (inductively coupled plasma-mass spectrometry), and gold accumulation was seen in the tumor tissue of all 6 of these patients. **Conclusions:** Macrodosing of the nanotherapeutic NU-0129 was well tolerated in glioblastoma patients with no unexpected adverse effects and showed initial evidence of crossing blood brain barrier. Immunohistochemistry for Bcl2L12 expression, apoptotic markers, and PK studies are pending. The demonstration of gold nanoparticles in the tumor tissue validates this approach for drug delivery. Clinical trial information: NCT03020017.

3013 Poster Discussion Session; Displayed in Poster Session (Board #5), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

Phase 1, first-in-human study of TRAIL receptor agonist fusion protein ABBV-621.

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Background: ABBV-621 is a potent tumor-necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor agonist fusion protein that induces apoptotic cell death, particularly in DR4/5 expressing tumor models. **Methods:** Patients (pts) with previously treated solid tumors and ECOG 0–2 were administered ABBV-621 (2.5–15 mg/kg IV) on day (D) 1 (dose level [DL] 1) or D1D8 (DL2 and beyond) of each 21-day cycle. Dose escalation (DE) was guided by a Bayesian continual reassessment method. In addition to PK studies, blood-based PD markers of apoptosis (M30, M65) and drug binding were assessed. **Results:** As of 14 December 2018, 57 pts were enrolled in the DE portion, of which 30% had pancreatic, 23% colorectal cancer, and 47% other tumor types; 13 were KRAS mutant. Median age was 61 yrs. 60% were male; pts had a median of 4 prior regimens (range 1–10). Pts per DL: 2.5 (5 on D1, 16 on D1D8), 3.75 (12), 5 (6), 6.5 (6), 8.5 (4), 11 (4), and 15 mg/kg (4). Median duration of ABBV-621 exposure was 2 cycles (range 1–11). Seven pts had dose-limiting toxicities: respiratory failure (5 mg/kg; Grade 5, the only treatment-related death), blood bilirubin increased (3.75, 6.5 mg/kg), nausea (3.75 mg/kg), fatigue (3.75 mg/kg), increased ALT (2.5, 3.75, 6.5, 15 mg/kg), and increased AST (6.5 mg/kg). Summary of AEs is shown in Table. Clinical trial information: NCT03082209. A partial response (duration 20 weeks) was observed in a pt with pancreatic cancer (2.5 mg/kg D1D8). 27 pts had stable disease (6 pts for $>$ 12 weeks). ABBV-621 PK was linear (mean $\pm$ SD clearance was 1.79 mL/h/kg $\pm$ 0.44) with a terminal half-life of 36.7 $\pm$ 5.55 h (n = 49). ABBV-621 bound to decoy receptors on neutrophils for up to 168 h; the duration of binding was dose-dependent. M30 and M65 increased at 8, 24, and 48 h following ABBV-621, but effect was independent of dose. **Conclusions:** ABBV-621 shows evidence of antitumor activity and effect on blood-based markers of apoptosis, with acceptable toxicity (MTD not reached). NCT03082209.

AEs attributed to ABBV-621 by investigator, n (%)	AEs in ≥5 pts	Grade 3/4 AEs	Serious AEs
Increased ALT	11 (19)	7 (12)	2 (4)
Increased AST	10 (18)	5 (9)	2 (4)
Nausea	10 (18)	1 (2)	0
Diarrhea	7 (12)	1 (2)	0
Stomatitis	7 (12)	0	0
Pyrexia	6 (11)	0	0
Bilirubin increased	5 (9)	2 (4)	3 (5)
Decreased appetite	5 (9)	0	0
Fatigue	5 (9)	1 (2)	0
Vomiting	5 (9)	0	0

3014 Poster Discussion Session; Displayed in Poster Session (Board #6), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

Phase I trial of IACS-010759 (IACS), a potent, selective inhibitor of complex I of the mitochondrial electron transport chain, in patients (pts) with advanced solid tumors.

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Background: A subset of tumors possess genetic or microenvironmental alterations that render cells dependent on mitochondria oxidative phosphorylation (OXPHOS) for survival. IACS, a potent oral selective inhibitor of mitochondrial complex I, showed robust responses in multiple preclinical tumor models, providing strong rationale for clinical testing. **Methods:** Pts with advanced cancers received IACS in increasing dose levels (DL) using 3+3 dose escalation. 7-day QD induction of IACS was followed by maintenance weekly (QW) or twice weekly (BIW) dosing. Phamacokinetics (PK), lactate and pH were assessed serially. Paired tumor biopsies were assessed for pharmacodynamic and predictive biomarkers. **Results:** 18 pts were treated; M/F 16/2; ECOG PS 0/1: 3/15. Mean age 49 (23-69) yrs. Tumors comprised advanced colorectal (n = 4), castration resistant prostate cancer (CRPC) (n = 3), pancreatic (n = 2), other cancers (n = 9). DL1: 2mg QD 7 days induction/0.5mg QW maintenance (n = 3); DL2: 2.5mg QD 7 days/ 1mg QW (n = 3); DL3: 3mg QD 7 days/3mg QW (n = 3); DL4: 2.5mg QD 7 days/2.5mg BIW (n = 4); DL5: 2mg QD 7 days/2mg BIW (n = 5). IACS was well tolerated with 12 (67%) pts reporting G1-2 IACS related toxicities, such as raised lactate (n = 10), nausea (n = 8), fatigue (n = 7), vomiting (n = 5), myalgia (n = 4) and peripheral neuropathy (n = 4). 1 pt in DL3 and 2 pts in DL4 had ≥G3 IACS related toxicities, such as nausea (n = 2), vomiting (n = 1), raised lactate (n = 1), dehydration (n = 1), visual changes (n = 1), and peripheral neuropathy (n = 1). Raised lactate was not associated with acidosis. DL5 is now being expanded to assess the maximum tolerated dose (MTD). PK showed good oral bioavailability, with long $T_{1/2}$ and low intrapatient variability. Cmax = 14nM on Day 7 at the end of DL5 induction phase, confirming biologically active doses. 7 pts had best response of RECIST stable disease. A pt with heavily pretreated CRPC achieved RECIST partial response with resolution of CRPC related pain. **Conclusions:** IACS is well tolerated with preliminary evidence of antitumor activity. MTD expansions include CRPC, TNBC, pancreatic cancer and molecularly selected (ENO1 loss; *SMARCA4* mutation) tumor cohorts. Clinical trial information: NCT03291938.

3015 Poster Discussion Session; Displayed in Poster Session (Board #7), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

Phase I study of CC-90010 in patients with advanced solid tumors and relapsed/refractory non-Hodgkin lymphoma (R/R NHL).

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Background: Bromodomain and extra-terminal (BET) proteins are epigenetic readers that control expression of genes involved in cell growth and oncogenesis. CC-90010 is an oral, potent and reversible BET inhibitor that showed promising activity in lymphoma and solid tumor cell lines and reduced tumor growth in xenograft models. **Methods:** CC-90010-ST-001 (NCT03220347; 2015-004371-79) is a phase I, first-in-human study of CC-90010 in patients (pts) with advanced solid tumors and R/R NHL. Three schedules and 11 dose levels were evaluated (Table). Primary objectives were to determine safety, maximum-tolerated dose and/or recommended phase II dose (RP2D). Secondary objectives were the identification of early activity signals, pharmacokinetics and pharmacodynamics (PD). **Results:** As of 10 Dec 2018, 69 pts were enrolled, 67 with solid tumors and 2 with R/R NHL. Data shown are from all pts (N = 69). The median age was 57 y (range, 21–80), 38 (55%) were male, and the median number of prior systemic anticancer regimens was 3 (range, 1–9). The RP2Ds were dose cohorts 3A and 4B. Dose-limiting toxicities (n = 6) occurred in dose cohorts 3A, 3C, and 4B. Grade 3/4 treatment-related adverse events (TRAEs) occurred in 17 pts (25%), most commonly (≥2 pts) thrombocytopenia (7%), platelet count decreased (4%), fatigue (3%), and increased alanine aminotransferase (3%). No deaths from toxicity occurred. Two pts (endometrial carcinoma and astrocytoma) had a partial response (PR); 1 occurred after the data cutoff. Seven pts had prolonged stable disease (SD) > 9 mo. Exposures and PD marker regulation increased with dose in each dosing schedule; terminal half-life was ~ 73 h. **Conclusions:** Most of the TRAEs observed were mild or moderate in severity, reversible, and manageable by dose adjustments and/or supportive care. Promising ongoing anticancer activity with prolonged SD and PRs were observed. The preliminary clinical data provide the rationale for dose expansion of CC-90010 in pts with selected advanced malignancies. Clinical trial information: NCT03220347.

Dose Level:	1 (n = 7)	2 (n = 7)	3A (n = 4)	3B (n = 6)	3C (n = 6)	4A (n = 7)	4B (n = 7)	4C (n = 7)	5A (n = 6)	5B (n = 6)	5C (n = 6)
Dose, mg	15	15	25	30	15	40	45	25	30	55	35
Schedule, days on/off	3/4	3/11	3/11	4/24	2/5	3/11	4/24	2/5	3/11	4/24	2/5

3016 Poster Discussion Session; Displayed in Poster Session (Board #8), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

Design and development of the molecular analysis for Therapy Choice (NCI-MATCH) Designated Laboratory Network.

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Background: NCI-MATCH is a precision medicine trial that assigns treatment to refractory cancer patients by tumor mutation profile rather than by histology. After screening fresh tumor biopsies from nearly 6000 patients many treatment arms did not meet accrual due to the low prevalence of the eligible variants. NCI MATCH developed an approach to identify patients for the remaining arms utilizing a network of academic and commercial CLIA-certified labs that perform NGS assays as routine care at MATCH participating sites. **Methods:** Candidate labs were recruited through a notice in the Federal Register and posted on the NCI and ECOG ACRIN web sites. Twenty-seven labs (17 academic/10 commercial) submitted applications. After acceptance each lab analyzed a common set of 10 DNAs extracted from 8 cell lines and 2 clinical samples for concordance with the central NCI-MATCH NGS assay. **Results:** For the 17 labs with concordance results, a median of 8 (range 2 – 58) copy number variants (CNVs) were evaluated by the NGS assay of each DL, with the number evaluated depending on each lab's clinical assay panel content. CNV concordance between central and DL assays, as measured by positive percent agreement (PPA), averaged 98.7% (range 87.5% - 100%) with the central assay as referent and 94.1% (range 77.8% – 100%) with the DL assay as referent. For single nucleotide variants (SNVs) and Insertion/deletions (Indels) combined, a median of 19 variants (range 11 – 26) were evaluated by each DL for concordance. PPA between central and DL assays averaged 98.0% (range 87.5% – 100%) and 98.6% (range 90.0% – 100%) with central and DL assay as referents, respectively. Strong correlations were observed between central and DL assays for both CNVs (median r = 0.93; 0.33 – 1.00) and SNV/Indels (median r = 0.98; 0.67 – 0.99). **Conclusions:** Our results suggest that different NGS assay platforms using diverse strategies for target enrichment and data analysis may still achieve high concordance if pre-analytical variables are minimized and the common genomic regions interrogated by each assay are well-understood. The designated lab network allows for a wider search for rare variants in tumors and provides a model for conducting future clinical trials. Clinical trial information: NCT02465060.

3017 Poster Discussion Session; Displayed in Poster Session (Board #9), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

Efficacy of entrectinib in patients (pts) with solid tumors and central nervous system (CNS) metastases: Integrated analysis from three clinical trials.

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Background: Entrectinib potently inhibits kinases encoded by the *NTRK* and *ROS1* genes. It achieves therapeutic levels in the CNS with antitumor activity in intracranial tumor models. We report integrated data (31 May 2018 cut-off) from 3 Phase 1/2 entrectinib trials (ALKA-372-001, EudraCT 2012-000148-88; STARTRK-1, NCT02097810; STARTRK-2, NCT02568267) for a large cohort of adults with *ROS1* fusion-positive NSCLC (*ROS1*+) or *NTRK* fusion-positive solid tumors (*NTRK*+), with/without baseline CNS metastases. **Methods:** Pts had locally advanced/metastatic *NTRK*+ or *ROS1*+ tumors by nucleic acid-based confirmation. Baseline CNS metastases were identified by CT/MRI. Tumor assessments were at wk 4, then every 8 wk by blinded independent central review (RECIST v1.1). Primary endpoints: ORR, DOR. Secondary endpoints: CBR, PFS, OS, intracranial efficacy and safety. **Results:** Most pts had ≥1 prior therapy; 33% had baseline CNS metastases. Outcomes for the *ROS1*+ NSCLC (n = 53) and *NTRK*+ solid tumors (n = 54; 24% sarcoma, 18% NSCLC) efficacy evaluable data sets are shown (table). Entrectinib was tolerable with a manageable safety profile; most treatment-related AEs were grade 1–2. **Conclusions:** Entrectinib induced clinically meaningful durable responses in pts with *ROS1*+ NSCLC or *NTRK*+ solid tumors with or without CNS disease. Clinical trial information: NCT02097810; NCT02568267.

	ROS1+ (N = 53)		*NTRK*+ (N = 54)	
	Baseline CNS disease status			
	No (n = 30)	Yes (n = 23)	No (n = 42)	Yes (n = 12)
ORR, % (95% CI)	80.0 (61.4, 92.3)	73.9 (51.6, 89.8)	59.5 (43.3, 74.4)	50.0 (21.1, 78.9)
Complete response, n (%)	3 (10.0)	0	4 (9.5)	0
Partial response, n (%)	21 (70.0)	17 (73.9)	21 (50.0)	6 (50.0)
DOR*	24.6 (11.4, 34.8)	12.6 (6.5, NE)	12.9 (7.1, NE)	NE (4.2, NE)
CBR, % (95% CI)	80.0 (61.4, 92.3)	73.9 (51.6, 89.8)	61.9 (45.6, 76.4)	75.0 (42.8, 94.5)
PFS*	26.3 (15.7, 36.6)	13.6 (4.5, NE)	12.0 (8.7, 15.7)	7.7 (4.7, NE)
OS*	NE	NE (10.5, NE)	20.9 (16.8, NE)	14.3 (51, NE)
Intracranial	NE		NE	
ORR, % (95% CI)		55.0 (31.5, 76.9)[a]		54.5 (23.4, 83.3)[b]
DOR*		12.9 (5.6, NE)		NE (5.0, NE)
PFS*		7.7 (3.8, 19.3)		14.3 (5.1, NE)

*Median, months (95% CI). ORR, objective response rate; DOR, duration of response; CBR, clinical benefit rate; PFS, progression-free survival; OS, overall survival; NE, not evaluable
[a]n = 20; [b]n = 11

3018 Poster Discussion Session; Displayed in Poster Session (Board #10), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

Genome-wide cell-free DNA fragmentation profiling for early cancer detection.

Alessandro Leal, Stephen Cristiano, Jillian Phallen, Jacob Fiksel, Vilmos Adleff, Daniel C. Bruhm, Sarah Østrup Jensen, Jamie E. Medina, Doreen N. Palsgrove, Noushin Niknafs, Valsamo Anagnostou, Patrick M. Forde, Julie R. Brahmer, Remond Fijneman, Julia S. Johansen, Hans J. Nielsen, Gerrit A. Meijer, Claus Lindbjerg Andersen, Robert B. Scharpf, Victor E. Velculescu; Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Johns Hopkins Medical Institutions, Baltimore, MD; The Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Aarhus University Hospital, Aarhus, Denmark; Johns Hopkins Kimmel Cancer Center and Bloomberg-Kimmel Institute for Cancer Immunotherapy, Baltimore, MD; Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins, Baltimore, MD; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Oncology, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark; University of Copenhagen, Hvidovre, Denmark; Department for Molecular Medicine, Aarhus University Hospital/Skejby, Århus N, Denmark

Background: Analyses of cell-free DNA (cfDNA) in the blood provide a noninvasive diagnostic avenue for patients with cancer. However, cfDNA analyses have largely focused on targeted sequencing of specific genes, and the characteristics of the origins and molecular features of cfDNA are poorly understood. We developed an ultrasensitive approach that allows simultaneous examination of a large number of abnormalities in cfDNA through genome-wide analysis of fragmentation patterns. **Methods:** We used a machine learning model to examined cfDNA fragmentation profiles of 236 patients with largely localized breast, colorectal, lung, ovarian, pancreatic, gastric, or bile duct cancer and 245 healthy individuals. Estimation of performance was determined by ten-fold cross validation repeated ten times. **Results:** cfDNA profiles of healthy individuals reflected nucleosomal patterns of white blood cells, while patients with cancer had altered fragmentation patterns. The degree of abnormality in fragmentation profiles during therapy closely matched levels of mutant allele fractions in cfDNA as determined using ultra-deep targeted sequencing. The sensitivity of detection ranged from 57% to $>$ 99% among the seven cancer types at 98% specificity, with an overall AUC of 0.94. Fragmentation profiles could be used to identify the tissue of origin of the cancers to a limited number of sites in 75% of cases. Combining our approach with mutation-based cfDNA analyses detected 91% of cancer patients. **Conclusions:** This effort is the first study to demonstrate genome-wide cell-free DNA fragmentation abnormalities in patients with cancer. Results of these analyses highlight important properties of cfDNA and provide a facile approach for screening, early detection, and monitoring of human cancer.

3019 Poster Discussion Session; Displayed in Poster Session (Board #11), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

Multimodality liquid biopsy for early monitoring and outcome prediction in first-line metastatic HER2-negative breast cancer: Final results of the prospective cohort from the French Breast Cancer InterGroup Unicancer (UCBG)— COMET study.

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Background: Circulating Tumor Cells (CTC) are independent markers of progression-free survival (PFS) and overall survival (OS) in patients (pts) with metastatic breast cancer (MBC). Monitoring circulating tumor DNA (ctDNA) can detect mutation associated with resistance to treatment and its variations reflect changes in tumor burden. We prospectively monitored CTC, Circulating Endothelial Cells (CEC), serum markers and ctDNA during first line chemotherapy for MBC. **Methods:** The French cohort COMET is a prospective study including first line HER2 negative pts receiving weekly paclitaxel and bevacizumab . Blood samples were obtained at baseline (BL) and before the second cycle of chemotherapy (C2).We present here the final planned analysis. **Results:** From 09/2012 to 11/2014, 286 patients were included: 198 for ctDNA, 251 for CEC and 283 for CTC. Median age was 56 years and 23% of pts had triple negative BC. At baseline, 71% of pts had $\geq$1 detectable CTC per 7.5 ml of blood (median 4 CTC, range 1- 30,000). With a threshold of $\geq$5 CTC, 49% of pts were positive at baseline and 22% at C2. For ctDNA, out of the first 196 pts analyzed, 147 had at least one somatic mutation (SNV) detected in plasma (75%). The average number of mutations per pt was 2.4 (range 1 to 9). Most commonly mutated genes were TP53 and GATA3. ESR1 was mutated in 10.6% of the pts and restricted to the ER+ subgroup. PIK3CA was mutated in 23.2% of the pts. Median Allelic Frequency was 9.1% . Only 68 pts (36%) had detectable ctDNA at C2. At baseline, CTC and ctDNA levels were correlated ($r = 0.40$, $p < 0.0001$). Despite no complete overlap, 24 pts (12%) had no CTC nor ctDNA detected at baseline. Median follow-up was 53 months and median OS was 32 months. Detectable CTC and ctDNA at baseline and at C2 were significantly associated with decreased PFS and OS. CEC and serum markers level had no prognostic value. At multivariate analysis, triple negative status, detectable ctDNA at C2, CTC $\geq$5 at C2 and grade 3 on primary tumor were independent prognostic factors. **Conclusions:** This is the largest prospective cohort assessing the respective prognostic values of early CTC and ctDNA changes in homogenously treated first line MBC pts. Early decrease of CTC and ctDNA after one cycle of chemotherapy are independent predictive markers of favorable outcome, with a stronger value for ctDNA compared to CTC. Clinical utility of early ctDNA variations monitoring and changes in mutation profile remain to be demonstrated. Clinical trial information: NCT01745757.

3020 Poster Discussion Session; Displayed in Poster Session (Board #12), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:30 PM

Circulating androgen receptor (AR) gene amplification and resistance to 177Lu-PSMA-617 in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): Results of a phase II clinical trial.

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Background: Plasma *AR* gain is associated with poor prognosis in mCRPC pts treated with abiraterone/enzalutamide, however these pts could benefit from docetaxel (Conteduca et al, Eur Urol 2019). In a phase 2 clinical trial with 177Lu-PSMA-617 in mCRPC pts who progressed after standard survival-prolonging treatments, we aimed to determine if plasma AR gene status enable early assessment of 177Lu-PSMA-617 activity for mCRPC. **Methods:** Between April 2017 and November 2018, 43 mCRPC pts were treated with 177Lu-PSMA-617 in a phase 2 study. Pts younger than 75 years and not heavily pretreated received 5.5 GBq of 177Lu-PSMA-617, while other pts received 4.2 GBq per cycle, for a total of 4-6 cycles, q8 weeks. We determined AR copy number by droplet digital polymerase chain reaction (ddPCR) on pretreatment plasma samples. We evaluated associations between plasma *AR* amplification and PSA response ($\geq$50% PSA decline from baseline) and imaging response/progression (as measured by bone scan, CT, and PSMA PET/CT). Logistic regression was used to estimate the odds ratio (OR) and 95% confidence intervals (95% CI) in order to evaluate the independent relevance of *AR* status and pts without PSA response and those with early progressive disease defined as treatment interruption occurring within 4 months of the start of 177Lu-PSMA-617. **Results:** Forty of 43 pts (median age: 72 years, range 54-86) were fully evaluable for this analysis. A PSA response was reported in 15 (37.5%) of the 40 pts, 3 of 15 (20%) with AR gene gain, and 12 of 25 (48%) with no gain (P = 0.080). Early progressive disease was observed in 17 (42.5%) of the 40 pts, 12 of 15 (80%) with *AR* gene gain and 5 of 25 (20%) with no gain (P = 0.0002). The OR for pts without PSA response (decline $<$ 50%) having AR gain was 3.69, 95% CI 0.83-16.36, p = 0.085. The OR for pts with early PD having *AR* gain was 16.00, 95% CI 3.23-79.27, p = 0.0007. The evaluation of germline alterations in DNA damage repair (DDR) genes is ongoing (i.e., BRCA2, BRCA1, ATM). **Conclusions:** Plasma *AR* status assessment using ddPCR identifies mCRPC resistant to 177Lu-PSMA-617. These data suggest potential better activity of 177Lu-PSMA-617 in earlier phases of prostate cancer. Prospective evaluation of treatment decision making based on plasma AR status is warranted. Clinical trial information: NCT03454750.

3021 **Poster Session (Board #13), Sat, 8:00 AM-11:00 AM**

A phase I study of pazopanib with weekly paclitaxel and carboplatin in advanced solid tumors.

Nancy Chan, Daniella E. Portal, Rebecca Anne Moss, Ann W. Silk, Mark N. Stein, Joseph Aisner, Jyoti Malhotra, Weichung Shih, Hongxia Lin, Michael P. Kane, Janice M. Mehnert, Antoinette R. Tan; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Levine Cancer Institute, Atrium Health, Charlotte, NC

Background: Pazopanib (pazo) is an oral tyrosine kinase inhibitor of VEGFR, PDGFR and c-Kit. It is a weak inhibitor of CYP3A4 and CYP2C8 and may decrease paclitaxel (P) clearance. Daily pazo with P and carboplatin (C) every 21 days was not feasible on a previous study. We hypothesized that pazo dosed intermittently and on a different day from P and C may be tolerable. We sought to determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and pharmacokinetics (PK) of pazo with weekly P and C. **Methods:** Using a 3+3 standard design, a schedule of P 60-80 mg/m^2 and C AUC2 on days 1, 8, and 15 with pazo 400-800 mg on days 2-5, 9-12, and 16-26 on a 28-day cycle was evaluated. Pazo alone could be continued if P and C were omitted due to maximal benefit or toxicity. PK was collected during cycles 1 and 2. **Results:** 34 patients (pts) were treated over 6 dose levels (Table). Mean age 57 (37-79). Tumor types: breast (22), lung (3) and other (9); 27 had prior platinum. Delay in starting cycle 2 due to grade 3 neutropenia was a DLT at dose level 2 and 5. Pts on 5A missed dosing during C1 and C2 due to neutropenia and required subsequent growth factor, and this was deemed unlikely to be sustainable long-term. All grade toxicities included anemia (62%), neutropenia (59%), and thrombocytopenia (56%). Protocol-defined MTD was not determined. PK analysis showed a dose proportional increase in pazo concentration, consistent with previous reports. Pazo did not alter the PK of C. C_{max} of P was higher C2D1 vs C1D1; mean C_{max} ratio between C2D1:C1D1 was 1.63 (95% CI:1.29-1.96). There were 11 objective responses (3 CRs, 8 PRs). Five breast pts were on pazo alone for a median of 9 cycles (2-52) with CR (2), PR (2) and SD (1); a squamous cell of unknown primary in CR received 22 cycles. Clinical trial information: NCT01407562. **Conclusions:** PK confirm that pazo is a weak inhibitor of CYP3A4 and CYP2C8. Myelosuppression was a major adverse event at all dose levels. MTD was not determined. Antitumor activity was achieved with this alternate combination schedule and sustained responses from sequential pazo monotherapy was observed.

Dose Level	Paclitaxel	Carboplatin	Pazopanib	No. of Pts	No. of Pts with DLT
1	60 mg/m^2	AUC 2	400 mg	3	
2	60 mg/m^2	AUC 2	600 mg	9	1
3	70 mg/m^2	AUC 2	600 mg	7	
4	70 mg/m^2	AUC 2	800 mg	4	
5	80 mg/m^2	AUC 2	800 mg	8	1
5A	80 mg/m^2	AUC 2	600 mg	3	

3022 **Poster Session (Board #14), Sat, 8:00 AM-11:00 AM**

Exceptional responders to abexinostat (ABX) plus pazopanib (PAZ) in pretreated renal cell carcinoma (RCC) and other solid tumors: Long-term follow-up of a phase 1b study.

Rahul Raj Aggarwal, Scott Thomas, Nela Pawlowska, Jennifer A. Grabowsky, Susan Calabrese, Phu Lam, Kathleen Comerford, Daphne Bautista, Pamela N. Munster; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; University of California San Francisco, San Francisco, CA; UC San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; UC San Francisco, San Francisco, CA

Background: We previously reported the initial phase 1b study results of PAZ + ABX, a potent pan-HDAC inhibitor, demonstrating acceptable toxicity profile and encouraging anti-tumor activity (Aggarwal et al. JCO 2017). We report the long-term follow up of exceptional responders and additional correlative analyses associated with clinical outcomes. **Methods:** Key efficacy endpoints included objective response rate and duration of response. Peripheral blood histone acetylation, HDAC expression, and plasma VEGF levels were analyzed and associated with clinical outcomes. **Results:** 51 pts (RCC subset; N = 22) were enrolled between June 2012 and October 2015. 10 pts (20%) had experienced disease progression on prior PAZ; 59% had received any prior VEGF-targeting therapy. 9 evaluable pts (18%) (N = 6 RCC; 2 thyroid; 1 mesothelioma) achieved partial tumor response (PR), of which 6 had prior progression on VEGF-targeting therapy. 7/10 (70%) of pts with prior disease progression on PAZ monotherapy had reduction in tumor burden on study. The median duration of response was 9.1 months (range 1.2 to 70+), and clinical benefit rate (PR or stable disease $>$ 6 months) was 33%. Five treatment-refractory pts achieved durable PRs lasting for $>$ 2 years duration, and one previously PAZ-refractory patient with RCC remains on treatment with ongoing PR for $>$ 6 years. Higher HDAC2 expression was associated with prolonged progression-free survival (median PFS 5.9 vs. 3.5 months, log-rank p = 0.02). Induction of histone acetylation on ABX lead-in treatment was associated with subsequent time to progression (p = 0.002). On-treatment plasma VEGF levels were inversely correlated with PBMC histone acetylation (p = 0.02). **Conclusions:** Markedly durable responses with PAZ + ABX are achievable, including in pts with PAZ- and VEGF-refractory RCC and other solid tumor malignancies. Host factors including HDAC expression and acetylation status may identify those most likely to benefit. A randomized phase 3 study is underway of PAZ + ABX as a first- or second-line therapy in pts with locally advanced or metastatic RCC (RENAVIV; NCT03592472). Clinical trial information: NCT01543763.

3023 **Poster Session (Board #15), Sat, 8:00 AM-11:00 AM**

Phase 1a study results investigating the safety and preliminary efficacy of ABL001 (NOV1501), a bispecific antibody targeting VEGF and DLL4 in metastatic gastrointestinal (GI) cancer.

Jeeyun Lee, Seung Kim, Su Jin Lee, Se Hoon Park, Joon Oh Park, Eunsin Ha, Doo-Hong Park, Neunggyu Park, Hoon-Kyo Kim, Sang Hoon Lee, Weon-Kyoo You, Ho Yeong Lim, Young Suk Park, Won Ki Kang; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; National OncoVenture, Goyang, South Korea; National Oncoventure, Goyang, South Korea; National OncoVenture, National Cancer Center, Goyang, South Korea; National OncoVenture, National Cancer Center, Korea, Goyang, South Korea; ABL Bio, Goyang, South Korea; ABL Bio Inc., Seoul, South Korea; Samsung Medical Center, Sungkyunkwan University, Seoul, South Korea

Background: Antiangiogenic therapy has been a successful clinical strategy for the treatment of various cancer types. To date, all approved antiangiogenic drugs primarily inhibit the VEGF/VEGFR pathway. Delta-like ligand 4 (DLL4) has been identified as a potential drug target in VEGF-independent angiogenesis. A dual blockade of both VEGF and DLL4 could be a promising strategy to overcome anti-VEGF therapy resistance. ABL001 (NOV1501) has been developed as a bispecific antibody to bind and inhibit both DLL4 and VEGF thereby significantly suppressing tumor angiogenesis. **Methods:** In a classical 3+3 dose-escalation design, ABL001 was administered IV at doses ranging from 0.3, 1, 2.5, 5, and 7.5 mg/kg biweekly (NCT03292783: the next doses of ABL001 are 10 and 12.5 mg/kg). After the first administration of ABL001 in each cohort, DLT (dose limiting toxicity) was observed for 3 weeks. Tumor assessments were performed every 6 weeks and cardiac assessments were performed every cycle. **Results:** From 2017 November to February 2019, 18 patients were enrolled on this trial. All patients were heavily pre-treated with at least 3 prior lines of chemotherapy. All patients in cohort 4 and 5 were either metastatic colorectal cancer or gastric cancer. Of the 5 cohorts, there was no DLT observed during dose escalation. In addition, there was no maximum tolerated dose identified up to 7.5 mg/kg dose. The most common treatment-related adverse events (AEs) (including all dose levels and all grades) occurred were hypertension, anorexia, general weakness, headache and anemia. Preliminary results of pharmacokinetic (PK) analysis demonstrated slightly shorter mean half-life than conventional monoclonal tantibodies due to the bispecific nature of the ABL-001. In addition, preliminary pharmacodynamic (PD) biomarker analysis using PBMC and plasma samples showed engagement of both VEGF/VEGFR and DLL4/Notch1 pathway modulation after ABL001 administration. One gastric cancer patient at 7.5 mg/kg achieved unconfirmed partial response at the time of this writing. **Conclusions:** ABL001 therapy has been well tolerated up to 7.5 mg/kg with no significant treatment related adverse events and showed preliminary anti-tumor activity in heavily pre-treated cancer patients. After completion of this ongoing phase 1a study, phase 1b/2a study is planned in combination of ABL001 with chemotherapy or anti-PD-1 antibody. Clinical trial information: 03292783.

3024 **Poster Session (Board #16), Sat, 8:00 AM-11:00 AM**

The dynamic detection of drug area under curve (AUC) guides clinical usage of docetaxel in solid tumors.

Yan Zhang, Yuan Wu, Xiaomei Zhang, Deliang Yang, Bo Shen, Geyu Liang, Martin Qi; Internal Medicine-Oncology, Jiangsu Cancer Hospital, The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, China; Research Section, Jiangsu Cancer Hospital, The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, China; School of Public Health, Southeast University, Nanjing, China; The Medical Department, 3D Medicines Inc., Shanghai, China

Background: The dosage of most chemotherapy drugs were performed based on the patients' body surface area (BSA), including docetaxel (DTX). Previous studies showed that this conventional administration of DTX might cause adverse event, such as neutropenia, and neutropenia was proved to associate with DTX area under curve (AUC). This study was designed to evaluate the effect of dose-administration of DTX based on dynamic detection of DTX AUC on clinical outcomes. **Methods:** A total of 209 patients with DTX chemotherapy (one cycle every 3 weeks) were enrolled, and all patients received 2-6 cycles of treatment. In the first cycle, dosage of DTX based on BSA was administrated in all study population. From the second cycle, one group patients (control group) received DTX according to traditional BSA and the other group patients (experimental group) on the basis of dynamic detection of DTX AUC. The primary outcome was incidence rate of neutropenia and the second outcome was disease control rate (DCR). **Results:** Patients with grade 3 or higher neutropenia from the fourth to sixth cycle of DTX chemotherapy were significantly lower in the experimental group compared with the control group (P= 0.039, 0.012, and 0.001, respectively). In the experimental group, compared with the first cycle, and the number of patients falling within the therapeutic window increased by 27.19% in the sixth cycle after dose adjustment according to the AUC value of previous cycle. The DCR in the experimental and control group is 85.32% and 72.00%, respectively (P= 0.018). **Conclusions:** The administration method based on dynamic detection of AUC of DTX could significantly reduce incidence rate of neutropenia and received a higher DCR, but the result needed to be confirmed in further studies.

3025 **Poster Session (Board #17), Sat, 8:00 AM-11:00 AM**

A polymorphism within the mismatch repair gene predicts prognosis and adjuvant chemotherapy benefit in gastric cancer patients.

Deqiang Wang, Deyu Chen, Bo Shen, Xiaofeng Chen, Mingzhe Xiao, Xiaoqin Li, Yongqian Shu; Department of Medical Oncology, Cancer Therapy Center, Affiliated Hospital of Jiangsu University, Zhenjiang, China; Department of Radiotherapy, Cancer Therapy Center, Affiliated Hospital of Jiangsu University, Zhenjiang, China; Department of Medical Oncology, The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, P.R. China, Nanjing, China; Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; The Medical Department, 3D Medicines Inc., Shanghai, P.R. China, Shanghai, China; Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, P.R. China, Nanjing, China

Background: Radical surgery with subsequent adjuvant chemotherapy was effective treatment for early-stage gastric cancer (GC) patients. Unfortunately, after optimal multimodality therapy, up to 30% to 40% of patients undergoing resection will relapse within 5 years. There are no validated prognostic and predictive biomarkers for GC patients who receive adjuvant chemotherapy, and current patient selection is based mainly on postoperative pathological staging. Defective mismatch repair (MMR) or microsatellite instability (MSI) may affect GC outcome. Polymorphisms of MMR genes with a low-penetrant effect can cause heterogeneous MMR capability among individuals. It is not known about the impact of these polymorphisms on GC outcome. **Methods:** The polymorphisms rs1800734 in MLH1, rs2303428 and rs3732183 in MSH2, rs735943 in EXO1, and rs11797 in TREX1 were selected and analyzed in independent discovery and validation sets that included 167 and 593 patients, respectively. MSI was determined. **Results:** In the discovery set, both the rs2303428 TC+CC and the rs11797 GA+AA genotypes significantly correlated with poor overall survival (OS; $P < 0.05$). In the validation set, we confirmed the prognostic association for the rs2303428 TC+CC genotype ($P = 0.036$) but not for the rs11797 GA+AA genotype ($P = 0.737$). Furthermore, the prognostic role of the rs2303428 TC+CC genotype was observed in non-cardia ($P = 0.005$) but not in cardia GC ($P = 0.934$). The multivariate model showed that the rs2303428 TC+CC genotype was an independent predictor for OS in non-cardia patients (HR = 1.54; 95% CI: 1.02-2.32; $P = 0.040$). Moreover, fluoropyrimidines-based adjuvant chemotherapy significantly improved OS (HR = 0.29; 95% CI: 0.15-0.58; $P < 0.001$) for non-cardia patients with the rs2303428 TC+CC genotype but not for those with the rs2303428 TT genotype. The rs2303428 genotypes were not associated with MSI frequency. **Conclusions:** The rs2303428 TC+CC genotype may predict prognosis and adjuvant chemotherapy benefit in non-cardia GC patients independent of MSI. To our knowledge, our study is the first to report the prognostic and predictive roles of MMR genotype in GC. Although prospective validation is necessary, our findings have the potential to improve patient selection for adjuvant chemotherapy and spare large numbers of GC patients' unnecessary therapy.

3026 **Poster Session (Board #18), Sat, 8:00 AM-11:00 AM**

A phase I dose-finding and pharmacokinetics study of CPC634 (nanoparticle entrapped docetaxel) in patients with advanced solid tumors.

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Background: CPC634 is a novel product with docetaxel temporarily entrapped within stabilized CriPec nanoparticles. We performed the first-in-human study with CPC634 (NCT02442531). **Methods:** Patients ($\geq$18 years) received CPC634 intravenously either 3-weekly (Q3W) (part 1, 15-100 mg/m^2), 2-weekly (Q2W) (part 2, 45 mg/m^2) or Q3W with dexamethasone premedication (part 3) following a 3+3 design. Primary objectives were to assess safety, establish the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), and to evaluate the pharmacokinetic (PK) profile of CPC634. **Results:** Thirty-three patients (part 1; n = 24, part 2; n = 3, part 3; n = 6) were treated. Skin toxicity was dose limiting at doses $>$ 60 mg/m^2 in part 1, and at a 45 mg/m^2 dose in part 2. Skin toxicity was cumulative but resolved after ceasing treatment. The MTD in part 1 was set at 70 mg/m^2. In part 3, the 60 mg/m^2 was explored which resulted in improved skin tolerability even after repeated administrations without dose limiting toxicities. The RP2D was therefore set at 60 mg/m^2 with dexamethasone premedication. Grade $\geq$3 adverse events (CTCAE version 4.03) were skin toxicity (21%), fatigue (8%), neutropenia (6%), peripheral sensory (8%) and motor neuropathy (4%), stomatitis (4%), infections (4%) and hypomagnesemia (3%). Alopecia grade 1 was reported in 15% of patients. CPC634 exhibited a dose-proportional PK profile. One partial response and sixteen cases of stable disease (RECIST 1.1) were confirmed in part 1 and in part 3 as best response. **Conclusions:** CPC634 could be administered safely but showed cumulative, though reversible skin toxicity at high doses. The RP2D was set at 60 mg/m^2 Q3W with dexamethasone premedication. Additional studies assessing the intratumoral exposure to CPC634 (NCT0371243) and a phase II efficacy study of CPC634 in patients with platinum resistant ovarian cancer (NCT03742713) is currently ongoing. Clinical trial information: NCT02442531.

3027 **Poster Session (Board #19), Sat, 8:00 AM-11:00 AM**

Phase I trial of chloroquine (CQ)/hydroxychloroquine (HCQ) in combination with carboplatin-gemcitabine (CG) in patients with advanced solid tumors.

Nagla Fawzy Abdel Karim, Imran Ahmad, Ola Gaber, Ihab Eldessouki, Olugbenga Olanrele Olowokure, Maria Farooq, John Charles Morris; The University of Cincinnati, Cincinnati, OH; Augusta University, Augusta, GA; University of Central Florida, Orlando, FL; University of Cincinnati Cancer Institute, Cincinnati, OH

Background: Autophagy is a catabolic process triggered in cells during periods of stress to enable their survival. Established tumors utilize autophagy to survive periods of metabolic or hypoxic stress. Inhibition of early stage autophagy can rescue cancer cells, while inhibition of late stage autophagy will lead to cell death due to accumulation of damaged organelles. The antimalarial drugs CQ and HCQ inhibit late phase autophagy. The goal of our study is to assess the safety, tolerability and activity of combining CQ/HCQ with CG in advanced solid tumor patients who either progressed on other therapies or in whom CG is a therapeutic option. **Methods:** This single institution phase 1 dose-escalation study was designed to evaluate the maximum tolerated dose (MTD) of CQ, later substituted with HCQ, in combination with CG in patients with previously treated advanced solid tumors. Secondary objectives were to determine ORR, PFS and OS. A starting dose of 50 mg of CQ/HCQ was used in conjunction with CG, and increased in increments of 50 mg in each dose cohort. Grade 3 or greater toxicity that is treatment-related, and was not self-limited, or controlled in less than 7 days was considered dose limiting toxicity (DLT). **Results:** Twenty-three patients were enrolled with a median follow up of 6 months. HCQ 100 mg was found to be the MTD in combination with CG with ≥Grade 3 thrombocytopenia and/or neutropenia as dose-limiting. Median OS was 11 months, and the 1- and 3- year overall survival rates were 30% and 7%, respectively. Median progression free survival was 5 months and the 6-, 12-, and 18-months progression-free survivals were 48%, 21% and 14%, respectively (Table). **Conclusions:** The MTD identified for CQ/HCQ was lower than previously reported with concomitant use of chemotherapeutic regimes, likely due to the myelosuppressive nature of CG. Clinical trial information: NCT02071537.

Outcome	Number of patients (N=)	Percentage (%)
Response Rate (RR)PR	1	5
SD	15	68
PD	6	27
Disease control Rate(DCR)		
>6 months		48
>12 months		21
>18 months		14

3028 **Poster Session (Board #20), Sat, 8:00 AM-11:00 AM**

Prospective cohort study of the impact of hospital-wide dihydropyrimidine dehydrogenase (*DPYD*) genotype testing for fluoropyrimidine-based chemotherapy on adverse events and hospital costs.

Theodore John Wigle, Brandi Povitz, Wendy Teft, Robin Legan, John Gordon Lenehan, Markus Gulilat, Stephanie Nevison, Justin Kritzinger, Veera Punaganty, Denise Keller, Suhair AlShanteer, Robin Francis, Victoria Siebring, Sisira Sarma, Yun-Hee Choi, Stephen Welch, Eric Winquist, Ute Schwarz, Richard B. Kim; University of Western Ontario, London, ON, Canada; Lawson Health Research Institute, London, ON, Canada; London Regional Cancer Program, London, ON, Canada; University of Toronto, Mississauga, ON, Canada; London Health Sciences Centre, London, ON, Canada; South West Regional Cancer Program, London, ON, Canada; London Health Sciences Centre-University Hospital, London, ON, Canada; Univeristy of Western Ontario, London, ON, Canada

Background: Fluoropyrimidines remain integral components of modern chemotherapy for solid tumors, and their toxicities can be reduced by pretreatment *DPYD* genotyping. Our main objective was to demonstrate the feasibility of implementing a hospital-wide pretreatment *DPYD* testing service based on the CPIC 2013 guideline on fluoropyrimidines and *DPYD.* **Methods:** We enrolled participants prior to planned fluoropyrimidine treatment as well as those who had experienced adverse events (AEs) after initiation of therapy, from December 1, 2013 to November 30, 2018. The patients tested pretreatment were analyzed as a prospective cohort to assess AEs within 90 days of fluoropyrimidine initiation and associated hospital cost. The primary outcome was the rate of severe global fluoropyrimidine-related toxicity in the pretreatment cohort (grade≥3, CTCAE v.4.0.3). **Results:** Of 1362 patients genotyped for *DPYD* within the study period 1041 were enrolled pretreatment and included in the primary analysis. The median age was 65 years (19-90), 57% male, 51% 5-FU, and 49% capecitabine. Dose reductions were recommended for 21 *DPYD* variant carriers who were detected pretreatment. There was no significant difference in the primary outcome between *DPYD* variant (29%) and wild type (18%) patients (Fisher's exact test p = 0.25). Costs associated with ER visits and hospitalizations at our tertiary care centre were $1,268 (89-8,562) (Median (IQR)) and $2,961 (341-13,567) for DPYD variant (n = 4) and wild-type (n = 99) patients respectively. Post-AE genotyping (n = 70) found five *DPYD* variant patients; all experienced grade≥3 toxicity, costs were $15,825 (10,962-25,310), and one poor metabolizer died due to complications. Targeted next generation exome sequencing of *DPYD* wild-type patients who experienced severe AEs identified five potentially deleterious genetic variants in ABC efflux transporters. **Conclusions:** Pretreatment *DPYD* genotype guided dosing of fluorouracil and capecitabine is feasible and benefits patients, health care providers, and hospitals. Our data supports adoption of pretreatment *DPYD* genotyping as a standard of care.

3029 **Poster Session (Board #21), Sat, 8:00 AM-11:00 AM**

PDX validation of a 3D microtumor platform.

Ellen Sampson, Katya Nikolov, Paul T. Henderson, Christian Apfel, Chong-xian Pan, Maike Zimmermann, Ai-Hong Ma; SageMedic Corp, Redwood City, CA; University of California Davis Comprehensive Cancer Center, Sacramento, CA; University of California San Francisco, San Francisco, CA; Division of Hematology/Oncology, University of California Davis Cancer Center, Sacramento, CA

Title: Patient-derived xenograft validation of a 3D microtumor platform **Background:** Patient-derived xenograft (PDX) mouse models are thought to most closely reflect the biology of a patient's cancer. Unfortunately, growing sufficient tumor in a PDX model takes several months and more often than not, the tumor fails to grows at all. The SAGE Direct Platform, an in-vitro model, can create hundreds of live microtumors from virtually every patient's viable biopsy and test a panel of clinically relevant drugs within no more than 1 week. Thus, concordance of results from a PDX model with results of the SAGE Direct Platform would support a rational for the platform to be potentially useful to predict tumor response in cancer patients. **Methods:** A bladder cancer from a 77 year old female was used to establish a PDX model. Mice were divided into three groups receiving either saline (control), cisplatin, or gemcitabine intraperitoneal on the days 1, 8, and 13, and tumor growth was observed. One tumor sample was used to create 3D microtumors and those were tested using the same drugs. **Results:** Tumor growth (exceeding 1,000 mm^3) was similar after cisplatin compared to control (4.8 vs. 3.7 weeks). After gemcitabine tumors initially shrank and only started growing a couple of weeks after the end of treatment so that 1,000 mm^3 was only reached after 10.2 weeks ($p<0.001$ compared to cisplatin and control). In the SAGE Direct Platform the EC_{50} of cisplatin was 97.3 μM and thus two orders of magnitudes higher than the EC50 of gemcitabine, which was 0.7 μM. **Conclusions:** Both the PDX model and the SAGE Direct Platform have shown this bladder cancer to be virtually resistant to cisplatin while very sensitive to gemcitabine. The next steps of these preliminary data could be to repeat this experimental design with other tumors and/or to start an observational cohort study in patients correlating the SAGE Direct Platform results to patient outcomes.

3030 **Poster Session (Board #22), Sat, 8:00 AM-11:00 AM**

Anticancer activity in patients with advanced ovarian and biliary tract cancers treated with NUC-1031 and a platinum agent.

Sarah Patricia Blagden, Jennifer Bré, Peter Mullen, Chathunissa Gnanaranjan, Essam Ahmed Ghazaly, Mairead Geraldine McNamara, Juan W. Valle; University of Oxford, Oxford, United Kingdom; School of Medicine, University of St Andrews, St Andrews, United Kingdom; University of St. Andrews, St. Andrews, United Kingdom; Barts Cancer Institute, London, United Kingdom; The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; University of Manchester/The Christie, Manchester, United Kingdom

Background: The inhibition of cellular nucleotide metabolism to promote apoptosis is a key principle of cancer therapy. This, in combination with platinum-induced DNA-damage, is key to promoting anti-cancer activity in a variety of tumors, including ovarian, biliary tract, lung, breast and bladder. NUC-1031, a phosphoramidate transformation of gemcitabine is designed to overcome resistance mechanisms that limit the efficacy of this nucleoside analog. NUC-1031 has shown broad clinical activity across multiple solid tumors as both a single agent and in combination with platinum agents. We show potential synergism between NUC-1031 and a platinum agent in advanced ovarian (OC) and biliary tract (BTC) cancers. **Methods:** *PRO-002* was a phase Ib study; 25 patients (pts) with recurrent OC who had exhausted all other therapy options received NUC-1031 + carboplatin. 17 pts were considered platinum resistant (10) or platinum refractory (7). *ABC-08* is a phase Ib study, 14 pts with advanced BTC treated in the first-line setting with NUC-1031 + cisplatin. **Results:** In PRO-002, strong efficacy signals were observed in non-platinum-responsive patients. Of the 17 response-evaluable platinum-resistant or refractory pts, 5 partial responses (PRs) and 11 stable diseases (SDs) were achieved, resulting in an ORR of 29% and a DCR of 94%. NUC-1031 + carboplatin was well-tolerated with no unexpected AEs; DLTs were myelosuppression and fatigue. Encouraging response rates were also observed in ABC-08 compared to historical standard of care (ABC-02). One CR (7%), 6 PRs (43%) and 1 SD (7%) were observed, resulting in an ORR of 50%. NUC-1031 + cisplatin was well-tolerated, with no unexpected AEs or DLTs. Complementary *in vitro* evidence suggests that the beneficial interaction occurs whereby platinum treatment sensitizes cells to NUC-1031. **Conclusions:** Increasing evidence suggests that NUC-1031 in combination with a platinum agent may have synergistic properties, leading to enhanced anti-cancer activity. In both OC and BTC, durable tumor shrinkage was observed. This was particularly encouraging in a platinum resistant/refractory OC population. Future studies utilizing both NUC-1031 plus a platinum agent will further elucidate the potential of this therapeutic combination.

3031 **Poster Session (Board #23), Sat, 8:00 AM-11:00 AM**

Phase I study of the Aurora A kinase (AurA) inhibitor TAS-119 with paclitaxel (P) in advanced solid tumors.

Dana Backlund Cardin, Haeseong Park, Jennifer Robinson Diamond, Alexander E. Drilon, Wendy L. VerMeulen, Xiaomin He, Hiroshi Hirai, Nital Soni, Jordan Berlin; Vanderbilt-Ingram Cancer Center, Nashville, TN; Washington University School of Medicine, St. Louis, MO; University of Colorado, Aurora, CO; Memorial Sloan Kettering Cancer Center, New York, NY; Vanderbilt Ingram Cancer Ctr, Brentwood, TN; Taiho Oncology, Princeton, NJ; Tsukuba Research Institute, Ibaraki, Japan; Vanderbilt University, Nashville, TN

Background: AurA is a key regulator of cell division, including mitotic spindle assembly. However, elevated levels of AurA have been reported to abrogate the mitotic spindle checkpoint activated by taxanes leading to treatment resistance. Preclinical studies of TAS-119 + P showed enhanced antitumor activity and suggested an optimal timing window of the combination. Study objective was to assess the safety of TAS-119 + P in adult patients (pts) with advanced solid tumors. **Methods:** Dose escalation used a 3+3 design to determine the maximum tolerated dose (MTD); 7 dose levels (DLs) were explored, starting with 25 mg TAS-119 BID dosed 4 days/week (d/wk) and weekly 90 mg/m^2 P for 3 weeks of a 4 week cycle (DL1). Plasma samples were collected during cycle 1 to evaluate pharmacokinetics. In expansion, pts with advanced breast/ovarian cancers were treated at the MTD. **Results:** Dose escalation enrolled 26 pts with various cancers, the majority being pancreas, colon, and ovarian; 2 pts were not evaluable for DLT assessment and replaced. A DLT (neutropenia and elevated AST) was observed in 2/3 pts in DL1. Dosing was modified to 25 mg TAS-119 BID 2 d/wk and P 70 mg/m^2 (DL2) and no DLTs were observed. Zero DLTs were observed in the next 4 doses: 70 mg/m^2 P + TAS-119 2 d/wk at 50 mg BID (DL3) or 75 mg BID (DL4), or 80 mg/m^2 P + TAS-119 at 75 mg BID 2 d/wk (DL5) or 75 mg BID 3 d/wk (DL6). TAS-119 was escalated to 100 mg BID 3 d/wk (DL7) and 3 DLTs (n=1, elevated ALT; n=1, diarrhea and mucositis) occurred in 2/3 pts. Three additional pts were then enrolled at DL6 to confirm the MTD. One breast and 2 ovarian pts were enrolled in expansion before the trial was suspended by the company. Toxicities observed in $\geq$30% of pts were diarrhea, nausea, and fatigue (most $\leq$Gr2). Plasma TAS-119 exposure increased dose-proportionally in 2 d/wk and 3 d/wk schedules; no impact of TAS-119 on PK of paclitaxel was found. The disease control rate was 59% (17/29); 4 of these pts had a partial response. **Conclusions:** The combination had a manageable toxicity profile at the MTD of 80 mg/m^2 P + TAS-119 at 75 mg BID 3 d/wk. Preliminary clinical activity was seen in 59% of pts, including tumor responses in a majority (4/7) of pts with ovarian/fallopian tube cancers. Clinical trial information: NCT02134067.

3032 **Poster Session (Board #24), Sat, 8:00 AM-11:00 AM**

A phase I study of the oral administration of irinotecan in combination with the potent P-glycoprotein (P-gp) inhibitor HM30181A.

Antonio Jimeno, Mateusz Opyrchal, Jennifer Robinson Diamond, Christos Fountzilas, Bradley Corr, Ildiko Bezi, Hui Wang, Rudolf Kwan, Jay Zhi, David Cutler, Patrick McKay Boland; University of Colorado, Aurora, CO; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Athenex, Cranford, NJ; Athenex Inc., Buffalo, NY; Athenex, Inc., Buffalo, NY; Roswell Park Cancer Institute, Buffalo, NY

Background: Irinotecan is a prodrug of the potent topoisomerase inhibitor SN-38. In animals, oral administration of irinotecan with the selective minimally absorbed P-gp inhibitor HM30181A increased the bioavailability of irinotecan. Oral administration of irinotecan may also increase the conversion to SN-38. **Objectives:** To determine the MTD and DLT of orally administered irinotecan in combination with HM30181A 15 mg on day 1 of a 21-day cycle. Additional objectives include determining the recommended phase 2 dose and the PK of irinotecan and SN-38. **Methods:** This was a phase 1 dose escalation study enrolling cohorts of 3-6 patients with advanced malignancies. Patients had Hb $\geq$9 gm/dL, ANC $\geq$ 1.5x10^9/L, platelets $\geq$ 100x10^9/L, adequate hepatic and renal function, ECOG 0-1 and were not homozygous for UGT1A1*28. Patients were administered HM30181A 15 mg and oral irinotecan 20, 40, 80, 120, 160, 200, 240, 280 and 320mg/m^2. **Results:** Thirty male and female patients, mean age 60.9 (range 33-78) were enrolled into this ongoing study. The most common cancers were ovarian (6), colorectal (4), breast (4), endometrial (3), and pancreatic (3). The median number of cycles administered was 3 (range 1-9). Treatment-related Grade 3-4 AEs were experienced by 12 (40%) subjects. The most common were nausea 7 (23%), vomiting 6 (20%) and abdominal pain 3 (10%). Treatment-related SAEs were experienced by 6 (20%) patients (nausea or vomiting in 4 subjects). DLTs occurred in 2 patients at the 320 mg/m^2 dose level (neutropenia and C. Difficile diarrhea) and additional patients are being enrolled at the 280mg/m^2 dose level to define the MTD. Acute cholinergic diarrhea has not been observed. The best response was stable disease in 9/21 evaluable patients. PK at the three highest dose levels is summarized below. **Conclusions:** Oral administration of HM30181A in combination with irinotecan tablets results in pharmacologically active concentrations of SN-38. Confirmation of the MTD when dosed on a 21-day cycle is ongoing. Phase 2 studies are being planned. Clinical trial information: NTC02250157.

Dose (mg/m^2) N = 3	Irinotecan				SN38			
	t_{max} (h)	C_{max} (ng/mL)	AUC_{24h} (ng•h/mL)	$t^{1/2}$ (h)	t_{max} (h)	C_{max} (ng/mL)	AUC_{24h} (ng•h/mL)	$t^{1/2}$ (h)
240	3.0	798	6.960	11.1	3.0	28.3	264	20.0
280	2.0	763	6,040	12.2	1.5	37.6	293	18.5
320	3.0	1,055	11,297	18.7	2.0	38.5	300	20.4

3033 **Poster Session (Board #25), Sat, 8:00 AM-11:00 AM**

Risk of QTc interval prolongation among cancer patients treated with tyrosine kinase inhibitors.

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Background: QTc interval prolongation can lead to life-threatening complications such as torsade de pointes (TdP), ventricular tachycardia (VT), and sudden cardiac death (SCD). It can occur with various tyrosine kinase inhibitors (TKIs) but comparative analyses on the incidence and complication rates are scarce. We thus conducted a comprehensive analysis of TKI use and QTc prolongation in clinical practice. **Methods:** We retrospectively reviewed the electronic medical records of all cancer patients who were treated with TKI between 01/2005 and 12/2018 at our institution. QTc prolongation was defined as a QTc $\geq$ 450 ms or 460 ms among male or female patients, respectively. For each type of TKIs, we determined the administration rate and incidence of QTc interval prolongation. We also studied the frequency of QTc prolongation $\geq$ 500 ms, rate of increase of the QTc interval by $\geq$ 60 ms, and the development of complications (VT, TdP and SCD). **Results:** In the present study, we analyzed the data of 685 cancer patients (431 male and 254 female), including 299 patients with RCC, 188 with chronic leukemia, 55 with acute leukemia, 65 with thyroid cancer, 48 with lung cancer and 39 with GIST. These patients received 902 TKI administrations and QTc prolongation was reported in 1/3 of these (289 administrations). The highest frequency was seen with imatinib, nilotinib and dasatinib (30, 40 and 50%). Among cases of QTc prolongation, a QTc interval $\geq$ 500 ms was documented in 53 (18.3%) and QTc progression $\geq$ 60 ms in 72 (25%). Complications were found in 14 cases (5%) including VT in 9, TdP in 2 and SCD in 3 administrations. **Conclusions:** The current findings suggest that TKI therapy leads to QTc prolongation in 1/3 of patients on average and most commonly with the Bcr-Abl TKIs, imatinib, nilotinib and dasatinib. While SCD is rare (1%) it can still evolve and in 5% of all QTc prolongations with TKIs are potentially life-threatening. These data support recommendations for serial ECGs in cancer patients undergoing TKI therapy.

	Total	Prolonged QTc	QTc ≥ 500	QTc progression ≥ 60	VT	SCD	TdP
Imatinib	165	54	13	10	2		
Nilotinib	75	33	8	19			
Dasatinib	115	58	10	16	2	0	1
Sunitinib	134	31	1	2	1	1	
Pazopanib	165	36	5	6	2	1	
Axinitinb	45	9	3	3			
Sorafenib	41	14	2	2			
Cabozantinib	33	9	1	2	1	1	1
Others	129	45	10	12	1	0	0

3034 **Poster Session (Board #26), Sat, 8:00 AM-11:00 AM**

Phase I study of DFP-11207, a novel oral 5-FU with enhanced PK and improved tolerability, in patients with solid tumors.

Jaffer A. Ajani, Milind M. Javle, Cathy Eng, David R. Fogelman, Barry Douglas Anderson, Chun Zhang, Kenzo Iizuka; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Theradex, Princeton, NJ; Delta-Fly Pharma, Inc., Tokushima, Japan

Background: DFP-11207 combines a 5-fluorouracil (5-FU) pro-drug with a reversible dihydropyrimidine dehydrogenase inhibitor and a potent inhibitor of orotate phosphoribosyl transferase resulting in enhanced pharmacological activity of 5-FU with decreased gastrointestinal and myelosuppressive toxicity. **Methods:** Patients with advanced solid tumors were treated in this single arm, dose escalation study. Accelerated dose escalation using single pt cohorts was followed until drug-related Gr2 adverse events occurred; then a 3+3 design was followed to determine maximum tolerated dose (MTD). Pts were dosed daily in 28-day cycles until intolerable toxicity or disease progression. PK sampling was performed for DFP-11207 metabolites on all pts and a 6 pt cohort received DFP-11207 in fed and fasted states to determine drug bioavailability. **Results:** Primary tumors among the 23 enrolled pts included esophageal, colorectal, gastric, pancreatic and gallbladder. Seventeen pts were treated at 8 dose levels of oral DFP-11207 administered daily, ranging from 40 to 440 mg/m^2/d. At 440 mg/m^2/d one pt experienced drug-related Gr3 dehydration and mucosal inflammation, and Gr4 febrile neutropenia; a second pt experienced Gr4 febrile neutropenia. One DLT of Gr3 vomiting occurred among 6 pts treated at 330 mg/m^2/d dosed q12hrs confirming the MTD. Six pts were administered 300 mg DFP-11207 q12 hrs in a fed or fasted state to determine drug bioavailability. Among all pts, the most frequently reported drug-related TEAEs were fatigue (47.8%), nausea (47.8%), decreased appetite (39.1%), diarrhea (26.1%), vomiting (21.7%), anemia (13.0%), dysgeusia (13.0%), mucosal inflammation (13.0%) and palmar-plantar erythrodysaesthesia syndrome (13.0%). PK analyses of pts treated at 330 and 440 mg/m^2/d indicate 5-FU concentrations of ~20 ng/mL throughout the dose cycle. There was no substantial difference in DFP-11207 bioavailability among pts in a fed or fasted state. Out of 21 efficacy evaluable pts, 7 pts had stable disease (33.3%), of which 2 had prolonged stable disease of $>$ 6 months. No pts achieved CR or PR. **Conclusions:** DFP-11207 at the dose of 330 mg/m^2/d q12hrs is well-tolerated in pts with solid tumors with mild myelosuppressive and gastrointestinal side effects, and results in circulating 5-FU levels conducive to an anti-tumor effect. DFP-11207 can be explored as monotherapy or substitute for 5-FU, capecitabine or S-1 in combination treatment regimens. Clinical trial information: NCT02171221.

3035 **Poster Session (Board #27), Sat, 8:00 AM-11:00 AM**

Associations of insulin-like growth factor binding proteins and adiponectin with disease progression and mortality in metastatic colorectal cancer: Results from CALGB/SWOG 80405 (Alliance).

Brendan John Guercio, Alan P. Venook, Sui Zhang, Fang-Shu Ou, Donna Niedzwiecki, Heinz-Josef Lenz, Federico Innocenti, Michael N. Pollak, Andrew B. Nixon, Michelle R. Mahoney, Bert O'Neil, James Edward Shaw, Blase N. Polite, Crystal S. Denlinger, James Norman Atkins, Richard M. Goldberg, Robert J. Mayer, Charles David Blanke, Charles S. Fuchs, Jeffrey A. Meyerhardt; Brigham & Women's Hospital, Boston, MA; University of California San Francisco, San Francisco, CA; Dana-Farber Cancer Institute/Partners Cancer Care, Boston, MA; Mayo Clinic, Rochester, MN; Duke University Medical Center, Durham, NC; University of Southern California, Los Angeles, CA; The University of North Carolina at Chapel Hill, Chapel Hill, NC; McGill University, Montréal, QC, Canada; Indiana University School of Medicine, Indianapolis, IN; Medstar Washington Hospital Center, Washington, DC; The University of Chicago, Chicago, IL; Fox Chase Cancer Center, Philadelphia, PA; Southeast Clinical Oncology Research Consortium, Goldsboro, NC; West Virginia University Cancer Institute, Morgantown, WV; Dana-Farber Cancer Institute, Boston, MA; Oregon Health and Science University, Portland, OR; Yale Cancer Center, New Haven, CT; Dana-Farber Cancer Institute/Partners CancerCare, Boston, MA

Background: Energy balance-associated biomarkers such as insulin-like growth factors (IGFs) and IGF-binding proteins (IGFBPs) have been associated with risk and prognosis of various malignancies. Their relationship to disease progression and mortality in metastatic colorectal cancer (mCRC) requires further study. **Methods:** In a prospective cohort study, baseline plasma IGFBP-3, IGFBP-7, C-peptide, IGF-I, and adiponectin were measured at trial registration among 1,086 patients participating in a National Cancer Institute-sponsored clinical trial of first-line therapy for mCRC. We used Cox proportional hazards regression to adjust for confounders and examine associations of biomarkers with overall (OS) and progression-free survival (PFS). **Results:** Higher plasma IGFBP-3 was associated with longer OS (adjusted $P_{trend} < .001$) and PFS (adjusted $P_{trend} = .003$). Compared to patients in the lowest IGFBP-3 quintile, patients in the highest quintile experienced an adjusted HR for all-cause mortality of 0.58 (95% CI 0.42 to 0.78) and for disease progression or mortality of 0.60 (95% CI 0.45 to 0.82). Higher plasma IGFBP-7 was associated with shorter OS (adjusted $P_{trend} < .001$) and PFS (adjusted $P_{trend} = .02$). Compared to patients in the lowest IGFBP-7 quintile, patients in the highest quintile experienced an adjusted HR for all-cause mortality of 1.52 (95% CI 1.24 to 1.88) and for disease progression or mortality of 1.28 (95% CI 1.05 to 1.57). C-peptide and IGF-I were not significantly associated with patient outcomes (adjusted $P_{trend} = .73$ and .30 for OS). Adiponectin was not associated with OS; there was a U shaped association between adiponectin and PFS, wherein low and high values were associated with shorter PFS ($P_{non\text{-}linear\ trend} = .03$). **Conclusions:** In patients with mCRC, high plasma IGFBP-3 and low IGFBP-7 were associated with reduced risk of disease progression and mortality. These data suggest that energy-balance associated biomarkers may offer prognostic and biologic insights into mCRC. Support: U10CA180821, U10CA180882, BMS, Genentech, Pfizer, Sanofi; https://acknowledgments.alliancefound.org.

3036 **Poster Session (Board #28), Sat, 8:00 AM-11:00 AM**

Predictive and prognostic values of circulating tumor DNA (ctDNA) clearance in osimertinib treated advanced non-small cell lung cancer cohort.

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Background: Although growth advantage of certain clones would ultimately translate into a clinically visible disease progression, radiological imaging does not reflect clonal evolution at the molecular level. CtDNA, validated as a tool for mutation detection in lung cancer, reflects dynamic molecular changes. Here, we evaluated the potential of ctDNA in monitoring molecular changes and predicting clinical outcomes of *EGFR* T790M-positive osimertinib treated NSCLC pts. **Methods:** This prospective multicenter study, enrolled 72 T790M positive osimertinib-treated advanced NSCLC pts who progressed on prior EGFR-TKI to evaluate the potential of ctDNA in monitoring, is part of the ongoing ASTRIS study (NCT02474355). Longitudinal plasma samples, collected from 52 pts, were subjected to sequencing using a panel consisting of 168 lung cancer-related genes. **Results:** Genomic profile prior to the initiation of osimertinib revealed that mutations participating in cell cycle (14 pts, p = 0.004) and P53 pathways (43 pts, p = 0.032) were associated with shorter OS (*p53* was excluded from analysis due to high mutation frequency). Interestingly, pts with undetectable ctDNA at first follow-up (within 50 d, n = 41) were correlated with longer PFS (p = 0.009) and OS (p = 0.022). With a median follow-up of 168 d (ranged from 40 - 550 d), 32 pts experienced radiological disease progression. Among them, 11 (34%) experienced molecular progression reflected by emergency of new mutation or increased allelic frequency of existing mutation prior to radiological progression, with an average leading time of 74 days. Pts with molecular PD prior to radiological PD were more likely to harbor any gene copy number amplification (CNA, p = 0.035) and *p53* (p = 0.023) mutations at radiological PD. In addition, pts with CNA at radiological PD had shorter PFS (p = 0.002) and OS (p = 0.052). **Conclusions:** This clinical trial study demonstrates that ctDNA clearance at first follow-up can serve as a predictive and a prognostic marker for pts undergoing osimertinib treatment. Furthermore, it revealed the potential of ctDNA in early detection of disease progression, preceding imaging modalities with an average lead time of 74 days.

3037 **Poster Session (Board #29), Sat, 8:00 AM-11:00 AM**

Progastrin, a novel ubiquitous cancer blood biomarker for early detection and monitoring.

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Background: The successes of recent publications on "multi-tumor" circulating markers highlight the relevance of novel universal diagnostic cancer serum biomarkers. Since the Wnt/ß-catenin/Tcf4 pathway, activated in many tumors, induces the GAST Gene encoding progastrin synthesis, we hypothesized that progastrin, easily measurable in the blood, might be a "multi-tumor" diagnostic biomarker. **Methods:** Progastrin levels were measured in the blood samples of 1319 patients with 12 different cancer origins, and compared to those of 557 asymptomatic 18-75 years old blood donors. Moreover the longitudinal kinetics of progastrin concentrations were serially assessed during treatments in 168 patients with ovarian cancers enrolled in the randomized CHIVA trial (NCT01583322, GINECO), 191 patients with peritoneal involvement from gastro-intestinal cancers enrolled in BIG-RENAPE trial (NCT03787056), and in 95 HCC patients. The progastrin was measured using an ELISA test developed by ECS Progastrin (Prilly, Switzerland). **Results:** Compared to healthy blood donors, progastrin was found at higher concentrations in the plasma of cancer patients: median 4.47 vs 0.20 pM, $P < 0.0001$; diagnostic discriminative power, ROC analysis AUC = 0.86 (95% CI, 0.83-0.89; $P < 0.0001$). Progastrin levels were found elevated in all cancer groups, regardless of disease stages, and of pathology origins: ROC AUCs ranged from 0.71 to 0.93, all $P < 0.0001$ (Table). The longitudinal progastrin changes during treatments, suggest relationships to tumor burden, and potential monitoring value. **Conclusions:** Progastrin is a novel ubiquitous cancer biomarker, easily detectable in the blood using an affordable ELISA test (CancerRead Lab test(R)). It may change the future paradigms about screening (in particular for populations at higher or lower risks of cancer), cancer diagnostic & monitoring.

	Oesophagus/Gastric	**Colorectal**	**Pancreas**	**HCC**
Gastro-Intestinal	**0.95 [0.92-0.96]**	**0.84 [0.80-0.89]**	**0.93 [0.88-0.98]**	**0.85 [0.79-0.90]**
Genito-Urinary	Prostate	Kidney		
	0.82 [0.77-0.87]	0.92 [0.89-0.95]		
Gynecology	Breast	Ovarian	Uterus	
	0.81 [0.75-0.87]	0.83 [0.79-0.88]	0.81 [0.75-0.88]	
Others	Lung	Melanoma	Brain	
	0.88 [0.82-0.93]	0.83 [0.75-0.91]	0.71 [0.64-0.79]	

3038 **Poster Session (Board #30), Sat, 8:00 AM-11:00 AM**

Can the enumeration of circulating tumor cells (CTCs) and the characterization of circulating tumor DNA (ctDNA) provide insight into organ tropism in metastatic breast cancer (MBC)?

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Background: Liquid biopsy provides *real-time* data about prognosis and actionable mutations in MBC. The aim of this study was to explore the combination of ctDNA analysis and CTCs enumeration in estimating target organs more susceptible to MBC involvement. **Methods:** This retrospective study analyzed 85 MBC patients (pts) characterized for both CTCs and ctDNA at baseline. CTCs were isolated through the CellSearch kit (Menarini Silicon Biosystems, PA), while ctDNA was analyzed using the Guardant360 NGS-based assay (Guardant Health, CA). Pts with $\geq$ 5 CTC/7.5 ml of blood were defined as Stage IV aggressive as previously reported (Cristofanilli et al 2019). Statistical associations were explored through uni- and multivariate logistic regression and Fisher's exact test. **Results:** 37% of pts were diagnosed with hormone receptor positive (HRpos) MBC, 26% with HER2-positive MBC and 37% with triple negative MBC (TNBC), 28 pts (33%) were defined as stage IV aggressive. The most observed metastatic sites were bone (37%), lymph nodes (29%), lung (27%) and liver (25%). In multivariate analysis, IBC and *ESR1* mutations were the only significant factors associated with liver metastases (respectively, OR 0.12, P = 0.038 and OR 24.01, P = 0.019), while no associations were found with respect to lung localizations. Intriguingly, all HRpos MBC pts with *ESR1* mutations had bone metastases (P = 0.022), while IBC and Stage IV aggressive were independently associated with bone metastases (respectively OR 0.10, P = 0.006 and OR 19.92, P = 0.003). *FGFR1* and *NF1* were associated with lymph node localizations (OR 3.68, P = 0.046, OR 4.39, P = 0.031, respectively), while *CDK6* and *TP53* alterations were associated with serosal involvement (OR 14.34, P = 0.029, OR 0.08, P = 0.031, respectively). Notably, TNBC and IBC were both associated with soft tissue spreading (respectively OR 3.7, P = 0.011, OR 2.79, P = 0.018). **Conclusions:** These results suggest that ctDNA and CTCs enumeration could give useful insights on MBC organotropism, suggesting a possible role for future monitoring strategies that dynamically focus on high-risk organs defined by tumor biology.

3039 **Poster Session (Board #31), Sat, 8:00 AM-11:00 AM**

Development and analytical validation of a 523-gene clinical assay for cell-free DNA.

Robin Harrington, Biswajit Das, Tingting Jiang, Jennifer S. LoCoco, Rajesh Patidar, Amanda Peach, Chen Zhao, Corinne Camalier, Ting-Chia Chang, Alice P. Chen, Li Chen, Thomas Forbes, Sigrid Katz, Nikitha Nair, David J. Sims, Geraldine Helen O'Sullivan Coyne, Naoko Takebe, Paul M. Williams, Chris Alan Karlovich, James H. Doroshow; Molecular Characterization Laboratory, Frederick National Laboratory for Cancer Research, Frederick, MD; Illumina, Inc., San Diego, CA; Developmental Therapeutics Clinic/Early Clinical Trials Development Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD; Developmental Therapeutics Clinic/Early Clinical Trials Development Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, MD; Early Clinical Trials Development Program, DCTD, National Cancer Institute at the National Institutes of Health, Bethesda, MD

Background: Liquid biopsies are emerging as a powerful complement to tumor biopsies for the clinical management of cancer patients. A large gene panel with robust analytical performance that accurately assesses variants, tumor mutational burden (TMB), and microsatellite instability in plasma would be of high value for immunotherapy studies, monitoring minimal residual disease and early cancer detection. To this end, we have completed the initial validation for the cell-free DNA (cfDNA) assay, TruSight Oncology 500 (TSO500), which interrogates the full coding region of 523 genes plus selected intronic regions for fusion detection in 23 driver genes. **Methods:** Cell-free DNA was extracted from plasma collected from Streck or EDTA blood tubes and quantitated to achieve an assay input of $\geq$10 ng. Libraries were constructed using unique molecular identifiers (UMIs) and duplex barcodes for error correction, then enriched by target capture and sequenced on a NovaSeq 6000. Healthy donor (HD) specificity assessment used matched white blood cell results to filter germline and clonal hematopoiesis variants. Contrived specimens were used to evaluate sensitivity. Single nucleotide variants (SNVs) (n = 36), insertion/deletions (indels) (n = 19), copy number variants (CNVs) (n = 6), and fusions (n = 5) were tested in 2 multi-site replicates. **Results:** Sensitivity of detection at 0.5% variant allele fraction (VAF) was $>$ 95% and $>$ 97% for SNVs and indels, respectively. All expected CNVs were identified at the targeted threshold of $\geq$1.3X change and showed strong correlation with matched digital PCR results. All fusions were identified at $\geq$0.4% VAF. Specificity in HD was $>$ 99.99%. In 22 temporally matched tumor and blood samples from late-stage patients, 58% of all reportable mutations in tumor were identified in cfDNA. Preliminary TMB analysis identified one TMB high case with POLE p.P286R observed in both tissue and cfDNA. **Conclusions:** In this initial validation study the TSO500 cfDNA assay exhibited high sensitivity and specificity consistent with requirements for clinical applications. Ongoing studies will further evaluate TSO500 as a complement or potential alternative to tissue biopsy for the genomic profiling of cancer patients.

3040 **Poster Session (Board #32), Sat, 8:00 AM-11:00 AM**

Dynamic monitoring of circulating tumor DNA next-generation gene sequencing as a predictive biomarker of response and progression-free survival after pembrolizumab monotherapy in patients with advanced NSCLC.

Charu Aggarwal, Jeffrey C. Thompson, Austin Chien, Katie Quinn, Martina Lefterova, Rebecca Nagy, Stephanie Yee, Christine Agnes Ciunci, Evan W. Alley, Joshua Bauml, Roger B. Cohen, Corey J. Langer, Erica L. Carpenter; University of Pennsylvania, Philadelphia, PA; Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; University of Pennsylvania Health System, Philadelphia, PA; Guardant Health, Redwood City, CA; Guardant Health, Inc., Redwood City, CA; Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; University of Pennsylvania Abramson Cancer Center, Philadelphia, PA

Background: Circulating tumor DNA next generation sequencing (ctDNA NGS) is increasingly being used to detect mutations (MT) in patients (pts) with metastatic (m) NSCLC. Limited data exist on the correlation of baseline ctDNA NGS profile and serial ctDNA NGS monitoring to response to immunotherapy. **Methods:** We conducted a prospective study in pts with mNSCLC receiving pembrolizumab monotherapy. Plasma was collected at weeks 0 (T0), 9 (T1), and 18 (T2). ctDNA NGS was performed using a 73 gene panel. Number of MTs and variant allelic fraction (VAF) were determined at baseline, and serially; change in mean VAF was calculated between T1-T0, and T2-T0. Response rate (RR) was assessed using RECIST 1.1. Correlations were made for pt characteristics, RR, progression free survival (PFS), and overall survival (OS). **Results:** We analyzed 95 samples from 33 pts, 21 female, median age 69 (range 51-89 years), smokers (n = 29), adenocarcinoma (n = 23), 25 pts enrolled at initial diagnosis, majority had high PD-L1 $\geq$50% (n = 29, 88%). At T0, 32 pts had detectable MT, median number of MTs was 4 (range 0-21), (non-synonymous MT = 3), most common MT was *TP53* (n = 21). Confirmed PR was 27% (n = 9), clinical benefit rate (SD+PR) was 64% (n = 21), and 2 pts were not evaluable for response. Smokers were more likely to have higher number of MT at T0 (4 vs. 1 p = 0.003); there was no correlation with smoking and overall RR (p = 0.17). RR was not related to number of MT at T0, p = 0.37. A decrease in ctDNA VAF was seen in 6/9 pts with PR (mean VAF change range -0.11 to -0.001); 2/5 pts with PD showed an increase in mean VAF while 3 showed decrease. At median follow up of 9.26 months (mos), median PFS and OS were 7.4 and 10.5 mos, respectively. Median PFS was longer for pts with a decrease in ctDNA VAF at both T1-T0 (8.9 vs. 5 mos, p = 0.02) and T2-T0 (9.1 vs. 5.5 mos, p = 0.006). OS and additional biomarker analyses including correlation of response to a 2mb ctDNA plasma-based NGS panel will be reported at the meeting. **Conclusions:** Our results demonstrate that it is feasible to serially monitor plasma NGS, decline in mean ctDNA VAF correlates with radiographic response and PFS on immunotherapy with pembrolizumab.

3041 **Poster Session (Board #33), Sat, 8:00 AM-11:00 AM**

Whole-genome cell-free DNA (cfDNA) changes as a dynamic blood-based biomarker for early response assessment of advanced tumors.

Andrew A. Davis, Wade Thomas Iams, David Chan, Michael S Oh, Robert William Lentz, Neil Peterman, Alex Robertson, Abhik Shah, Rohith Srivas, Nicole Lambert, Timothy Wilson, Peter George, Becky Wong, Ayse Tezcan, Ram Yalamanchili, Ken Nesmith, John C Spinosa, Haluk Tezcan, Young Kwang Chae; Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL; Vanderbilt University Medical Center, Nashville, TN; Cancer Care Assoc-TMPN, Redondo Beach, CA; Northwestern University Feinberg School of Medicine, Chicago, IL; Northwestern University Internal Medicine, Chicago, IL; Lexent Bio, Inc., San Francisco & San Diego, CA; Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL

Background: Liquid biopsies have potential clinical utility as dynamic biomarkers for treatment response. We analyzed serial changes in whole-genome (WG) cfDNA to identify patients with disease progression prior to routine imaging. **Methods:** We prospectively collected clinical data and blood from 69 advanced cancer patients (28 lung, 25 breast, 16 other). Blood was collected at baseline prior to initiation of a new treatment and at one or two additional timepoints (median 21 and 42 days). We isolated plasma cfDNA and prepared sequencing libraries for WG sequencing or WG bisulfite sequencing (median depth 20X). We quantified changes in the fraction of tumor-derived cfDNA over the initial course of treatment to predict progression vs. no progression. Treatment response at first post-treatment imaging was determined by RECIST 1.1 and clinical assessment. Study endpoints were agreement with first post-treatment imaging and progression-free survival (PFS) by cfDNA prediction. **Results:** Median age of patients was 70 and 59% were female. Patients were treated with the following therapies: chemotherapy (37), immunotherapy (17), endocrine (9), or targeted therapy (6). Patients with predicted progression by cfDNA (14), indicated by an increase in tumor fraction at either post-treatment blood collection, had shorter PFS (median 63 days) compared to patients without an increase (N = 55; median 255 days), with hazard ratio of 10.3 (95% confidence interval 4.6-23.4, log-rank $P = 1x10^{-11}$). Positive predictive value was 100% for disease progression and negative predictive value was 78%. These findings were consistent in subset analyses of patients with lung (log-rank $P = 2x10^{-5}$), breast (log-rank $P = 3x10^{-4}$), and those treated with immunotherapy (log-rank $P = 5x10^{-6}$). **Conclusions:** Our results show the ability to detect early disease progression with high fidelity using WG cfDNA prior to first imaging. These findings were consistent across multiple tumor types and treatments, including immunotherapy patients. Once validated, this dynamic, predictive, blood-based biomarker could aid in clinical decision making for early treatment change as a novel and cost-effective approach.

3042 **Poster Session (Board #34), Sat, 8:00 AM-11:00 AM**

A prospective study tracking longitudinal changes in genome-wide cell-free DNA (cfDNA) methylation to identify early nonresponders to cancer treatment.

Andrew A. Davis, Wade Thomas Iams, David Chan, Michael S Oh, Robert William Lentz, Rohith Srivas, Nicole Lambert, Alex Robertson, Neil Peterman, Abhik Shah, Timothy Wilson, Jason Close, Peter George, Haleigh Wood, Ayse Tezcan, Ram Yalamanchili, Ken Nesmith, John C Spinosa, Haluk Tezcan, Young Kwang Chae; Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL; Vanderbilt University Medical Center, Nashville, TN; Cancer Care Assoc-TMPN, Redondo Beach, CA; Northwestern University Feinberg School of Medicine, Chicago, IL; Northwestern University Internal Medicine, Chicago, IL; Lexent Bio, Inc., San Francisco & San Diego, CA; Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL

Background: Methylation is an epigenetic modification linked to cancer pathogenesis. The aim was to determine if changes in cfDNA methylation patterns before and after initiation of treatment could predict non-response to treatment prior to routine imaging and clinical follow-up. **Methods:** We prospectively collected clinical data and blood from 28 patients with metastatic malignancies (13 lung, 11 breast, 4 other). Blood was drawn prior to start of a new treatment, after first cycle (median 30 days), and/or second cycle (median 57 days). We performed whole-genome (WG) bisulfite sequencing (median depth 18X) on plasma cfDNA to determine methylation levels. By tracking how methylation levels deviate from unaffected individuals, from baseline to subsequent timepoints, we classified patients as either progressors (greater deviance) or non-progressors. Treatment response at first follow-up imaging (FUI) was determined by RECIST 1.1. Study endpoints were agreement with first FUI and progression-free survival (PFS) by cfDNA classification. **Results:** The cohort consisted of 68% females and the median age was 70. Main treatment regimens were chemo- (N = 12), immuno- (6), endocrine (5), or targeted-therapy (5). PFS was significantly shorter (log-rank $p = 8 \times 10^{-7}$) in patients classified as progressors by cfDNA (N = 8; median: 62 days) compared to non-progressors (N = 20, median: 263 days). For patients classified as progressors, the cfDNA assay preceded imaging and clinical evaluation by a median of 34 days. 7 out of 8 patients classified as cfDNA progressors were later confirmed to progress at first follow-up evaluation (88% positive predictive value). The one patient who was classified as progressor based on cfDNA was stable based on FUI (day 93 of treatment) but was later confirmed as progression on day 128 by FUI. For the remaining patients, 18 of 20 did not progress (90% negative predictive value). Thus, sensitivity for the assay for identifying progression was 78% and specificity was 95%. **Conclusions:** Our results show that WG cfDNA methylation change is a novel signature with potential to identify patients whose treatment regimen is ineffective prior to imaging.

3043 **Poster Session (Board #35), Sat, 8:00 AM-11:00 AM**

NMR-metabolite-resonance signature to predict HR+ breast cancer patient response to CDK4/6 inhibitors.

Bo Zhang, Jason Warner, Christopher Pinto, Dejan Juric, Elizabeth ODay; Olaris Therapeutics, Cambridge, MA; Massachusetts General Hospital Cancer Center, Boston, MA; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

Background: Advanced ER+ breast cancer patients have reported prolongation of stable disease when treated with a CDK4/6 inhibitor as a monotherapy or in combination with endocrine treatment. However ~20% of patients are intrinsically resistant and all patients eventually acquire resistance to these therapies. There is a critical need to identify biomarkers that accurately predict response and resistance to CDK4/6 inhibitors. ER-positivity, luminal patterns of gene expression, Rb function, overexpression of cyclin D1, cyclin E, CDK6 and low levels of p16 are biomarkers that do not accurately match clinical outcomes. **Methods:** We performed a retrospective study analyzing plasma-based metabolites from a baseline (pre-dose) and ~2 months post treatment of 21 women with estrogen-receptor-positive (ER+) metastatic breast cancer treated with CDK4/6 inhibitors. **Results:** By correlating the metabolite expression profiles to clinical outcomes we were able to identify a metabolic signature that could differentiate the CDK4/6 responders and resistant patients with a predictive accuracy of $>$ 90%. Further we were able to identify independent signatures predictive of response for individual CDK4/6 inhibitors palbociclib and ribociclib. **Conclusions:** The results of this study could lead to a paradigm shift in the administration of CDK4/6 inhibitors wherein prior to treatment and during treatment patient plasma is screened to determine whether that individual patient is responsive or resistant to a CDK4/6 inhibitor.

3044 **Poster Session (Board #36), Sat, 8:00 AM-11:00 AM**

Mastocheck: Notable plasma protein biomarker for diagnosis of breast cancer in the real clinical practice by using multiple reaction monitoring-based mass spectrometry.

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Background: Breast cancer is the most frequently diagnosed cancer and the most leading cause of cancer-related deaths among women worldwide. Although screening mammography is available, there is an ongoing interest in improved early detection and prognosis. And also, serum tumor marker levels, such as CA 15-3 and others, may reflect disease progression and recurrence, they have not proven to be sensitive for early disease detection. Research investigating biomarkers for early detection, prognosis and the prediction of treatment responses in breast cancer is rapidly expanding. However, no validated biomarker currently exists for use in routine clinical practice, and breast cancer detection and management remains dependent on invasive procedures We aimed to develop biomarker for diagnosis of breast cancer in the real clinical practice by using proteomics technology. **Methods:** Based on our previous studies, we performed verification and validation of 124 candidate proteins by using proteomics approach. Among these 124 candidate proteins, the three proteins (neural cell adhesion molecule L1-like protein, apolipoprotein C-1, carbonic anhydrase-1) with highest statistical significance were selected. We created the performance algorithm of the 3-protein diagnostic model to predict of the breast cancer. We performed several experiments for establishment and validation of cut-off value. Furthermore we conducted test for acquisition of sample stability and more experiments to achieve the reproducibility and level of evidence, compared with other cancers (colon, thyroid, ovary, pancreas and lung cancer) and established effect of anesthesia. **Results:** Total 1226 samples (532 patients of breast cancer, 562 healthy women and 100 sample of other cancers) was analyzed. The sensitivity, specificity and accuracy from confirmation experiment was 71.58%, 85.25% and AUC 0.8323, respectively. The result of comparison with other cancers, there are no statistical significant difference and no relevance with effects of anesthesia. With these results, we recently got permission it to use for in vitro diagnostic use from Korea Food and Drug Administration. **Conclusions:** In this study, we developed a plasma protein biomarker that may help to diagnosis of breast cancer in the real clinical practice. By using MRM approach, the 3-protein biomarker was validated in an independent cohort with acceptable accuracy for early diagnosis of breast cancer.

3045 **Poster Session (Board #37), Sat, 8:00 AM-11:00 AM**

Circulating bacterial DNA as a tool towards noninvasive biomarkers for colorectal adenocarcinoma and adenoma.

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Background: The gut microbiota is closely associated with the progression of colorectal neoplasia. While most metagenomics studies utilized fecal samples, circulating bacteria DNA in colorectal adenocarcinoma (ADC) or adenoma (ADM) patients remain unexplored. This study aimed to characterize microbiota DNA in plasma samples and build a machine-learning model for ADC and ADM early detection. **Methods:** In this proof-of-concept study, we performed whole genome sequencing (~30X) of plasma samples from 25 ADC patients, 10 ADM patients, and 22 healthy controls (HC). Significant biomarkers were identified in the discovery cohort (12 ADC and 11 HC) and built into a random-forest model which was tested in the validation cohort (13 ADC and 11 HC). These biomarkers were further examined in ADM and tested for abundance difference with ADC and HP. **Results:** In the discovery cohort, 111 species had increased relative abundance in ADC compared to HC and 165 species had decreased relative abundance. Alteration in several species such as *Flavobacterium* and *Ruminococcus torques* were consistent with previously published results in faecal and gut microbiome samples. The random forest-recursive feature elimination model selected 28 significant species from the discovery cohort (mean AUC = 0.98, repeated 2-fold cross-validation) and yielded an AUC of 1 in the validation cohort. Interestingly, most biomarker species in ADM patients, with abundance intermediate between ADC and HC, were distinguished from HC. To further test the clinical utility of this model, sequencing data were randomly down-sampled to 1X and the model performance remained robust (AUC = 1) at distinguishing ADC and ADM from HC. **Conclusions:** This study is the first effort to characterize circulating bacteria DNA in patients with ADC and ADM. Our findings revealed significant difference in relative abundance of several bacterial species between ADC, ADM and HC. A predictive model constructed with selected microbial features accurately distinguished ADC and ADM from HC. Circulating bacteria biomarkers represent potential non-invasive tools for early diagnosis of colorectal neoplasia.

3046 **Poster Session (Board #38), Sat, 8:00 AM-11:00 AM**

Comprehensive genomic profiling of circulating cell-free DNA (cfDNA) distinguishes focal amplification (amp) from aneuploidy among *MET* amps in diverse advanced cancer types.

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Background: MET amps can occur from focal gene copy number gain (e.g. MET-driven) or gain of chromosome 7 (e.g. aneuploidy); however, the contribution of each to MET amp is not well established. MET inhibitor-sensitive lung cancers harboring high-level MET amp have been reported in the absence of other sensitizing MET alterations (alts), e.g. exon 14 skipping, particularly among those with higher MET to chromosome 7 ratios. **Methods:** 3,114 samples from 2,902 Asian patients with advanced solid tumors were tested with a comprehensive cfDNA NGS panel (Guardant360) between Oct 2015-Dec 2018. This 70-73 gene assay evaluates single nucleotide variants (SNV), selected insertion-deletions (indels), fusions, and copy number gains. Focal amp was determined bioinformatically as having statistically higher copy number relative to other genes, such as BRAF, or CDK6, in the same chromosome arm. **Results:** MET alts associated with aberrant signaling were found in 223 pts (7.7%) with 18 different cancer types, most commonly lung (128/1,678), colorectal (36/349), and prostate (11/48). Among 223 pts, 189 pts (84.8%) had amps, 38(17.0%) had exon 14 skipping, and 8 (3.6%) had activating SNVs. 39.7% of MET amp was focal but differed by cancer type; highest prevalence was in gastroesophageal (80%) and lowest in prostate cancers (9%). Samples with focal MET amp had higher plasma copy number compared to those with non-focal MET amp (mean 5.8 vs. 2.5; $p < 0.0001$) and lower total number of alts per sample (8.8 vs. 11; $p = 0.0122$). Focal MET amp was more common than non-focal MET amp among 419 EGFR mutated samples (6.9% vs. 3.8%, $p = 0.05$) suggesting focal MET amp may be biologically more relevant as a mechanism of EGFR TKI resistance. **Conclusions:** This is the first study to use cfDNA to examine focal vs. non-focal MET amp. Focal MET amp accounted for ~40% of all MET amps, was found in 2.6% of pts with diverse cancers, was associated with higher plasma copy number, and found in a higher proportion of EGFR mutated lung cancer samples. The ability to differentiate may be clinically relevant given higher MET to chromosome 7 ratios have been associated with improved therapeutic response.

3047 **Poster Session (Board #39), Sat, 8:00 AM-11:00 AM**

Tumor specific DNA in bronchial lavage as a new diagnostic tool in lung cancer.

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Background: A considerable fraction of lung cancer patients raise diagnostic challenges requiring invasive procedures with a certain risk of complications. Therefore, new diagnostic tools are of major interest. Aberrant methylation of the HOXA9 gene occurs in almost all malignant lung tumors and HOXA9 methylated DNA (meth-ctDNA) is shed into the circulation. The present study aimed at a prospective investigation of the possible diagnostic value of HOXA9 meth-ctDNA in bronchial lavage (BL). **Methods:** Patients enrolled were referred from the general practitioner suspecting lung cancer. The diagnostic package according to national guidelines includes chest and abdominal CT scan, bronchoscopy, relevant blood tests, and histopathological or cytological verification. Twelve ml liquid was collected at bronchoscopy for analysis of meth-ctDNA based on ddPCR technology according to our published method. The analysis was performed blinded to the clinical data and compared to the final diagnosis. **Results:** Eighty-nine patients were consecutively included from the 1 November 2018 to 31 January 2019. Fifty-six patients (62.9%) were diagnosed with lung cancer and 33 (37.1%) with a variety of benign diseases. Meth-ctDNA was found in 42/56 of the patients with a malignant tumor, sensitivity = 75.0% (95%CI=61.6-85.6%), whereas 31/33 of the patients without cancer were negative, specificity = 93.9% (95%CI= 79.8-99.3%). Table summarizes the results. The false negative samples were mainly from patients with peripheral tumors. The two false positive patients included one patient with Cryptogenic Organizing Pneumonia and one with unspecific nodule. **Conclusions:** The presence of meth-ctDNA in BL has a high sensitivity and specificity. If validated, the analysis represents a valuable adjunct in the diagnosis of lung cancer. Potentially, it could save the patients from numerous examinations with potential harmful risks and ensure a fast diagnosis. The relation between meth-ctDNA and final lung cancer diagnosis (N= 89).

Final lung cancer diagnosis.			
Presence of meth-ctDNA	**Yes**	**No**	**Total**
Positive	42	2	44
Negative	14	31	45
Total	56	33	89

3048 **Poster Session (Board #40), Sat, 8:00 AM-11:00 AM**

Polymorphisms in the dopamine (DA) signaling to predict outcome in patients (pts) with metastatic colorectal cancer (mCRC): Data from TRIBE, MAVERICC, and FIRE-3 phase III trials.

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Background: Strong evidence supports the critical role of the gut-brain axis in modulating gastrointestinal function and homeostasis. Available data suggest an involvement of the dopaminergic pathway in CRC dynamics. DA could inhibit proliferation and migration of tumor endothelial cells and enhanced 5-fluorouracil efficacy in CRC preclinical models. Hence, we hypothesized that genetic variants in DA signaling may predict treatment outcomes in mCRC pts. **Methods:** The impact on outcome of 22 selected single nucleotide polymorphisms (SNPs) in 9 genes of the DA signaling pathway (*DRD1, DRD2, DRD3, DRD4, DRD5, TAAR1, SLC6A3, SLC18A2, PPP1R1B*) was analyzed on a total of 884 pts enrolled in three independent randomized first-line trials: TRIBE (n = 324), MAVERICC (n = 324), and FIRE-3 (n = 236). Genomic DNA from blood samples of pts was genotyped through the OncoArray, a custom array manufactured by Illumina. A meta-analysis approach using the METASOFT software was used to quantify SNPs prognostic effects and heterogeneities across treatment arms. *P* values were adjusted for multiple testing using the false discovery rate (FDR) method. **Results:** Overall, *DRD3* rs3732790, rs9817063 and rs2134655 showed a significant nominal *p* value (*P*) in association with tumor response (TR) across trials (*P*= 0.032, *P*= 0.021, *P*= 0.027, respectively). *TAAR1* rs8192620 showed an association with both progression free survival (PFS) (*P*= 0.01) and overall survival (OS) (*P*= 0.033), similar to DA transporter *SLC6A3* rs6347 (*P*= 0.016 and *P*= 0.002, respectively). *SLC6A3* rs6347 association with OS remained significant after FDR (P_{FDR}= 0.045). Subgroup analyses showed a significant association with PFS for *DRD1* rs267410 and *SLC6A3* rs2652510 in females (P_{FDR}= 0.056), and between *SLC6A3* rs6347 and OS (P_{FDR}= 0.041) and *SLC6A3* rs6876890 and TR (P_{FDR}= 0.05) in *KRAS* wild type. **Conclusions:** Our results suggest that SNPs in DA signaling may have a prognostic value in mCRC pts receiving first-line treatment. Upon validation, these findings may provide novel insight on the role of DA signaling in CRC and possibly contribute to open novel therapeutic perspectives.

3049 **Poster Session (Board #41), Sat, 8:00 AM-11:00 AM**

Genome-wide cell-free DNA (cfDNA) methylation signatures and effect on tissue of origin (TOO) performance.

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Background: For multi-cancer detection using cfDNA, TOO determination is critical to enable safe and efficient diagnostic follow-up. Previous array-based studies captured $<$ 2% of genomic CpGs. Here, we report genome-wide fragment-level methylation patterns across 811 cancer cell methylomes representing 21 tumor types (97% of SEER cancer incidence), and define effects of this methylation database on TOO prediction within a machine learning framework. **Methods:** Genomic DNA from 655 formalin-fixed paraffin-embedded (FFPE) tumor tissues and 156 isolated cells from tumors was subjected to a prototype 30x whole-genome bisulfite sequencing (WGBS) assay, as previously reported in the Circulating Cell-free Genome Atlas (CCGA) study (NCT02889978). Two independent TOO models, one with and one without the methylation database, were fitted on training samples; each was used to predict on the test set. A WGBS classifier was used to detect cancer at 98% specificity; reported TOO results reflect percent agreement between predicted and true TOO among those detected cancers (166 cases: 81 stage I-III, 69 stage IV, 16 non-informative). **Results:** Genome-wide methylation data generated from this database allowed fragment-level analysis and coverage of ~30 million CpGs across the genome (~60-fold greater than array-based approaches). Incorrect TOO assignments decreased by 35% (20% to 13%) after incorporating methylation database information into TOO classification. Improvement was observed across all cancer types and was consistent in early-stage cancers (stage I-III). Respective performances in breast cancer (n = 23) were 87% vs 96%; in lung cancer (n = 32) were 85% vs 88%; in hepatobiliary (n = 10) were 70% vs 90%; and in pancreatic cancer (n = 17) were 94% vs 100%. Results using an optimized approach informed by these results in a large cohort of CCGA participants will be reported. **Conclusions:** Incorporating data from a large methylation database improved TOO performance in multiple cancer types. This supports feasibility of this methylation-based approach as an early cancer detection test across cancer types. Clinical trial information: NCT02889978.

3050 **Poster Session (Board #42), Sat, 8:00 AM-11:00 AM**

CTC versus biopsy tissue sequencing: A concordance analysis of genomic copy number profile from mCRPC patients (pts).

Howard I. Scher, Jerry Lee, Angel E. Dago, Ethan Barnett, Ramsay Sutton, Emily Carbone, Nicole A. Schreiber, Melanie Hullings, Nadia Ebrahim, Mark Andrew Landers, Yipeng Wang, David B. Solit, Michael F. Berger, Nikolaus Schultz, Ryan Dittamore; Memorial Sloan Kettering Cancer Center, New York, NY; Epic Sciences, Inc., San Diego, CA; Epic Sciences, San Diego, CA

Background: MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets), is a high throughput, targeted-DNA-sequencing panel for somatic mutations created by the Department of Pathology at Memorial Sloan Kettering Cancer Center (MSK). The MSK-IMPACT is FDA approved for tumor tissue profiling to guide treatment selection. Recognizing access to tumor tissue in many cancers is difficult and may harbor inter & intra lesional heterogeneity, we sought to evaluate concordance of sequencing single CTCs vs. paired biopsy analyzed by MSK-IMPACT, to assess CTC vs. tumor clonality, and their relationship to outcomes. **Methods:** 148 biopsy samples from 138 mCRPC pts were submitted for IMPACT analysis and a blood draw within 30-day prior to initiation of a new line of treatment. Blood samples were sent to Epic Sciences for CTC detection. The detected CTCs underwent single cell low pass whole genome sequencing for copy number variation (CNV). For each set of matched samples, DNA copy number profiles from IMPACT and CTC sequencing were compared for similarity. **Results:** Of the 114 successfully sequenced samples 58 were from lymph nodes, 23 from bone, 25 from liver or lung, and 8 from other soft tissue. Of the 111 patients with CTCs analyzed, a total of 1073 CTCs were sequenced (range 1-27, median = 4 per pt). Of patients with both IMPACT & CTC, >80% pts had multiple subclones with distinguishable CNV. Concordance of genomics clones was found in 63%, and discordant in 37% cases. The clonal concordance between tissue biopsy and CTC was higher when the biopsy was obtained from bone marrow or a visceral site (71% concordance) than from a lymph node (53% concordance). **Conclusions:** Single CTC sequencing is often concordant to metastatic tissue, but unique CTC clones and the presence of multi-clonal disease highlight the potential to be underrepresented through tissue biopsy, especially when taken from the lymph node.

Cohort (n=148)	Frequency of Observation
IMPACT result	77% (114/148)
CTC result	75% (111/148)
Both CTC & IMPACT	61% (90/148)
IMPACT only	16% (24/148)
CTC only	14% (21/148)
No results	9% (13/148)

3051 **Poster Session (Board #43), Sat, 8:00 AM-11:00 AM**

Identification and validation of a serum microRNA panel for detection of early-stage breast cancer.

Ruiyang Zou, Lihan Zhou, Sau Yeen Loke, Heng-Phon Too, Ann Lee; MiRXES Pte Ltd, Singapore, Singapore; National Cancer Centre Singapore, Singapore, Singapore; National University of Singapore, Singapore, Singapore

Background: The implementation of mammogram-based screening has significantly improved the early detection of breast cancer in the west. However, the use of screening mammography is less prevalent in Asia partly due to social and cultural reasons. The aim of this study was to determine if a serum microRNA (miRNA) panel could be used as biomarkers to assist in the early detection of breast cancer. **Methods:** We conducted a multi-center, multi-ethnic study to identify and validate miRNA biomarkers for the early detection of breast cancer. A total of 1070 subjects including 550 breast cancer cases (predominantly stage 1 and 2) and 520 matched controls from 6 independent sources were included in this study. Among these, there were 768 American and European subjects recruited by biobanks and 302 Singaporean Asian Subjects recruited at the National Cancer Centre Singapore and the National University Hospital. The study was conducted in 3 phases. First, 119 European Caucasian serum samples (Discovery Cohort) were interrogated to identify differentially expressed miRNAs between early-stage breast cancer cases and matched controls, among 520 circulating miRNA candidates by quantitative RT-PCR using MiRXES assays. The remaining 951 subjects from 5 independent sources were assigned into two groups for biomarker optimization/algorithm development (Optimization Cohort, n = 451) and validation (Validation Cohort, n = 500). **Results:** Among the 520 circulating miRNAs measured, 241 were quantified in absolute copy numbers for 119 subjects in the Discovery Cohort. Thirty-two candidate miRNAs were identified. These miRNAs consistently showed differential expression between cancer and control subjects in the Optimization Cohort. A multi-variant panel of 8 miRNAs and an algorithm was developed using the combined Discovery and Optimization Cohorts, with an AUC of $>$ 0.90. When validated in the independent Validation Cohort, the panel demonstrated an AUC of $>$ 0.85. **Conclusions:** We developed and validated a serum miRNA panel that is both sensitive (~70%) and specific (~90%) in detecting early-stage breast cancer.

3052 **Poster Session (Board #44), Sat, 8:00 AM-11:00 AM**

Cell-free methylated DNA (cfMeDNA) immunoprecipitation and high throughput sequencing technology (cfMeDIP-seq) in patients with clear cell renal cell carcinoma (ccRCC).

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Background: CfmeDNA is a promising biomarker for non-invasive assessment of solid tumors: i) MeDNA is tissue- and tumor-specific ii) cfDNA methylation changes are stable unlike DNA alterations iii) 'methylation target size' is larger than identifying specific genomic alterations and, therefore, more sensitive. CfMeDIP-seq is a sensitive assay for genome-wide bisulfite-free cfMeDNA profiling, that requires 1-10 ng input DNA. We tested the feasibility of cfMeDIP-seq to detect ccRCC across TNM stages. **Methods:** We evaluated plasma cfDNA collected prior to nephrectomy in 46 pts with ccRCC: 25 stage I, 7 stage II, 6 stage III, 8 stage IV. cfMeDIP-seq involves four steps: 1) cfDNA end-repair, A-tailing, and adapter ligation 2) cfMeDNA immunoprecipitation and enrichment using an Ab targeting 5-methylcytosine (quality control by qPCR to ensure $<1\%$ of unMeDNA and $>99\%$ reaction specificity) 3) adapter-mediated PCR to amplify cfMeDNA 4) high-throughput NGS for cfMeDNA data. A previously-derived model (Shen et al, *Nature*, 2018) was used to classify pts as having ccRCC or not based on cfMeDNA. cfMeDIP-seq paired end data was reduced to 300 bp windows of the genome that map to CpG islands, shores, shelves, and FANTOM5 enhancers; a classifier was then built using the top 1,000 most variable fragments between pts with ccRCC and cancer-free controls. Statistical comparisons were performed in the R statistical environment, with the *caret* package being used for classifier construction and evaluation. **Results:** The average amount of cfDNA isolated from 1 ml of ccRCC plasma was 19.8 ± 39.8 ng/μL [1.95-260]. Greater than 99% specificity of reaction and $<1\%$ of unMeDNA was achieved in 46/46 samples (100%). The previously-derived classifier of ccRCC correctly predicted 46/46 pts (100%) as having ccRCC. Across 3 rounds of 5-fold cross-validation, the classifier performed with a Cohen's Kappa of 0.93. **Conclusions:** CfMeDIP-seq is a non-invasive, cost-effective, and sensitive assay to detect cancer-specific cfmeDNA in ccRCC pts prior to nephrectomy. With further validation, cfmeDNA may detect minimal residual disease after nephrectomy for 'precision' adjuvant therapy.

3053 **Poster Session (Board #45), Sat, 8:00 AM-11:00 AM**

Training and validation study for sequential monitoring of CAMLs in circulation to predict ongoing progression in lung cancer patients undergoing definitive radiotherapy.

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Background: Cancer Associated Macrophage-Like cells (CAMLs) are a recently described circulating stromal cell common in the peripheral blood of cancer patients that are prognostic for progressive disease. Further, it has been shown that changes in CAML size (i.e. enlargement above 50μm) can predict progression free survival (PFS) in thoracic cancers (e.g. lung). We enrolled 104 unresectable non-small cell lung cancer (NSCLC) patients, with an initial training set review of 54 patients, to determine if change in CAML size after radiation therapy was predictive PFS. **Methods:** A 2 year single blind prospective study was undertaken to test the relationship of $\geq$50μm CAMLs to PFS based on imaging in lung patients before and after induction of chemo radiation, or radiation therapy. To achieve a 2-tailed 90% power ($\alpha = 0.05$) we recruited a training set of 54 patients and validation set of 50 patients all with pathologically confirmed unresectable NSCLC: Stage I (n = 14), Stage II (n = 16), Stage III (n = 61) & Stage IV (n = 13). Baseline (BL) blood samples were taken prior to start of therapy & a 2nd blood sample (T1) was taken after completion of radiotherapy (~30 days). Blood was filtered by CellSieve filtration and CAMLs quantified. Analysis by CAML size of $<$ 49 μm or $\geq$50 μm was used to evaluate PFS hazard ratios (HRs) by censored univariate & multivariate analysis. **Results:** CAMLs were found in 95% of samples averaging 2.7 CAMLs/7.5mL sample at BL, with CAMLs $\geq$50 μm having reduced PFS (HR = 2.2, 95%CI1.3-3.8, p = 0.003). At T1, 18 patients had increased CAML size $\geq$50 μm with PFS (HR = 4.6, 95%CI2.5-8.3, $p < 0.001$). In total, $\geq$50 μm CAMLs at BL was 76% accurate at predicting progression within 24 months while $\geq$50 μm CAMLs at T1 was 83% accurate at predicting progression. **Conclusions:** In unresectable NSCLC patients, enlargement of CAMLs during treatment is an indicator active progression. We identify that a single $\geq$50 μm CAML after induction of radiotherapy, in our training set and confirmed in our validation set, is an indicator of poor prognosis. We suggest that changes in CAML size during therapy may indicate the efficacy of therapy and could potentially help shape subsequent therapeutic decisions.

3054 **Poster Session (Board #46), Sat, 8:00 AM-11:00 AM**

Associations between baseline serum biomarker levels and cachexia/precachexia in pretreated non-small cell lung cancer (NSCLC) patients.

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Background: We previously reported associations of pretreatment serum biomarkers with clinical outcomes in a cohort of advanced NSCLC patients that progressed on front-line therapy. This study aims to elucidate mechanisms underlying cancer cachexia/ pre-cachexia by evaluating relationships between baseline serum biomarker values and sequential changes in body weight, body mass index (BMI), and neutrophil/lymphocyte ratio (NLR) in NSCLC patients. **Methods:** We used Luminex immunobead assays to survey 101 protein biomarkers in sera from advanced NSCLC (n = 138) collected prior to their salvage regimen. Serial parameters associated with cancer cachexia included body weight, BMI, and NLR. Outcome variables (progression-free survival (PFS) and overall survival (OS)) were extracted with full IRB-approval. Biomarkers were evaluated as continuous variables with the cachexia surrogates using Pearson correlations, whereas associations of PFS and OS were accomplished with the Cox PH test. **Results:** High baseline values of BMI and low baseline NLR were associated with both OS and PFS (each $p < 0.05$), though weight failed to reach significance. PFS and OS were similarly associated with percent changes (relative to baseline) in weight ($p < 0.01$), BMI ($p < 0.01$), and NLR ($p < 0.001$). Thirteen biomarkers were found to be associated ($p < 0.05$) with baseline BMI values, including positive correlations with leptin, sol.VEGFR2, and c-peptide and inverse correlations with adiponectin, ferritin, ghrelin, IGFBP-1 and IL-8; fifteen biomarkers were associated with baseline NLR (all $p < 0.05$), including positive correlations with visfatin, insulin, and serum amyloid A and inverse correlations with IGF-II. Fifteen biomarkers were found to be associated ($p < 0.05$) in common with percent weight and BMI changes, including positive correlations with IGFBP-3 and inverse correlations with insulin, FGF-2, TNF-alpha, and resistin. Only prolactin and placental growth factor were found to be associated ($p < 0.05$) with percent change in NLR. **Conclusions:** A series of circulating protein biomarkers primarily connected with metabolic regulation and systemic inflammation/ acute phase response were found to be associated with cachexia/ pre-cachexia in NSCLC patients. Additional cohorts are currently being tested to verify these findings.

3055 **Poster Session (Board #47), Sat, 8:00 AM-11:00 AM**

Efficacy of tyrosine kinase inhibitors (TKIs) based on the ALK resistance mutations on amplicon-based liquid biopsy in ALK positive non-small cell lung cancer (NSCLC) patients (pts).

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Background: Acquired *ALK* resistance mutations (mut.) are the main mechanism of tyrosine kinase inhibitor (TKI) resistance (30-50%). While next-generation TKIs are more active on mut. than earlier TKIs, compound *ALK* resistance are associated with failure to next-generation TKIs. We evaluated the clinical utility of detecting *ALK* resistance mutations in blood to predict TKI efficacy. **Methods:** *ALK* positive advanced NSCLC pts were prospectively enrolled between Oct. 2015 and Aug. 2018 in 8 French institutions. Prospective samples were collected; ctDNA was analyzed by amplicon-based Inivata InVisionFirst-Lung. **Results:** A total of 101 pts with advanced *ALK* positive NSCLC were enrolled and 328 samples collected. In samples collected at TKI failure (N=74), we detected 9 single and 7 complex ($\geq$2) *ALK* resistance mut. (22%), associated with *EML4-ALK* variant 3 (38%) vs. variant 2 (13%) vs. variant 1 (none); 30% had other somatic mut. (mainly *TP53* and *KRAS, PI3KCA*, *MET,* etc.). No mutations were detected in 48% of samples (ctDNA^{neg}). *ALK* mut. were more frequent after 2nd/3rd generation TKI (43% *post*-lorlatinib (7), 29% *post*-2nd gen. (31), 11% *post*-crizotinib (36)). *ALK*G1202R was the most common, as single (n=3) or complex mut. (n=4). The median overall survival (mOS) was 100.4 mo. (95% CI 41.9-158.9) and the median progression free-survival (mPFS) to subsequent line was 2.8 mo. (0.7-4.9). Patients with ctDNA^{neg} had mOS of 105 mo. (39.3-172.1) vs. 58.5 mo. (33.1-84.0) if $\geq$1 *ALK* mut. vs. 44.1 mo. (20.0-68.2) if others (*P*=0.001). Pts with the complex *ALK* mut. had worse OS compared to singles *ALK* mut. (mOS 26.9 mo. vs. 58.5 mo., *P*=0.001); *ALK* complex mut. were associated with poor efficacy to subsequent therapy (PFS $<$3 mo. in 57%; no cases with PFS $>$6 mo.) vs. single mut., with longer PFS (PFS $>$6 mo. in 56%). Detectable *ALK*G1202R mut. were associated with shorter median OS (58.3 mo.; 7.9-109.1) vs. overall population; 86% of cases developed rapid PD (PFS $<$3mo.) to subsequent therapy with only one durable response to lorlatinib (PFS $>$6mo.). **Conclusions:** The absence of ctDNA mutations at TKI failure was associated with prolonged OS, whereas complex *ALK* mutations at TKI failure may predict resistance to subsequent therapy. Larger and specifically designed studies should be performed to validate these findings.

3056 **Poster Session (Board #48), Sat, 8:00 AM-11:00 AM**

Baseline cfDNA characteristics and evolution of cfDNA profile during treatment with selective FGFR inhibitor TAS-120.

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Background: There is an increasing role for cfDNA in monitoring response and mechanisms of resistance. We performed cfDNA analysis in a subset of patients enrolled on a Phase I trial with an irreversible, selective FGFR1-4 inhibitor, TAS-120. **Methods:** 58 plasma samples from 17 patients (13 with cholangiocarcinoma) were analyzed on a 73-gene, next-generation sequencing panel. Selected patients(pts) had longitudinal samples. **Results:** At least one alteration was detected in 46 cfDNA samples, in 16 (94%) of 17 pts – a pt with GBM had no alterations detected. 14 pts had alterations in *FGFR2/3* by genomic testing of archival tumor samples, comprising 20 total alterations (18 unique). 10 of 20 *FGFR2/3* alterations were also detected by cfDNA testing: 4/5 SNVs, 1/2 amplifications, 5/13 fusions. Three pts had FGFR/FGF alterations not included (thus not detected) in the cfDNA panel: 2 with *FGF* ligand amplification, and one *FGFR4* mutation. 6 pts (35%) had PR, 5 (29%) had SD and 6 (35%) PD as a best response to TAS-120. Four pts had prior FGFRi: 2 had a PR, 1 SD, and 1 PD on TAS-120. Baseline cfDNA mutations became undetectable during treatment in 4/6 pts with PR. 4 of 6 PD pts had other driver mutations at baseline including mutations in *PIK3CA*, *KRAS*, *IDH1*, *BRCA2*, or amplifications in *PIK3CA, PDGFR.* 9 pts with cfDNA available at progression after SD/PR: 3 had acquired *FGFR2* mutations (one each of V564L, V564F, or N549K). Two also acquired alterations in other candidate resistance genes (*PTEN and MAP2K1*). Another pt had low variant allele frequency (VAF) *NRAS* G12D and *BRAF* A694T pretreatment and had SD. At progression, cfDNA revealed an increase in *NRAS* VAF and mutations acquired in the MAPK pathway. One pt with prior FGFRi acquired *FGFR2* V564I and V564K detected by cfDNA prior to initiation of TAS-120, and had a PR on TAS-120. There was a drop in *FGFR2* V564I VAF with response that subsequently increased with progression. The patient also acquired a *FGFR2* V564L mutation at progression. **Conclusions:** *FGFR* alterations can be detected by cfDNA. cfDNA may detect potential resistance mechanisms, including PI3K or MAPK pathway alterations and acquired *FGFR2* mutations. Patients with gatekeeper mutations in cfDNA at baseline may still respond to TAS-120. Further study is needed to determine the impact of *FGFR2* mutations and co-alterations on TAS-120 sensitivity.

3057 **Poster Session (Board #49), Sat, 8:00 AM-11:00 AM**

Analytical validation of a tumor-agnostic integrated multianalyte circulating tumor DNA (ctDNA) assay in early-stage cancer.

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Background: ctDNA sequencing has been rapidly adopted for the identification of targetable somatic alterations (alts) in patients with advanced cancers. However, early stage disease detection has been hindered by low levels of ctDNA in circulation and the presence of confounding non-tumor-related somatic alts. We developed and validated a ctDNA assay that combines somatic and epigenomic signals to detect early stage tumors without tumor tissue or white blood cells (WBC). **Methods:** Using a single input sample, our assay integrates the sensitive detection of genomic alts with quantification of epigenomic signals associated with cancer. Non-tumor alts (e.g., clonal hematopoiesis of indeterminate potential; CHIP) are excluded using a newly developed bioinformatic classifier. To assess analytical sensitivity, specificity, and positive and negative reproducibility, we tested 337 clinical and contrived samples. **Results:** Clinical specificity was determined using 80 plasma samples from 50-75 year old presumptive cancer-free donors, and resulted in a single false positive (99% specificity). Analytical sensitivity (limit of detection) was established using a dilution series of 4 different late stage CRC pts tested in triplicate at a clinically relevant DNA input (30 ng) across multiple batches. 100% sensitivity was maintained even at the lowest tested level (estimated 0.1% tumor level). Positive/negative reproducibility was assessed by testing triplicates of diluted late stage samples and age-matched healthy donors, respectively, across different cfDNA inputs, and multiple reagent lots. Both positive and negative calls were 100% concordant across all replicates. Independent estimation of tumor levels from epigenomic or genomic signals produced highly concordant results (correlation r-value: 0.82, p-value: 3e-16). **Conclusions:** We designed and validated a highly specific ctDNA assay that integrates both genomic and epigenomic signals to allow for accurate and quantitative tumor level detection in early stages of the disease without requiring tumor tissue or WBC.

3058 **Poster Session (Board #50), Sat, 8:00 AM-11:00 AM**

Changes in DNA hydroxymethylation for the detection of multiple cancers in plasma cell-free DNA.

Anna Bergamaschi, Francois Collins, Chris Ellison, Yuhong Ning, Gulfem Guler, Tierney Phillips, Erin McCarthy, Wendy Wang, Michael Antoine, Jeremy Ku, Aaron Scott, Paul Lloyd, Alan Ashworth, Samuel Levy; Bluestar Genomics, San Diego, CA; UC San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Background: Methylation and hydroxymethylation of cytosines enable the epigenomic regulation of gene suppression and activation. 5-hydroxymethyl-cytosine (5hmC) is globally decreased in tumor tissue. However, genome-wide analysis using precise 5hmC labelling techniques reveals more nuanced changes upon tumorigenesis and raises the possibility that this loss could be exploited for developing a cancer biomarker. This suggests that 5hmC profiles might enable discrete classification of not only tumor tissue but also of tumor cell-free DNA (cfDNA). We sought to identify genome-wide 5hmC changes in plasma based cfDNA from cancer patients representing multiple disease types, stages and clinical characteristics in comparison with non-cancer patients. **Methods:** cfDNA was isolated from plasma, enriched for the 5hmC fraction using chemical labelling, sequenced, and aligned to the genome to determine 5hmC counts per genomic feature. Regularized regression models were constructed to classify cancer samples (age matched or corrected for smoking status) on non-overlapping training (80% of all samples) and test sample sets (20% of all samples). **Results:** 226 non-cancer patients and 278 cancers across four cancer types (breast, colorectal, lung-squamous and pancreas) were included in this study, where more than 60% of cancer samples were early stage disease (I or II). Upon comparison with non-cancer samples, 5hmC peaks have reduced enrichment in exons in breast, colorectal and lung cancer but not in pancreatic cancer. Further, 5hmC peaks in pancreas show different patterns of enrichment in 3'UTR, translational termination sites, promoters and LTR. Overall 5hmC signal density was reduced in late stage cancers across all four diseases. The ability to classify non-cancer versus cancer patients was evaluated via cross-validation of out of fold prediction in the training set with AUC $>$ 0.84 for all four cancer types. Further, test set sensitivity across all four cancer types was found to be $>$ 66% with 98% specificity. **Conclusions:** These findings suggest that 5hmC changes in plasma cfDNA enable classification of early stages of breast, colorectal, lung-squamous and pancreas cancer and are promising biomarkers for disease detection.

3059 **Poster Session (Board #51), Sat, 8:00 AM-11:00 AM**

Pooled analysis of phase I dose-escalation and dose cohort expansion studies of IMP4297, a novel PARP inhibitor, in Chinese and Australian patients with advanced solid tumors.

Junning Cao, Pin Zhang, Paul L. de Souza, Bo Gao, Mark Voskoboynik, Dongmei Ji, Weina Shen, Sheng Yang, Yinglei Zhou, Rong Zhang, Jason D. Lickliter, Siao-Nge Hoon, David Palmieri, Suixiong Cai, Ye Edward Tian, Ning Ma, Cong Xu, Stone Yang, Shuaishuai Zhang, Binghe Xu; Fudan University Shanghai Cancer Center, Shanghai, China; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; University of Western Sydney School of Medicine, Sydney, Australia; Blacktown and Westmead Hospitals, Sydney, Australia; Nucleus Network, Melbourne, Australia; Blacktown Hospital, Sydney, Australia; IMPACT Therapeutics Inc., Shanghai, China

Background: Poly (ADP-ribose) polymerase (PARP) enzymes play critical roles in DNA damage detection and repair. IMP4297 is a novel, potent PARP1/2 inhibitor (IC_{50} 6.27nM/1.57nM) and has demonstrated to be 20-fold more potent than Olaparib in anticancer animal models. Two phase I studies were performed to evaluate and characterize the tolerability and safety, pharmacokinetics, and antitumor activity of single agent IMP4297 in Chinese and Australian patients with advanced ovarian, breast, prostate and other solid tumors. **Methods:** Dose escalation used a 3+3 design with a modified Fibonacci escalation. Dose cohort expansion was planned after efficacy was observed at the lowest dose level. Patients received IMP4297 monotherapy orally once a day until disease progression or unacceptable toxicity. **Results:** As of Jan 12, 2019, 56 patients, including 23 BRCA mutation carriers (BRCA+), had been enrolled at 2-100 mg dose level. No DLT was observed. In these two studies, the most frequent treatment-related adverse events (TRAEs) were leukopenia (20%), followed by anemia (18%), nausea (18%) and thrombocytopenia (14%). The majority of TRAEs were grade 1 or 2. Grade 3 TRAEs occurred in five patients (anemia, n=2; vomiting, n=1; thrombocytopenia, n=1; elevated AST, n=1). Only one patient had a dose reduction due to grade 3 thrombocytopenia. No serious TRAEs were observed. In 15 BRCA+ patients who had measurable lesions, the ORR was 33% and the DCR was 80%. There were 4 BRCA+, platinum-sensitive ovarian cancer patients with an ORR of 75% and a DCR of 100%. One patient with somatic BRCA mutated urothelial carcinoma showed a 76% decrease in tumor size. **Conclusions:** IMP4297 has been well-tolerated with significant anti-tumor activity. The 100 mg daily dose was selected as the RP2D based on safety, pharmacokinetics and clinical activity, and will be further characterized in dose expansion and phase II studies. Tumor response to treatment (RECIST 1.1) in patients with measurable lesions. Clinical trial information: NCT03508011 and NCT03507543.

	BRCA+ (n)	PR (n)	%
20mg	4	2	50%
60mg	4	1	25%
80mg	3	1	33%
100mg	2	1	50%
platinum-sensitive ovarian cancer patients	4	3	75%

3060 **Poster Session (Board #52), Sat, 8:00 AM-11:00 AM**

Is the optimal biological dose of oncologic molecular-targeted therapies also clinically effective?

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Background: The determination of the optimal biological dose (OBD) defined as the lowest safe dose associated with biological efficacy, appears to be a promising endpoint for defining the recommended phase 2 trial dose (RP2D) of novel oncologic targeted therapies in early-phase clinical trials. However, the clinical relevance of OBD is still unknown. We conducted a review to assess if the OBDs of molecular targeted therapies defined during early phase trials were useful during subsequent drug development and for oncologic drug approvals. **Methods:** A systematic review was conducted to identify all the molecular targeted therapies approved by FDA in solid and hematological malignancies, and for which early phase trials defined OBDs. The publications of efficacy trials leading to the first FDA approvals were reviewed, as were the FDA approved doses and dosing schedules, which were compared to OBDs found in the early phase trials. **Results:** OBDs were reported in the early phase trial articles of 39.5% (32/81) FDA approved targeted therapies from 1999 to 2017 (19 small molecules and 13 monoclonal antibodies (mAbs)). The maximum tolerated doses (MTD) had not been reached for 59.4% (19/32) of these drugs. When both MTD and OBD had been defined, OBD were lower than MTD in 84.6% of cases, and equal for the others. The OBDs were chosen as the RP2Ds for 56.3% of the molecules. In that case, the final FDA approved doses were consistent with the OBDs for 83.3% of the drugs. These percentages did not differ in between small molecules and mAbs. OBDs mainly relied on indirect effects on the involved signaling pathway elements for small molecules (11/19, 57.9%), and on involved receptor occupancies for mAbs (6/13, 46.2%). In total, 23.5% of all FDA approved molecular targeted therapies were approved at their OBDs. **Conclusions:** Although still poorly investigated, OBD may represent a relevant complementary endpoint in in early phase trials of novel anti-cancer targeted therapies, as OBDs are selected as the final FDA approved doses in 83.3 % of cases when chosen as the RP2Ds, which is much higher than the previously reported 58.0 % when MTDs are chosen as the RP2Ds (Fontes-Jardim et al. *JNCI* 2015).

3061 **Poster Session (Board #53), Sat, 8:00 AM-11:00 AM**

A phase I multiple-dose escalation study to assess the safety, tolerability, and pharmacokinetics of VEGF-receptor inhibitor telatinib (EOC315) in Chinese patients with advanced solid tumors.

Hongming Pan, Tianshu Liu, Jason Tsai, Yapeng Zhao; Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China; Zhongshan Hospital, Fudan University, Shanghai, China; EOC Pharma, Shanghai, China

Background: Telatinib (EOC315) is a highly selective inhibitor of VEGFR/PDGFR (VEGFR 1-3, PDGFR-β, and c-Kit tyrosine kinases). This phase I study was to assess the safety, tolerability, and pharmacokinetics (PK) of Telatinib in Chinese patients with advanced solid tumors. **Methods:** Telatinib was administered to Chinese patients with advanced refractory solid tumors as a single agent in 3+3 dose escalation design, starting from 600mg and escalated to 900mg and 1200mg, given orally twice daily. The PK profile, safety, and tolerability were evaluated per protocol. Efficacy was evaluated with RECIST 1.1 criteria every 6 weeks. **Results:** A total of 15 subjects (6 colorectal cancer, 4 lung cancer, 1 head and neck cancer, 1 melanoma, 1 thymic carcinoma, 1 esophageal carcinoma,1 peritoneal carcinoma) were enrolled per protocol between July 2017 and August 2018, and 13 subjects received at least second line therapies before enrollment. Telatinib was well tolerated in the three dose arms. No dose limiting toxicities (DLTs) occurred during the dose escalation phase. CTC grade 3 AEs observed include hypertension (46.7%, 7/15), fatigue (6.7%, 1/15), transaminase elevation (6.7%, 1/15), hand-foot syndrome (6.7%, 1/15), oral mucositis (6.7%, 1/15), neutropenia (6.7%, 1/15), urobilinogen elevation (6.7%, 1/15), left ventricular systolic dysfunction/decreased ejection fraction (6.7%, 1/15). No CTC grade 4 AE were observed. There were 2 drug related SAEs (hospitalization due to high blood pressure. The PK profile of Telatinib (EOC315) at 600, 900, 1200 mg in Chinese patient cohorts is summarized in Table. For 12 evaluable patients, DCR was 58.3%. For all patients, mPFS was 15 weeks (3.3-34.3w). **Conclusions:** This study demonstrated the safety and tolerability of Telatinib (EOC315) in a multiple dose escalation design at 600, 900, and 1200 mg PO bid in Chinese patients with advanced refractory solid tumor. Telatinib AUC increased dose-proportionally from 600 mg to 900 mg bid, where 900 mg Telatinib bid is the maximum feasible and recommended dose for future studies in Chinese patients with advanced tumors. Clinical trial information: NCT03175497.

Telatinib multiple does pharmacokinetic parameters (D14).

Dose (mg)	$t_{1/2}$ (h)	$AUC_{0\text{-}12h}$ (h*ng/mL)	Vz/F (L)	CLss/F (L/h)	$RAUC_{0\text{-}12h}$
600 (N=3)	6.20±2.36	5309.36±3661.96	1259.21±828.99	146.25±72.37	1.63±1.13
900 (N=3+6)	3.90±1.81	9708.02±2687.77	543.42±145.27	99.00±27.58	1.17±0.74
1200 (N=3)	7.98	7243.44±2776.60	2723.15	181.06±61.05	0.78±0.39

3062 **Poster Session (Board #54), Sat, 8:00 AM-11:00 AM**

Modular phase I/II clinical trial evaluating the selective MET-kinase inhibitor OMO-1 in patients with advanced malignancies: Safety and proof of mechanism.

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Background: MET kinase is a therapeutic target in a range of cancer indications; it is a primary oncogenic driver and a mechanism of therapy resistance. OMO-1 is a highly potent, selective oral inhibitor of MET kinase and Organic Cation Transporter 2 (OCT2). **Methods:** This study assesses the safety, tolerability, pharmacokinetics (PK) and preliminary activity of OMO-1 in patients (pts) with advanced malignancies (NCT03138083). Module 1 data, evaluating ascending doses of OMO-1 monotherapy, are reported here. **Results:** As of January 16, 2019, 34 pts were enrolled at 5 twice-daily (BD) dose levels of OMO-1: 100, 200, 250, 350, and 400 mg, including 10 with MET gene amplified or mutated tumours. OMO-1 was generally well tolerated between 100 - 250 mg BD; pts were in the study for an average of 94 days (range: 15-291 days) and 20/34 pts discontinued due to disease progression. Most frequently-reported AEs were nausea (17/34), vomiting (14/34) and fatigue (14/34), mainly G1-2. Notably, no peripheral oedema, cardiovascular events or non-malignancy related LFT abnormalities were observed. A total of 36 SAEs were reported: 17 in 11 subjects were considered related to OMO-1, and included nausea (3/17), vomiting (4/17), chills, diarrhoea, influenza-like illness (2/17), increased blood bilirubin, blood creatinine (3/17) and neutrophil count, and sepsis. A dose of 250 mg BD was determined as the recommended Phase 2 dose (RP2D); doses $\geq$350mg BD were not in keeping with optimum long-term dosing: at 400 mg BD, 2/3 subjects experienced influenza-like illness (G2 and G3) and at 350 mg BD 2/5 subjects had G2 fatigue and nausea/vomiting. OMO-1 has a half-life of 2.5-3 hrs and plasma exposure is dose-proportional without accumulation. Elevated creatinine was observed across all dose levels, consistent with OCT2 inhibition. IHC analysis on paired tumour biopsies from a MET-mutated NSCLC pt dosed at 200 mg BD showed near-complete inhibition of phosphorylated MET, without affecting total MET. **Conclusions:** OMO-1 has a favourable safety profile at a RP2D of 250mg BD. Expansion cohorts for MET mutated/amplified tumour types are enrolling. Clinical trial information: NCT03138083.

3063 **Poster Session (Board #55), Sat, 8:00 AM-11:00 AM**

First-in-human phase I and pharmacological study of TAS-119, a selective Aurora A (AurA) kinase inhibitor, in patients (pts) with advanced solid tumors.

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Background: AurA is a serine threonine kinase regulating cell division and cell cycle progression and has a role in carcinogenesis. This clinical trial investigated safety, pharmacokinetics and -dynamics and antitumor activity of the selective oral AurA kinase inhibitor TAS-119. **Methods:** Pts with advanced solid tumors were enrolled into 6 dose escalation cohorts (70-300 mg BID 4 days on/3 days off; every 3 out of 4 weeks; or the same schedule in a continuous weekly schedule). In the expansion phase (intermittent schedule), pts with small-cell lung cancer (SCLC), breast cancer, or MYC-amplified/B-catenin mutated (MT) tumors were enrolled, and pts with other solid tumors in a basket cohort. **Results:** Overall, 34 pts were enrolled to the escalation (median age 67 years; 45.3% $>$ 2 prior therapies); DLT was observed in 5 (16.1%) of 31 DLT evaluable pts; 1/10 at 150 mg, 1/6 at 200 mg, 1/5 at 250 mg, and 2/2 at 300 mg BID (fatigue, nausea, dry eyes, corneal epithelial microcysts). The maximum tolerated dose (MTD) was 250 mg BID and recommended Phase 2 dose (RP2D) was 200 mg BID. The most frequent treatment-emergent adverse events were diarrhea (28.3%), eye disorders (27%), fatigue (22.9%), and decreased appetite (14.8%). Grade 3 ocular toxicity were corneal epithelial microcysts in 1 pt (300 mg cohort) and punctate keratitis (expansion breast cancer cohort) in 1 pt. Toxicity grade $\geq$ 3 in $\geq$ 10% of pts were diarrhea (escalation part only), and increased lipase. Plasma exposure was dose-proportional and accumulation ratio was low. Pharmacodynamic data demonstrated target inhibition. Overall, 40 pts were enrolled to multiple expansions (10 SCLC, 9 breast cancer, 13 MYC-amp/B-cat MT tumors, 8 other; median age 60 years; 72.5% $>$ 2 prior therapies). Median delivered relative dose intensity was 89.1% (47.9% - 100%). Stable disease was reported in 37.8% of patients but no complete or partial responses. **Conclusions:** TAS-119 demonstrated favorable safety and tolerability. Low-grade eye toxicity was a dose-dependent toxicity. Preliminary anti-tumor activity of monotherapy TAS-119 is limited. A Phase 1 trial combining TAS-119 with paclitaxel was conducted in parallel. Clinical trial information: NCT02448589.

3064 **Poster Session (Board #56), Sat, 8:00 AM-11:00 AM**

Rethinking about the dose limiting toxicities (DLTs): They can be equivocal!

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Background: The primary goal of oncology phase I trials is to determine the maximum tolerated dose (MTD) in a small number of patients. Within the standard design methodology currently employed there remains many challenges and one pertains to the variability around defining dose limiting toxicities (DLTs). The pre-specified DLT criteria may not well reflect the clinician's practical experience with some adverse events, while others may actually be related to the disease status more than the investigational drug and could be misclassified. DLT misclassification seen in testing a small sample size from each dose group could generate a large bias on dose finding and the MTD estimation. **Methods:** To mitigate the risk of dichotomizing and misclassifying DLTs, we proposed a strategy that introduced the new concept of "equivocal" DLT or AE. A novel dose escalation approach is applied to increase the variability associated with less interpretable AEs so that the model recommendations are more weighted towards the unequivocal AEs/DLTs. To evaluate this novel approach, we established a framework incorporating two types of systematic measurement errors on DLT misclassification, one for the misclassified DLT that is not related to the drug treatment while the other for the non-DLT AE that should be considered severe and relevant to dose finding. In our simulation studies, the Bayesian logistic regression model (BLRM) was used to guide dose escalation in simulated trials to compare the novel weighting approach with the traditional approach. A few numerical examples were also included for method illustration. **Results:** For different types of measurement errors, simulation studies showed that the weighting approach could successfully improve the trial performance, with higher chance of finding the correct MTD and treating more patients at the MTD level. **Conclusions:** The DLT weighting strategy provides a flexible but powerful tool that may incorporate the clinician's valuable experience on some specific DLTs/AEs and improve MTD estimation in oncology phase I dose-escalation trials.

3065 **Poster Session (Board #57), Sat, 8:00 AM-11:00 AM**

Effectiveness of ASCO's adverse event reporting decision aid: Results from an interventional study.

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Background: Investigators often send adverse event (AE) reports to sponsors that are incorrectly categorized as serious or attributed to the investigational drug. Such errors contribute to a high volume of uninformative IND safety reports that sponsors submit to FDA and all participating investigators, straining stakeholder resources and impeding the detection of valid safety signals. To improve the quality of AE reporting, ASCO developed and tested a Decision Aid Tool (DAT). **Methods:** An interventional study with a cross-over design was conducted. Physician investigators and research staff were randomized to receive case studies. Cases were assessed for seriousness and attribution, first unassisted and then with the DAT. Participants completed a feedback survey. Effectiveness of reporting and attribution were assessed using logistic regression. Results are reported as odds ratios (OR) with 95% confidence intervals (CI). **Results:** Most of the 29 participants reported that the DAT was helpful (93%), improved their decision-making time (69%) and confidence in reporting (83%), and that they would use it in practice (83%). The DAT did not significantly affect accuracy of determining seriousness (OR, 0.87; 95% CI: 0.31, 2.46) but it did significantly increase accuracy of attributing a serious AE to a drug (OR, 3.60; 95% CI: 1.15, 11.4). **Conclusions:** The DAT shows promise as a method to reduce errors in attribution of AEs, which may help to ensure the detection of valid safety signals. Many participants were experienced clinical trialists, and the DAT may show greater utility as an educational tool for novice investigators, research staff, and students.

3066 **Poster Session (Board #58), Sat, 8:00 AM-11:00 AM**

The i3+3 design for phase I clinical trials.

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Background: Other than the 3+3 design, new model-based statistical designs like the mTPI design (Ji and Wang, 2013, JCO) are alternative choices for oncology dose-finding trials, including immune oncology dose-finding trials (Atkins et al., 2018, Lancet Oncology). One major criticism of the 3+3 design is that it is based on simple rules, does not depend on statistical models for inference, and leads to unsafe and unreliable operating characteristics. However, the rule-based nature allows 3+3 to be easily understood and implemented in practice, making it practically attractive and friendly. Can friendly rule-based designs achieve great performance seen in model-based designs? For four decades, the answer has been NO. **Methods:** We propose a new rule-based design called i3+3, where the letter "i" represents the word "interval". The i3+3 design is based on simple but more clever rules that account for the variabilities in the observed data. In short, the i3+3 design simply asks clinicians to compare observed toxicity rates with a prespecified toxicity interval, and make dose escalation decisions according to three simple rules. No sophisticated modeling is needed and the entire design is transparent to clinicians. **Results:** We compare the operating characteristics for the proposed i3+3 design with other popular phase I designs by simulation. The i3+3 design is far superior than the 3+3 design in trial safety and the ability to identify the true MTD. Compared with model-based phase I designs, i3+3 also demonstrates comparable performances. In other words, the i3+3 design possesses both simplicity and transparency of the rule-based approaches, and the superior operating characteristics seen in model-based approaches. An online R Shiny tool is provided to illustrate the i3+3 design, although in practice it requires no software to design or conduct a dose-finding trial using the design. **Conclusions:** The i3+3 design could be a practice-altering method for the clinical community. It may increase the safety and efficiency of dose finding trials.

3067 **Poster Session (Board #59), Sat, 8:00 AM-11:00 AM**

Safety and tolerability of veliparib, an oral PARP inhibitor, and M6620 (VX-970), an ATR inhibitor, in combination with cisplatin in patients with refractory solid tumors.

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Background: M6620 (M), a potent ATR inhibitor, has synergistic activity with cisplatin (C) in multiple preclinical models, resulting in DNA damage and antitumor activity. We hypothesize that inhibition of both homologous recombination and base excision repair through the combination of M6620 and veliparib (V, a potent inhibitor of PARP1/2) would result in accumulation of lethal double stranded breaks induced by cisplatin and increased antitumor activity and initiated a phase-1 dose escalation trial of this combination in patients (pts) with advanced solid tumors (NCT02723864). **Methods:** This is a standard 3+3 dose escalation design with 21-day cycles. M is given IV day 2 (D2) and D9; V orally twice daily D1-3 and D8-10; C IV D1 (and D8 from dose level 3 [DL3] onwards) at 40 mg/m^2 (with option of holding after cycle 6). Primary objectives: safety; tolerability; maximum tolerated dose (MTD). Secondary objectives: pharmacodynamic (PD) biomarkers; antitumor activity. Dose-limiting toxicity (DLT) evaluated during cycle 1, response using RECIST 1.1. **Results:** Thirty-seven patients enrolled, median 5 lines of prior therapy (Range 1-12). MTD: V 200 mg, M 210 mg/m^2, C 40 mg/m^2 (DL6). DLT: grade (gr) 4 thrombocytopenia (DL4), hypophosphatemia (not resolved in 24 hrs., DL3), infusion reaction (DL7). Common gr 3/4 toxicities: anemia (41%), thrombocytopenia (30%), neutropenia (27%), hyponatremia (11%) and hypophosphatemia (8%). Of 34 pts evaluable for response: 2 partial response (PR) (6%, 1 confirmed & 1 transient), 22 stable disease (SD) (65%, median 4 cycles, range 2-11). Of 24 pts with PR/SD, 22 had prior platinum chemotherapy. After July 2018, V was held for gr $\geq$2 anemia until improved to gr 1, followed by dose reduction. Of 5 pts treated in this period, 3 required V held. PD analysis of circulating tumor cells is underway to elucidate biomarkers of DNA damage and apoptosis. **Conclusions:** This combination of M6620, veliparib and cisplatin is safe, with activity seen in pts having received prior platinum. The most common toxicity was anemia, which prevented adequate delivery of veliparib. While MTD was established in a heavily pretreated population, consideration should be given to continued dose escalation in pts who have received fewer prior lines of therapy. Funded in part by NCI Contract No. HHSN261200800001E. Clinical trial information: NCT02723864.

3068 **Poster Session (Board #60), Sat, 8:00 AM-11:00 AM**

Image-guided surgery for tumor agnostic detection of solid tumors using the pH-activated micellar imaging agent ONM-100.

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Background: ONM-100, a micelle-based polymer imaging agent conjugated to indocyanine green (ICG) and with an exquisitely pH-sensitive binary activation mechanism, may be used for tumor detection. ONM-100 micelles dissociate in acidic environments resulting in activation of the fluorescent ICG tag. As nearly all solid cancer types are acidotic, ONM-100 has the potential to act as a broadly indicated tumor agnostic imaging agent. This first-in-human study investigates the safety and feasibility of ONM-100 as a tumor agnostic imaging agent for intra-operative fluorescent imaging of various solid tumors. **Methods:** ONM-100 was IV administered 24±8h prior to surgery in a dose escalation scheme (0.1-1.2mg/kg). Patients with histopathologically confirmed breast cancer (BC), head and neck squamous cell carcinoma (HNSCC), colorectal cancer (CRC) and esophageal cancer (EC) were included. Blood was drawn to assess safety and pharmacokinetic data. Intra-operative fluorescence images were collected before and after tumor excision. Post-excision fluorescence images were obtained from serially sliced specimens and correlated with standard histopathological assessment. **Results:** 30 patients (11 BC, 13 HNSCC, 3 EC, 3 CRC) were enrolled. No ONM-100 related serious adverse events were observed and the agent was well-tolerated. A strong and sharply demarcated fluorescent signal was observed in all patients with vital tumor tissue (median CNR ranging 1.85-14.05) which correlated with tumor on final histopathology. HNSCC and superficially located BC as well as peritoneal metastasis could be clearly visualized *in vivo* during surgery. In four patients (BC and HNSCC), perioperatively, tumors otherwise unnoticed by the surgeons were detected on the margin or wound bed using fluorescence imaging. Additionally, two BC tumor lesions were detected that were missed by conventional pre-operative imaging and pathological assessment. **Conclusions:** ONM-100 appears to be safe and enables fluorescent visualization of tumors both *in vivo* and *ex vivo*. The first-in-human data demonstrate the feasibility for potential use of ONM-100 for image guided surgery, margin assessment and detection of occult disease. Clinical trial information: NTR 7085.

3069 **Poster Session (Board #61), Sat, 8:00 AM-11:00 AM**

Radiomics features to identify distinct subtypes of triple-negative breast cancers.

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Background: We sought to gain new insight into triple-negative breast cancer (TNBC), an aggressive, clinically distinct subgroup of breast cancers, by applying a sequence of computational approaches to tumor segmentation, three-dimensional anatomic characterization, and tumor subtyping. We extracted algorithmically-derived quantitative imaging (radiomics) features from each TNBC lesion in breast magnetic resonance imaging (MRI) to identify underlying subtypes. **Methods:** We evaluated tumors on pre-treatment, post-contrast MRI from 90 patients with non-metastatic TNBC. We employed active contour segmentation and semi-automated identification of tumor regions-of-interest. We extracted 900 radiomics features from each segmented tumor using an algorithm that characterizes the size, shape, texture, and edge sharpness of tumors at the voxel level. We applied k-means consensus clustering, a statistical tool for unsupervised discovery, and performed 1000 bootstraps with resampling on the feature vectors to examine all resulting clusters from k=2 to 10. Based on two diagnostic metrics of consensus stability, we selected the optimum cluster number. We performed Significance Analysis of Microarrays to identify statistically significant radiomics features for each cluster. **Results:** We identified three distinct image-based clusters in 117 tumors from 90 TNBC patients (multifocal lesions in n=13). Cluster 1 (n=97) was distinguished by 330 radiomics features (False Discovery Rate [FDR] $<$5%) and Cluster 2 (n=13) by 85 features (FDR$<$5%), whereas Cluster 3 (n=7) was not significantly associated with features. Clinical characteristics did not differ across the three clusters, with mean age (49.1$\pm$11.7) and clinical stage distributions (stage I: 20.7%, II: 55.4%, III: 23.9%) for the cohort mirroring those of individual clusters. Among those who received neoadjuvant therapy, we observed pathologic complete response in 50% (23 of 46, 95% CI, 0.36-0.64) of patients in Cluster 1, 83% (5 of 6, 95% CI, 0.54-1.0) in Cluster 2, and 0% (0 of 3) in Cluster 3. **Conclusions:** Radiomics features providing voxel-level characteristics of tumor morphology differentiated TNBC into three distinct subtypes. These subtypes, defined by radiomics biomarkers, may be associated with clinical response to neoadjuvant therapy.

3070 **Poster Session (Board #62), Sat, 8:00 AM-11:00 AM**

[^{18}F] Fluciclatide PET as a biomarker of clinical response to combination therapy of pazopanib and paclitaxel in patients with platinum-resistant or platinum-refractory advanced ovarian cancer: Results of a phase Ib study.

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Background: Angiogenesis has been shown to be a driver of platinum resistance in ovarian cancer. We assessed the effect of combination pazopanib and paclitaxel followed by maintenance pazopanib in patients with platinum resistant/refractory ovarian cancer. Integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ are both up-regulated in tumour-associated vasculature. [^{18}F]Fluciclatide is a novel PET tracer that has high affinity for integrins $\alpha_v\beta_{3/5}$, and was used to assess the anti-angiogenic effect of pazopanib. **Methods:** We conducted an open-label, phase Ib study in patients with platinum resistant/refractory ovarian cancer. Patients received 1 week of single agent pazopanib (800mg daily) followed by combination therapy with weekly paclitaxel 80mg/m^2. Following completion of 18 weeks of therapy, patients continued with single agent pazopanib until disease progression. Dynamic [^{18}F]Fluciclatide-PET imaging was conducted at baseline and after 1 week of pazopanib. Response (RECIST 1.1), toxicities and survival outcomes were recorded. Circulating markers of angiogenesis were assessed with therapy. **Results:** Fourteen patients were included in the intention-to-treat analysis. Complete and partial response was seen in 7 patients (54%). Median progression free survival (PFS) was 7.97 months, and overall survival (OS) was 18.5 months. A reduction in [^{18}F]fluciclatide uptake was observed following 1 week of pazopanib, and the reduction in uptake was predictive of long PFS. Elevated baseline circulating angiopoietin and FGF were predictive of greater reduction in $SUV_{60,mean}$ following pazopanib. Kinetic modelling indicated a reduction in K_1 and K_i following pazopanib indicating reduced radiotracer delivery and retention. **Conclusions:** Combination therapy followed by maintenance pazopanib is effective and tolerable in patients with platinum resistant/refractory ovarian cancer. We have shown that [^{18}F] fluciclatide-PET uptake parameters alter with pazopanib therapy indicating an anti-angiogenic response. Clinical trial information: NCT01608009.

3071 **Poster Session (Board #63), Sat, 8:00 AM-11:00 AM**

A functional measurement of MAPK pathway activation to predict response to MEK inhibitors in RAS-mutated patients.

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Background: MEK inhibitors can be used to treat patients with mutations that affect the MAPK pathway. Several MEK inhibitors are currently FDA-approved and effectively treat *BRAF*-mutated tumors, but *RAS*-mutated cancers are considered more resistant. However, it is unclear how the many distinct *RAS* variants impact the MAPK pathway and are affected by MEK inhibitors. We hypothesized that the level of MAPK pathway activation induced by different *RAS* mutations may predict response to MEK inhibition. **Methods:** Thirteen *RAS* mutations from 34 patients treated with MEK inhibitors at UCSD were synthesized, expressed in a HeLa-derived cell line and analyzed *in vitro* using a functional mutational analysis assay based on assessing downstream reporters in order to measure the activity of these mutations on the MAPK pathway. Each mutation received an activity score based on known oncogenic *RAS* mutation. **Results:** The most common type of cancer was colorectal cancer (N = 13). All patients received the MEK inhibitor, trametinib, based therapy. Patients were stratified into two groups: above an activity score of 1 (14 pts) or below it (20 pts). Median progression-free survival (PFS) after MEK inhibitor treatment correlated with higher MAPK activity score (9 vs 3 months; P = 0.041). **Conclusions:** Using a novel functional assay methodology for characterization of MAPK activation, we show that various *RAS* mutations activate the MAPK pathway to different levels. Higher activity is associated with longer PFS after MEK inhibitor treatment, suggesting that the relationship between signal transduction strength and clinical relevance merits additional exploration.

3072 **Poster Session (Board #64), Sat, 8:00 AM-11:00 AM**

Clinical impact of tissue of origin testing and mutation profiling in the Solving Unknown Primary Cancer (SUPER) national prospective study: Experience of the first two years.

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Background: Cancer of unknown primary (CUP) has a poor prognosis with a median survival of less than 12 months. SUPER is a prospective cohort study designed to create a national biobank of patients (pts) with no confirmed primary site following diagnostic work-up. Tumor and blood samples undergo mutational profiling for actionable mutations using the 386 gene PeterMac Comprehensive Cancer Panel (CCP) plus CUPGuide, a microarray gene-expression site-of-origin assay. We aimed to determine the clinical impact of CUPGuide and CCP profiling. **Methods:** 172 pts were enrolled between 2013-2015. Baseline demographics, treatments, investigations and clinico-pathological characteristics were collected over 12 months. Clinicians completed clinical management questionnaires before and after receiving results. **Results:** Molecular analysis was performed for 124/172 (72.1%) pts with sufficient DNA and/or RNA. CUPGuide was completed for 97/124 (78.2%); primary site predictions were made in 84/97 patients (86.6%). The most common primary site predictions were lung, gastric, ovary and breast. CUPGuide predictions resulted in a change in management in 10/84 (12%) of cases and confirmed current management already commenced by the clinician in 53/84 (63%). Mutation profiling was completed in 103/124 (83.1%) pts with actionable mutations found in 11 pts, 4 of whom received subsequent targeted therapy. Testing was considered to have a clinical impact in 70/120 cases (58%): either resulting in a change in treatment (n = 14), diagnosis of a pathogenic germline finding (n = 8) or a moderate/high confidence tissue of origin prediction (n = 58). There were two deaths prior to the availability of the CUPGuide results and eleven deaths prior to availability of the CCP results. **Conclusions:** Molecular analysis for CUP pts has clinical impact in the majority of cases. Timeliness of return of results, drug access and insufficient tissue for testing are barriers to greater impact that need to be addressed to improve the care of pts affected by CUP.

3073 **Poster Session (Board #65), Sat, 8:00 AM-11:00 AM**

No-cost next generation sequencing of advanced cancer patients within the Strata Precision Oncology Network supports clinical trial enrollment.

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Background: Widespread integration of systematized next generation sequencing (NGS)-based precision oncology is hindered by numerous barriers. Hence, we developed the Strata trial (NCT03061305), a screening protocol to determine the impact of scaled precision oncology. **Methods:** We implemented no-cost NGS on formalin fixed paraffin embedded (FFPE) clinical samples for all patients with advanced tumors, a common portfolio of partnered therapeutic clinical trials, and robust infrastructure development across the Strata Precision Oncology Network. **Results:** Across the network of 17 centers, specimens from 8673/9222 (94%) patients were successfully tested in the Strata CLIA/CAP/NCI-MATCH accredited laboratory using comprehensive amplicon-based DNA and RNA NGS. Patients were tested with one of three StrataNGS test versions; the most recent panel assesses all classes of actionable alterations (mutations, copy number alterations, gene fusions, microsatellite instability, tumor mutation burden and PD-L1 expression). Median surface area of received FFPE tumor samples was 25mm^2 (interquartile range 9-95mm^2), and the median turnaround time from sample receipt to report was 6 business days. 2577 (27.9%) patients had highly actionable alterations, defined as alterations associated with within-cancer type FDA approved or NCCN guideline recommended therapies (1072 patients), NCI-MATCH trial arms (1467 patients), Strata-partnered therapeutic trials (327 patients), or specific alteration-matched FDA approved therapies in patients with cancers of unknown primary (71 patients). Of the 1467 patients matched to an NCI-MATCH trial arm, 15 enrolled. Of the 327 patients matched to one of nine Strata-partnered clinical trials, 77 (24%) were screen failures, while 250 (76%) have either enrolled or are being actively followed for enrollment upon progression. **Conclusions:** Through streamlined consent methods, electronic medical record queries, and high throughput laboratory testing at no cost to patients, we demonstrate that scaled precision oncology is feasible across a diverse network of healthcare systems when paired with access to relevant clinical trials. Clinical trial information: NCT03061305.

3074 **Poster Session (Board #66), Sat, 8:00 AM-11:00 AM**

Genomic analysis of metastatic solid tumors in veterans: Findings from the VHA National Precision Oncology Program.

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Background: Scalable next generation sequencing (NGS) technologies have enabled incorporation of precision oncology into clinical practice, informing treatment decisions based on tumor genomics. The Veterans Health Administration (VHA) is the largest integrated healthcare system in the U.S., serving a higher percentage of rural patients (36%) than the national average (14%). To implement and standardize the practice of precision oncology across a diverse healthcare system, the VHA established the National Precision Oncology Program (NPOP). **Methods:** Tumor or peripheral blood specimens were collected from Veterans with advanced solid tumors who were eligible for treatment with targeted or immunotherapeutic drugs. Specimens were sequenced using cancer gene panels at two commercial laboratories. Annotated results were generated by the vendors and independently using IBM Watson for Genomics. Levels of evidence treatment recommendations were based upon OncoKB criteria. **Results:** Between July 2016 and June 2018, 3713 samples were collected from 72 facilities; the sequencing success rate was 86%. The majority of samples came from males with lung, prostate and colorectal cancers. Thirty-four percent of samples submitted were from rural patients. The most commonly mutated genes included *TP53*, *ATM* and *KRAS*. Over 70% of samples sequenced had at least one actionable mutation, and clinical trials were the recommended option in over 50%. The most frequent therapies prescribed in response to NGS testing were immune checkpoint inhibitors, EGFR kinase inhibitors and PARP inhibitors. Interestingly, prostate cancers among Veterans had a higher frequency of mutations in genes associated with a neuroendocrine phenotype compared with the general population. **Conclusions:** Implementation of precision oncology into clinical practice is feasible across the diverse VHA system, including rural community sites. Veterans have unique occupational exposures that might inform underlying causes of distinct mutational signatures identified here. Our results highlight the importance of increasing the availability of clinical trials for Veterans.

3075 **Poster Session (Board #67), Sat, 8:00 AM-11:00 AM**

Comparison of an automated cartridge-based system for mRNA assessment with central immunohistochemistry in the neoadjuvant GeparX trial.

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Background: Hormone receptors, HER2 and Ki-67 are prognostic values typically determined for breast cancer (BC) outcome and prediction of therapy response. A RT-qPCR based system, the Xpert Breast Cancer STRAT4, can be used to classify BC tissues regarding their hormone receptor status, HER2 and proliferation via Ki-67. We compared mRNA expression analysis of ER, PR, HER2, and Ki-67 by this automated *in-vitro* diagnostic platform (GeneXpert) (GX) with central immunohistochemistry (IHC) in a large clinical trial cohort. **Methods:** BC patients from the prospective GBG neoadjuvant trial GeparX (NCT02682693) (still recruiting) were included in this biomarker project. We used formalin-fixed paraffin embedded (FFPE) pretherapeutical core biopsies with a tumor content $>$ 10%. One 4 μm FFPE tissue section was first processed with the Xpert FFPE Lysis Kit, the sample lysate was placed in the STRAT4 cartridge system and then tested on the GX system in which the purification, amplification and real-time detection took place within two hours automatically. **Results:** A total of 503 (99%) of the 509 samples had a valid measurement of all four genes. 258 samples (51.3%) of the cohort were classified in central pathology as ER positive, 196 (39%) as PR positive and 78 (15.5%) as HER2-positive, and 421 samples (83.7%) were Ki-67-high ($>$ 20%). The simple kappa coefficient was for ER = 0.7938, PR = 0.6540, HER2 = 0.8172 and Ki-67 = 0.3655. This indicates, that the measurements for ER, PR and HER2 showed a high correlation between both methods, whereas the measurement of Ki-67 does not. The accuracy between the STRAT4 and IHC was 89.7% for ER, 83.3% for PR, 94.6% for HER2 and 86.7% for Ki-67. According to molecular subgroups, highest accuracy regarding Ki-67, was determined in TNBC (96.2%; luminal: 81.1%; HER2-positive: 76.9%). **Conclusions:** Our results show a high concordance between standardized central IHC and automated mRNA expression analysis for the most important BC biomarkers ER, PR and HER2. For the proliferation marker Ki-67, the concordance is slightly lower. The STRAT4 assay might offer additional option to conventional methods for BC biomarker assessment, in particular in settings where IHC is not feasible. To determine the clinical validity, additional outcome analyses are necessary. Clinical trial information: NCT02682693.

3076 **Poster Session (Board #68), Sat, 8:00 AM-11:00 AM**

Utility of somatic mutation panel testing in patients with advanced cancer receiving treatment in an Irish teaching hospital.

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Background: Tumor testing for potentially actionable somatic mutations via commercially available panel tests has entered routine clinical practice in many countries. In Ireland the cost of these tests is not covered by insurance companies and must be paid for by patients. Use of these tests is sporadic and depends on patient and clinician factors (including ability to pay). Existing data suggest that such testing results in a direct impact on patient therapy in a minority of patients only. We reviewed the impact of somatic mutation testing on treatment selection and outcomes in patients attending a medical oncology service in a teaching hospital in Ireland. **Methods:** We performed a retrospective study of patients who had commercial panel testing performed as part of routine oncology care. All patients opportunistically tested between 2013 and 2018 were included. Patients having focused molecular tests for approved therapies (e.g. *RAS* mutations in colon cancer, *EGFR* and *ALK* mutations in non-small cell lung cancer) were excluded.We reviewed medical records to assess the frequency and utility of mutations detected, the impact of testing on next and subsequent lines of therapy, and the effectiveness of therapy. **Results:** 74 panel tests were performed in 71 patients. 39 tests (53%) detected mutations, of which 21 (28%) were potentially actionable. 36 patients (51%) had further treatment after testing was performed. 9 tests (12%) led to test-based treatment. The mean duration of test-based treatment was 34 days (range 1-90 days). No patients had benefit from test based treatment, defined as tumour response or disease stabilisation on restaging scans. 23 patients died within 90 days of panel tests being requested. Among patients starting and completing a subsequent line of therapy after testing, the mean duration of therapy with test-based treatment was 39 days (range 6-90) and for standard of care treatment was 56 days (range 1-262 days). **Conclusions:** While testing for tumor-specific somatic mutations with proven predictive benefit is very useful, somatic mutation panel testing for non standard of care genetic alterations is not of utility in this real world setting. Its role in Ireland should be limited to identification of suitable early phase clinical trials. Discussions of panel testing should include frank discussion of expected benefits, and should also address factors such as patient ability to travel for clinical trials.

	Number	Percent
Total tests	74	100%
Mutation detected	39	53%
Potentially actionable	21	28%
Test-based treatment	9	12%

3077 **Poster Session (Board #69), Sat, 8:00 AM-11:00 AM**

Proteomic profile of high-risk luminal A early breast cancers.

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Background: Breast cancer is a heterogeneous disease with a wide range of outcomes. Among the intrinsic breast cancer subtypes, luminal A tumors are considered to have a favorable prognosis. However, molecular studies characterizing the genomic landscape of luminal A tumors revealed a molecular heterogeneity within this subtype, which also translated to variability in survival. A better understanding of the biology of this tumor subgroup is therefore needed to determine the appropriate therapeutic strategy. The aims of the study were to determine the frequency of high-risk luminal A tumors in a real life cohort of early breast cancers and provide a proteomic characterization of this subgroup using a mass spectrometry approach. **Methods:** 222 early breast cancer patients with hormone receptor positive and HER2 negative tumors treated at our institution had a PAM50-based genomic assay Prosigna to estimate their risk of recurrence. This assay assigned each tumor sample to an intrinsic molecular subtype of breast cancer. Luminal A and B tumors were analyzed with MALDI mass spectrometry imaging combined with microproteomics, a spatially-resolved on-tissue shotgun proteomic technology, to determine the proteomic profiles of both cancer cells and stroma. **Results:** Among the 129 luminal A breast cancers identified in our cohort, 67 (51%) had a risk of distant recurrence of 10% or more (32% had a 10% to 15% risk, and 19% a risk greater than 15%). High-risk luminal A tumors had a distinctive proteomic profile compared to low-risk luminal A or to luminal B tumors. Overexpression of the methionine biosynthesis pathway was the main differential protein expression observed in cancer cells and stroma of high-risk luminal A. Inflammation mediated by chemokine and cytokine signaling pathway and integrin signaling were also overexpressed in high risk luminal A compared to luminal B. In the stroma of luminal B tumors, EGR signaling, Ras and FGF pathways and angiogenesis were overexpressed compared to high-risk luminal A tumors. **Conclusions:** Real life data showed a significant proportion of high-risk luminal A breast cancers. MALDI mass spectrometry proteomics revealed distinctive tumor and microenvironment profiles in this breast cancer subgroup.

3078 **Poster Session (Board #70), Sat, 8:00 AM-11:00 AM**

MET kinase domain rearrangements across 10 cancer types.

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Background: MET is a transmembrane receptor tyrosine kinase and deregulated in many kinds of tumors by mutation, rearrangement and amplification. Since the first constitutively active *MET* rearrangement (*TPR-MET*) was discovered, many other *MET* rearrangements have been identified in various tumor types. However, the frequency and characteristic of *MET* rearrangement in Chinese cancer patients is still unclear. **Methods:** Targeted sequencing using 1021-gene panel or 59-gene panel was performed on 3952 tissue samples and 5100 blood-based ctDNA samples from 9052 unique patients across 10 cancer types. All *MET* exons were sequenced, but *MET* intronic breakpoints were not specifically baited. **Results:** 24 (0.27%) *MET* kinase domain rearrangements (KDRE) were identified in 9052 patients. Specifically, 0.25% (16/6284) in non-small cell lung cancer (NSCLC), 0.69% (2/290) in gastric adenocarcinoma, 0.32% (2/897) in colorectal cancer, 0.33% (2/610) in breast cancer, 0.3% (1/330) in hepatocellular carcinoma and 0.69% (1/145) in ovarian cancer, none in 139 pancreatic cancer, 136 thyroid cancer, 111 renal cell carcinoma and 110 esophageal squamous cell carcinoma. Among all of the *MET* KDRE, 17 were fusions with 5' identified partner, 3 were kinase domain duplication (KDD) and 4 were probable fusions with unidentified partner. The most common 5 'partner gene was *CAPZA2*, followed by *CD47* and *TES*. In the *MET* KDRE cases in NSCLC, 56.25% (9/16) did not found any clinical actionable variants referring to the NCCN guideline. In addition, *MET* amplification, *EGFR* L858R or exon 19 deletion and *KRAS* mutation co-occurred in 25% (4/16), 18.75% (3/16) and 12.5% (2/16) of NSCLC *MET* KDRE cases respectively. **Conclusions:** Our results, for the first time, illustrate the *MET* KDRE across 10 cancer types among Chinese population and might provide some novel targets to develop new therapies for patients with *MET* KDRE. *MET* KDRE across different tumor types.

Tumor Types	Total Samples (n)	Fusion with identified 5' partner (n)	KDD (n)	Probable fusion with unidentified partner (n)	5' partner
Non-Small Cell Lung Cancer	6284	12	2	2	*CAPZA2(2); CD47(2); TES; CAV1; ITGA9; HLA-DRB1; TFEC; CTTNBP2; ANK1; STARD3NL*
Colorectal Cancer	897	1	1	0	*ST7*
Breast Cancer	610	1	0	1	*TBX15*
Hepatocellular Carcinoma	330	1	0	0	*TPM1*
Gastric Adenocarcinoma	290	2	0	0	CAPZA2; TES
Ovarian Cancer	145	0	0	1	-

3079 **Poster Session (Board #71), Sat, 8:00 AM-11:00 AM**

An artificial intelligence approach to variant calling of ALK resistance mutations.

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Background: ALK tyrosine kinase inhibitors (TKIs) are effective in treating advanced anaplastic lymphoma kinase (ALK) fusion-positive non-small-cell lung cancers (NSCLC), and specific ALK variants are associated with the development of resistance to specific TKIs. Humans struggle to harness the full potential of the highly complex next-generation sequencing bioinformatics pipeline output. As a consequence, the decision to report a variant remains difficult, and we considered the discrete nature of the data and the binary decision (report vs. not-report) as an ideal setting to apply an artificial intelligence (AI) approach for variant reporting. **Methods:** We assessed diagnostic performance of an AI model in calling ALK-resistance mutations in n = 50 consecutive ALK fusion positive patients who relapsed on TKI-therapy and underwent repeat biopsy at MGH. The random forest model was derived from independent datasets (training and validation) capturing the reporting decision on $>$ 36,000 variants with ~500 features per variant resulting in a matrix of $>$ 18 million data points. The model output is a contiguous prediction score from 0 (not report) to 1 (report) and a visual drill-down functionality allows exploration of the underlying features that contributed to the decision. **Results:** Examination of n = 76 tests from n = 50 patients with a total of n = 130 reported variants (and = 115 not reported variants) included a total of n = 31 ALK point mutations: p.1156(n = 2), p.1171(n = 8), p.1174(n = 2), p.1180(n = 2), p.1196(n = 1), p.1198(n = 1), p.1202(n = 8), p.1203(n = 1), p.1204(n = 1), p.1206(n = 1), p.1269(n = 4). Setting a screening threshold of the model at $>$ 10% for reporting showed only one false-negative (p.Ile1171Asn) variant and 96.7% sensitivity. The average model score for ALK variants was 0.664 (range: 0.08–0.98; median 0.8) and did not show significant differences from other reported variants (0.636; 0–1; 0.7; t-test 0.66). The model would have called n = 18 of the non-reported control variants (average 0.07; range $<$ 0.001–0.64; P $<$ 0.0001) and was 84% specific. Review of the drill-down function identified prior call frequency, allelic ratio, and predicted transcript consequences as common model features. Importantly, the model is currently agnostic to the medical literature and does not take clinical parameters (e.g. TKI type) into account, which may further improve performance. **Conclusions:** Applying artificial intelligence to large discrete datasets is one approach to help identify clinically relevant variants in the setting of ALK resistance in ALK-fusion positive NSCLC.

3080 **Poster Session (Board #72), Sat, 8:00 AM-11:00 AM**

Whole transcriptome sequencing in metastatic cancer: A review of expression outliers in 113 metastatic breast cancer patients.

Nathalie LeVasseur, Veronika Csizmok, Melika Bonakdar, Yaoqing Shen, Lindsay Zibrik, Eric Yang Zhao, Sophie Sun, Karen A. Gelmon, Janessa J. Laskin, Marco A. Marra, Stephen K. L. Chia; BC Cancer Agency, Vancouver, BC, Canada; Canada's Michael Smith Genome Sciences Centre, Vancouver, BC, Canada; Canada's Michael Smith Genome Sciences Centre, British Columbia Cancer Agency, Vancouver, BC, Canada; Canada's Michael Smith Genome Sciences Centre, Vancouver, BC, Canada; BC Cancer, Vancouver, BC, Canada

Background: The genomic profiling of breast cancers has led to a greater understanding of the mutational landscape of metastatic breast cancer (MBC) with potential therapeutic implications. Despite these advances, there is a paucity of data regarding the additive value and relevance of gene expression across histological and molecular subtypes, which represents the majority of informative and actionable findings identified in the BC Cancer personalized oncogenomics program (POG). **Methods:** Informative findings with potential clinical application from whole genome sequencing (WGS) and whole transcriptome sequencing (WTS) in MBC patients between 2012-2018 were reviewed. Variants observed in pathway genes of potential clinical relevance, as defined by a curated list of genes, were examined across histological subtypes. High and low expression outliers relative to TCGA breast cases, defined as expression greater than 98th percentile and FC $>$ 2 compared to Illumina breast dataset and lower than 25th percentile and FC $<$ -2 compared to Illumina breast dataset, respectively, were then analyzed to establish how many outliers were observed in pathways of potential clinical relevance. **Results:** A total of 113 cases were included. WGS revealed that TP53 was the most frequent single nucleotide variant (SNV) in triple negative breast cancer (23/30, 77%), whereas PIK3CA (37/78, 47%), PTEN (11/78, 14%) and ESR1 (19/78, 24%) were most frequent in ER positive cases and CDKN2A (2/18, 11%) in HER2 positive cases. Across all subtypes, the mTOR and cell cycle pathways were found to have the highest frequency of SNVs, with the identification of 86 and 71 variants, respectively. Expression data for 113 RNA-sequenced patients revealed a high frequency of expression outliers in the mTOR pathway (26 high expression and 424 low expression outlier genes) and cell cycle pathways (35 high expression and 331 low expression outlier genes), but also in the WNT pathway (96 high expression and 490 lower expression outlier genes) and NOTCH pathway (84 high expression and 564 low expression outlier genes). **Conclusions:** Frequently identified SNVs across histological subtypes were correlated with expression outliers in pathways of clinical relevance in breast cancer. Additional informative findings, in pathways of potential clinical relevance not historically targeted in breast cancer, were identified with WTS. The clinical utility of these findings warrants further study.

3081 **Poster Session (Board #73), Sat, 8:00 AM-11:00 AM**

Transcriptome-based cancer type prediction for tumors of unknown origin.

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Background: Tumors of unknown origin occur in approximately 5% of newly diagnosed cancers and are difficult to treat without establishing the tissue type from which they derive. Establishing tumor origin guides standard of care treatment for several NCCN targeted therapy guidelines. Leveraging tissue specificity in gene expression profiles, classification models based on RNA expression offer a promising approach to identify the likely primary cancer site in tumors of unknown origin. **Methods:** In this study, we developed a transcriptome-based cancer type classifier trained on over 10,000 tissue samples annotated by pathologists and sequenced for RNA expression to identify conserved patterns of expression characteristic of 30 tumor types across primary and metastatic tissue sites. The classifier probabilistically ranks cancer of origin. **Results:** Overall, the accuracy of the most probable cancer prediction was 85%, 88% within primary tumors and 77% within metastatic tumors. The top three cancers types with the highest accuracy were colorectal (accuracy in metastatic: 93%, accuracy in primary tumors: 99%), breast (95%, 96%) and lung (87%, 94%). Classifier performance was lower in low-purity metastatic tumors where the surrounding normal tissue obscures the tumor transcriptional profile, though the classifier still achieves 71% accuracy on metastatic tumors with less than 50% purity. **Conclusions:** We present a novel method to probabilistically predict tumor type for cancers of unknown origin using RNA-Seq. Our method achieves robust classification that is applicable to primary and metastatic tumors and demonstrates the value of utilizing RNA-Seq to aid cancer diagnosis and treatment decisions.

3082 **Poster Session (Board #74), Sat, 8:00 AM-11:00 AM**

Observational, multicenter, prospective study to assess the impact on patients' outcome of a systematic screening of oncogenic drivers in advanced cancer: The GETHI XX-16 study.

Carmen Beato, Paloma Navarro, JF Rodriguez-Moreno, L Miguel Navarro, Beatriz Jimenez Munarriz, Gema Bruixola, Carmen Balana, MD Fenor, Jose Fuster, Francisco Zambrana, Elena Sevillano, Elena Vila-Navarro, Esther NoguerÃ³n, Xabier Mielgo Rubio, Antonio Viudez, Maria Dolores Mediano, Juan Antonio Virizuela, Sergio Ruiz, Elena Mata, Jesus Garcia-Donas, Spanish Groups for Orphan and Rare Cancer (GETHI); Hospital Virgen de la Macarena, Sevilla, Spain; Clara Campal Comprehensive Cancer Center, Madrid, Spain; Centro Integral Oncológico Clara Campal, Madrid, Spain; Department of Medical Oncology, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain; HM Hospitales, Madrid, Spain; Hospital Universitario y Politecnico La Fe, Valencia, Spain; Institut Catala Oncologia Badalona, Hospital Germans Trias I Pujol, Badalona/Barcelona, Spain; HM Hospitales-Centro Integral Oncológico HM Clara Campal, Madrid, Spain; Hospital Son Espases, Palma De Mallorca, Spain; Medical Oncology Department, Infanta Sofía University Hospital, Madrid, Spain; Hospital Clinic Barcelona, Barcelona, Spain; Complajo Universitario Albacete, Albacete, PR, Spain; Hospital Universitario Fundación Alcorcon (ONCOSUR), Madrid, Spain; Medical Oncology, Complejo Hospitalario de Navarra, Pamplona, Spain; Hospital Universitario Virgen del Rocío, Seville, Spain; Laboratory of Translational Oncology CIOCC, Madrid, Spain; Medical Oncology, Hospital Reina Sofia, Tudela, Spain; Fundacion Hospital de Madrid, Madrid, Spain

Background: Identification of "agnostic" genetic drivers in cancer is foreseen as a major step forward in precision medicine.Unfortunately, "off label" use of targeted therapies is not widely available and many oncogenic alteration do not present the same behaviour accross all tumor types.We aimed to analyze the real impact on patients management of the implementation of a systematic screening of genetic alterations in centers of the Spanish Group for Rare Cancer (GETHI). **Methods:** We designed an observational, prospective and multicenter study to molecularly characterize any adult patient with advanced cancer.Formalin fixed paraffin-embedded samples were studied by TrkA-C,ROS1 and ALK immunohistochemistry followed by RT-PCR when positive to confirm gene fusions. Additonally, the Next Generation Sequencing paltform ArcherFusion Plex (able to detect point mutations and rearrangements in 53 cancer related genes) was implemented.Clinical data regarding treatment administered and outcome, were collected from patients identified as harboring drugable alterations. **Results:** Up to 26 hospitals all over the country got involved in the study. 341 tumoral tissues, representing 41 different histologies were collected. Molecular studies could be performed in 292 samples that led to the identification of 33 patients as harboring somatic oncogenic mutations. 21 were considered druggable and 5 got targeted therapy directed against the alteration identified (three glioblastoma patients with EGFR mutations received erlotinib, one prostate cancer with a BRAF fusion received trametinib and one lung cancer with ALK translocation, previously deemed as negative by standard screening, received crizotinib). One of the glioblastoma patients achieved a long lasting stabilitation and both the prostate and lung tumors presented dramatic partial responses. **Conclusions:** Though only few cases harboring drugable alteratons got specif treatment, 50% achieved a meanignful benefit. A wide access to molecular screening and targeted drugs could improve the outcome of cancer patients.

3083 **Poster Session (Board #75), Sat, 8:00 AM-11:00 AM**

Machine learning algorithm analysis using a commercial 592-gene NGS panel to accurately predict tumor lineage for carcinoma of unknown primary (CUP).

Jim Abraham, Amy B. Heimberger, Zoran Gatalica, Wolfgang Michael Korn, David Spetzler; Caris Life Sciences, Phoenix, AZ; The University of Texas MD Anderson Cancer Center, Department of Neurosurgery, Houston, TX

Background: The diagnosis of a malignancy is typically informed by clinical presentation and tumor tissue features including cell morphology, immunohistochemistry, cytogenetics, and molecular markers. However, in approximately 5-10% of cancers, ambiguity is high enough that no tissue of origin can be determined and the specimen is labeled as a Cancer of Occult\Unknown Primary (CUP). Lack of reliable classification of a tumor poses a significant treatment dilemma for the oncologist leading to inappropriate and/or delayed treatment. **Methods:** 40,000 tumor patients with NGS data were used to construct a multiple parameter lineage-specific classification system using an advanced machine learning approach. The dataset for each classifier was split 50% for training and the other 50% for testing. The training task for each classifier was to identify the cases that were similar to the cases it was trained on against a backdrop of randomly selected cases of other histological origins. **Results:** Tumor lineage classifiers predicted the correct classifications where the primary site was known with accuracies ranging between 85% and 95%. When applied to CUP cases (n = 500), an unequivocal result could be obtained 100% of the time. **Conclusions:** Lineage predictors can render a histologic diagnosis to CUP cases that can inform treatment and potentially improve outcomes.

3084 **Poster Session (Board #76), Sat, 8:00 AM-11:00 AM**

Determining clinical relevance of genomic heterogeneity in an ethnically diverse cohort of newly diagnosed patients with breast cancer.

Padma Sheila Rajagopal, Nike Beaubier, Masaya Hattori, Lise Sveen, Galina Khramtsova, Taylor Abboushi, Mathew Barber, Fang Liu, Toshio Yoshimatsu, Yonglan Zheng, Kevin White, Dezheng Huo, Olufunmilayo I. Olopade; The University of Chicago, Chicago, IL; Tempus Labs, Chicago, IL; University of Chicago, Chicago, IL; Tempus, Inc., Chicago, IL; Center for Clinical Cancer Genetics and Global Health, Department of Medicine, University of Chicago, Chicago, IL; Tempus Health, Chicago, IL; Department of Public Health Sciences, University of Chicago, Chicago, IL

Background: The trajectory from early breast cancer to distant metastasis has not been precisely characterized. We are building an ethnically diverse, longitudinal cohort of prospectively ascertained breast cancer patients with integrated genomic, transcriptomic, epidemiological and clinical data, with the goal of identifying biomarkers that can improve on clinical predictors. **Methods:** Our goal is 500 histologically confirmed invasive cases with a minimum follow-up of 5 years. To date, Tempus Labs, Inc. has completed xT assays (595-gene panel DNA-seq and full-transcriptome RNA-seq) on 127 cases with matched tumor-normal samples. Clinical information was obtained from electronic health records and our cancer registry. **Results:** Median age of diagnosis was 51, with 47% African-Americans. 73% had stage 2 or 3 disease (2 patients were stage 4). 24.4% had TNBC; 30% had HER2+ and 62.2% HR+ status. Somatic alterations were identified in 560 genes with most common mutations in *TP53* (56%), *MCL1* (35%), *PIK3CA* (30%) and *ERBB2* (17%). Somatic mutations in *BRCA1* (10%) and *BRCA2* (5%) were associated with increased tumor mutation burden (TMB). 2 patients were MSI high; 6 were equivocal. After a median follow-up of 6.5 years, 46 patients died and 38 had recurrent disease. With adjustment for clinical factors, TMB showed a slight nonsignificant negative association with recurrence-free survival (HR: 0.97, 95% CI: 0.91-1.00, p = 0.31). *TP53* was associated with recurrence-free survival (HR: 1.76, 95% CI 0.94-3.29; p = 0.08) as was MSI (HR: 0.24, 95% CI: 0.06-1.06, p = 0.06). **Conclusions:** These data support the importance of integrating tumor sequencing in a diverse cohort with full clinical annotation to assess the diversity of actionable genomic alterations at the time of primary diagnosis to develop interventions for prevention of metastases.

3085 **Poster Session (Board #77), Sat, 8:00 AM-11:00 AM**

First-in-human study of AZD5153, a small molecule inhibitor of bromodomain protein 4 (BRD4), in patients (pts) with relapsed/refractory (RR) malignant solid tumor and lymphoma: Preliminary data.

Judy Sing-Zan Wang, Serena De Vita, Janet L. Karlix, Carl Cook, Gillian M. Littlewood, Maureen M. Hattersley, Ganesh Moorthy, Helena Edlund, Giulia Fabbri, Kris F. Sachsenmeier, Chris Davison, Edwin Clark, Kathleen N. Moore, Todd Michael Bauer, Susanna Varkey Ulahannan, Manish R. Patel, Erika Paige Hamilton; Florida Cancer Specialists and Sarah Cannon Research Institute, Sarasota, FL; AstraZeneca, Waltham, MA; Sarah Cannon Development Innovations, Nashville, TN; AstraZeneca, Cambridge, United Kingdom; AstraZeneca, Waltham, Boston, MA; Stephenson Cancer Center at the University of Oklahoma HSC and Sarah Cannon Research Institute, Oklahoma City, OK; Sarah Cannon Research Institute, Nashville, TN; Stephenson Cancer Center, Oklahoma City, OK; Tennessee Oncology, PLLC and Sarah Cannon Research Institute, Nashville, TN

Background: BRD4 is a bromodomain and extraterminal (BET) protein that regulates oncogenic programs by modifying gene transcription and additional mechanisms. AZD5153 is a novel, reversible BRD4 inhibitor with bivalent mechanism of action and enhanced antitumor activity in preclinical models. This phase 1, multicenter, dose escalation study (NCT03205176) assesses AZD5153's safety, pharmacokinetics (PK), and pharmacodynamics (PD). We report here preliminary, unvalidated data from AZD5153 monotherapy in pts with RR solid tumor, including lymphoma. **Methods:** Adult pts received oral AZD5153 QD/BID to determine the MTD. During dose escalation, a continual reassessment model was used to estimate toxicity and all final decisions were made by the Safety Review Committee. PK and PD were characterized using standard methods. **Results:** As of 1 Nov 2018, 28 pts (78.6% female, median age 66.5 y) were treated in 7 cohorts: 2 mg QD (3 pts), 5 mg QD (3 pts), 10 mg QD (3 pts), 10 mg BID (5 pts), 15 mg BID (4 pts), 20 mg BID (7 pts), and 30 mg QD (3 pts). Treatment was ongoing in 8 pts at data cut-off. Safety findings showed 50% of pts experienced treatment-related AEs. 25% of pts experienced treatment-related Grade $\geq$3 AEs, which were thrombocytopenia and fatigue (7.1% each), and anemia, diarrhea, and platelet count decreased (3.6% each). SAEs were observed in 25% of pts; none of the SAEs was attributable to AZD5153 alone. Dose-limiting toxicities of thrombocytopenia (1 pt) and diarrhea with herpetic rash leading to discontinuation (1 pt) occurred at 20 mg BID. 53.6% of pts discontinued due to disease progression. Total median treatment duration was 1.3 mo (range up to 8.9 mos). Dose proportional increase in C_{max} and AUC were observed across the dose range tested. T_{max} ranged from 0.5 to 3 h and $t_{1/2}$ was 6 h. Dose-dependent changes in expression of target genes (eg, *HEXIM1*, *HIST2H2BF*, *CD274*, and *CCR2*) and platelet counts were observed in the peripheral blood. **Conclusions:** AZD5153 monotherapy is safe and tolerated at doses up to 30 mg QD and 15 mg BID. Linear increase in PK was observed. Additional safety and efficacy updates will be reported at the annual meeting. Clinical trial information: NCT03205176.

3086 **Poster Session (Board #78), Sat, 8:00 AM-11:00 AM**

c-AMP/MAPK dysregulation and its impact on survival and response to immunotherapy in advanced melanomas.

Rami Al-Rohil, Etan Marks, Varshini Vasudevaraja, Stephen Kelly, Matija Snuderl, Douglas Buckner Johnson, George Jour; Duke University Medical Center, Durham, NC; NYU Langone, New York, NY; Vanderbilt University Medical Center, Nashville, TN

Background: Immunotherapies blocking the interaction of CTLA-4 or Programmed Death 1 (PD-1) with their ligands are the standard of care for advanced MEL although many pts fail to benefit from immunotherapy. Herein, we seek to identify epigenetic and genetic signatures associated with lack of response in patients treated with immunotherapy. **Methods:** We performed whole exome sequencing of 580 cancer-related genes and whole-genome DNA methylation arrays targeting > 850k CpG sites covering promoters, enhancers, and transcription factor sites in 28 MEL samples from patients treated with PD-1 +/- CTLA-4 inhibitors. Findings were correlated with collected clinical history. **Results:** Findings are summarized in the table. Unsupervised clustering and multi-parametric analysis showed a distinct methylation signature independent of age, sex, stage, site of metastasis, or type of treatment (adj. p<0.01). Pathway analysis identified *c-AMP/MAPK* and *PI3K-Akt* signaling pathways (adj. p=2.10E-05 and 8.19E-06, respectively) enrichment in non-responders. This coincided with significant increase of mutational events in c-*AMP/MAPK* and *PI3K-Akt* pathways (p= 0.0001) including deleterious events affecting *PDE4DIP (p=0.0002)*, a negative regulator of *mTORC1,* in non-responders. C-AMP/MAPK/PI3K genomic alterations were associated with a worse OS and PFS but not worse response rate (p=0.04, p=0.01, and p=0.20). *PDE4DIP* deleterious events were associated with decreased response rate, worse OS and PFS (p=0.002; p=0.002;p=0.00003). **Conclusions:** Convergent epigenetic dysregulation of *cAMP/MAPK* signaling and inactivation of *PDE4DIP* is associated with worse outcome and lack of response to immunotherapy, respectively.

Feature	Number	P- value
Gender		
Responders		p=0.98
Male	9 (64%)	
Female	5 (36%)	
Non-responders		
Male	9 (64%)	
Female	5 (36%)	
Metastatic Stage		p=0.24
Responders		
(M1a)	1 (6%)	
(M1b)	6 (36%)	
(M1c)	7 (58%)	
Non-responders		
(M1a)	4 (36%)	
(M1b)	3 (21%)	
(M1c)	7 (43%)	
Median OS/c-AMP/MAPK/PI3K pathway dysregulation		p=0.04
Present	48 months 95% CI (0.24;0.83)	
Absent	90 months 95% CI (0.21;0.90)	
Median PFS/c-AMP/MAPK/PI3K pathway dysregulation		p=0.01
Present	40 months 95% CI (0.40;0.80)	
Absent	95 months 95% CI (0.13;0.0.90)	
***PDE4P*deleterious events /Response rate**		p=0.0021
Present	4 (29%)	
Absent	10(71%)	
Median OS/*PDE4P* deleterious events		p= 0.002
Present	39 months 95% CI (0.27;0.97)	
Absent	90 months 95% CI (0.22;0.95)	
Median PFS/*PDE4P* deleterious events		p=0.00003
Present	9 months 95% CI (0.31-0.95)	
Absent	30 months 95% CI (0.36-0.90)	

3087 **Poster Session (Board #79), Sat, 8:00 AM-11:00 AM**

PIPA: A phase Ib study of selective ß-isoform sparing phosphatidylinositol 3-kinase (PI3K) inhibitor taselisib (T) plus palbociclib (P) in patients (pts) with advanced solid cancers—Safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) analysis of the doublet combination.

Juanita Suzanne Lopez, Manuel SelviMiralles, Malaka Ameratunga, Anna Minchom, Javier Pascual, Udai Banerji, Hannah Bye, Florence I. Raynaud, Karen E Swales, Jason Malia, Michael Hubank, Isaac Garcia-Murillas, Mona Parmar, Sarah Emily Ward, Laura Finneran, Emma Hall, Alison Joanne Turner, Johann S. De Bono, Timothy A Yap, Nicholas C. Turner; Drug Development Unit-The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Royal Marsden Hospital and The Institute of Cancer Research, London, United Kingdom; The Institute of Cancer Research and The Royal Marsden Hospital, London, United Kingdom; Royal Marsden Hospital and The Institute of Cancer Research, Sutton, United Kingdom; Royal Marsden NHS Foundation Trust, London, United Kingdom; The Institute of Cancer Research, London, United Kingdom; Institute of Cancer Research, London, United Kingdom; The Institute of Cancer Research, Sutton, United Kingdom; Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, United Kingdom; Royal Marsden Hospital, Sutton, United Kingdom; Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom; The Royal Marsden Hospital and The Institute of Cancer Research, London, United Kingdom

Background: Oncogenic hyperactivation of the PI3K pathway is common in multiple cancers, with preclinical data showing that CDK4/6 inhibitors sensitise *PIK3CA* mutant cancers to PI3K inhibitors. We report the activity of the P+T in solid tumors with PI3K pathway activation, along with the PD biomarker analysis. **Methods:** We previously reported the dose escalation phase identifying 125mg P given 3-weeks-on, 1-week-off in combination with T 2mg as the recommended phase 2 dose (R2PD, *Lim, ASCO 2017*). We report the results in solid tumors with confirmed activating mutations (mts) in the PI3K pathway, from dose escalation and expansion, with no prior exposure to CDK4/6 or PI3K pathway inhibitors. PD studies include analyses of platelet-rich plasma (PRP) and paired tumour biopsies. **Results:** 20 pts (median age 61, range 34-72) were treated at the doublet RP2D, M/F 7/13, with a median 4 prior treatments (range 2-11). Tumour types included colorectal, breast, lung, endometrial,oligodendroglioma and head and neck cancers. Durable disease control occurred in 3 patients with ER+ advanced breast cancer with responses lasting >6 months including 1 pt with a H1047R *PIK3CA*mt with an ongoing RECIST PR>36 cycles, 2 pts with *PIK3CA*mt colorectal cancer had RECIST SD for >5 months, and 1 patient with a *PIK3CG*mt anaplastic oligodendroglioma had clinical and radiological benefit lasting 5.5 months. Treatment was well tolerated with predictable G1-2 adverse events (AEs). G3 toxicities of neutropenia (n=6), thrombocytopenia (2), rash (2), mucositis (1) and raised transaminases (1 each) were all transient with no G4/5 AEs. Significant decreases in tumour pRb, and pAKT and pGSK3ß in PRP, confirmed modulation of both CDK4/6 and PI3K pathways at R2PD. **Conclusions:** Doublet P+T is well tolerated at the combination RP2D, with PD evidence of PI3K and CDK4/6 modulation in both plasma and tumor. Promising preliminary anti-tumor activity is seen in a mixed histology cohort selected for activating PIK3 mutations. Clinical trial information: NCT02389842.

3088 **Poster Session (Board #80), Sat, 8:00 AM-11:00 AM**

Distinct radiological patterns of drug-induced pneumonitis (R-DIP) in early-phase clinical trials and predictive factors affecting outcome: A 10-year systematic review from the Royal Marsden Hospital Phase I Drug Development Unit experience.

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Background: We studied clinical and radiological parameters influencing DIP in patients (pts) participating in phase I clinical trials, aiming to investigate predictive factors affecting DIP, in particular those affecting outcome. **Methods:** 2439 consecutive stage IV cancer pts on phase I clinical trials from 2007 to 2017 were identified. Pts with respiratory symptoms or abnormal lung imaging were reviewed in detail, with longitudinal analysis of imaging by an experienced radiologist. R-DIP was categorized according to internationally recognized criteria. **Results:** 60 pts developed R-DIP (overall incidence 2.5%); most frequent in pts receiving drug conjugates (31.1%) followed by targeted therapies (8.3%). Hypersensitivity pneumonitis was most common (33.3%) followed by non-specific interstitial pneumonitis (30%) and cryptogenic organising pneumonitis (26.7%). 45% pts who developed R-DIP were clinically asymptomatic. The number of affected lobes (OR 1.47, 95% CI: 1.19-1.81, $p < 0.001$) and the pattern of R-DIP (OR 5.83 for ARDS, 95% CI: 0.38-90.26, $p = 0.002$) were significantly associated with a higher CTCAE pneumonitis grading. 23% pts (14/60) had investigational medicinal product (IMP) temporarily discontinued or had a dose reduction while 42% pts (25/60) had IMP permanently discontinued. 48% pts were treated with steroids. The number of affected lobes, pattern of R-DIP and steroid therapy did not influence an improvement in R-DIP ($p = 0.65$, 0.27 and 0.23 respectively). Continuation of treatment resulted in worsening of DIP in 42.9% of cases. The only predictive factor for an improvement in DIP was an interruption of treatment (OR 0.05, 95% CI: 0.01-0.35, $p = 0.01$). 14 pts were retreated with a reoccurrence of R-DIP in 4 pts (28.6%). **Conclusions:** R-DIP from novel agents in early phase clinical trials presents in varied radiological patterns, with findings often preceding clinical symptoms. Treatment interruption leads to improvement of DIP and should be considered early. Close clinical and radiological surveillance is recommended should IMP be restarted.

3089 **Poster Session (Board #81), Sat, 8:00 AM-11:00 AM**

Phase 1 of ABTL0812, a proautophagic drug, in combination with paclitaxel and carboplatin at first-line in advanced endometrial cancer and squamous cell lung carcinoma.

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Background: ABTL0812 is a novel anti-cancer agent that induces a strong autophagy-mediated cell death by a dual mechanism. It inhibits the Akt/mTOR axis by upregulating TRIB3, an endogenous Akt inhibitor, and induces reticular (ER)-stress. Preclinical data in squamous non-small cell lung carcinoma (Sq-NSCLC) and endometrial cancer (EC) has indicated drug efficacy as a single agent and potentiation of chemotherapy. **Methods:** A phase 1 clinical study was designed where ABTL0812 was administered orally in combination with 175 mg/m^2 paclitaxel/carboplatin AUC5 D1 every 3 weeks (P/C), and posterior ABTL0812 as a maintenance therapy until disease progression or unacceptable toxicity. The study included first-line patients (pts) with advanced Sq-NSCLC or advanced/recurrent EC. The design included a 3+3 de-escalation trial followed by an expansion cohort, where the starting dose of ABTL0812 was 1300 mg tid and if at least 2 pts experienced a DLT, the dose level would be de-escalated to 1000 mg tid. Safety and tolerability were the primary endpoints and preliminary efficacy according to RECIST v1.1 criteria and pharmacodynamic biomarkers (TRIB3 and CHOP an ER-stress biomarker, by qPCR in whole blood) were the secondary endpoints. **Results:** 16 EC and 5 Sq-NSCLC pts were enrolled. One DLT, a grade 4 neutropenia, appeared in the first cohort of 6 pts and no de-escalation was applied. Fourteen pts were included in an expansion cohort with the same dose level (1300 mg tid), and 1 DLT, a grade 3 febrile neutropenia, was observed. Therefore, the dose of 1300 mg tid was selected as RP2D in combination with P/C. Most frequent grades 2-4 AEs were neutrophil count decreased (n = 9, 43%), nausea (n = 5, 24%), fatigue (n = 4, 19%), followed by anemia, vomiting, dyspepsia, platelet count decreased, arthralgia and neurotoxicity (n = 2, 10% each). Seventeen pts (13 EC and 4 Sq-NSCLC) who completed at least two treatment cycles were evaluable for efficacy; 1 CR (EC), 8 PR (7 EC and 1 Sq-NSCLC), 7 SD (5 EC and 2 Sq-NSCLC) and 1 PD (Sq-NSCLC) were observed. Pharmacodynamic biomarkers showed increased TRIB3 and CHOP levels. **Conclusions:** The combination of ABTL0812+P/C was safe and tolerated, efficacy signals were observed, and biomarker modulation confirmed drug activity. The triple combination is currently being evaluated in both indications in a Phase 2 study. Clinical trial information: NCT03366480.

3090 **Poster Session (Board #82), Sat, 8:00 AM-11:00 AM**

Design, engineering, and characterization of a novel long-acting (Pegylated) single isomer human arginase for arginine depriving anticancer treatment.

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Background: Arginine deprivation therapy is an attractive strategy to treat arginine-auxotrophic cancers with deficient expression of argininosuccinate synthetase, argininosuccinate lyase or ornithine transcarbamylase. We have designed and engineered a novel human arginase with single site pegylation exerting excellent preclinical pharmacologic profile to serve as a new class of therapy. **Methods:** Human arginase has three cysteines (at position 45, 168, 303) and none of them is in or close to the active site. Two cysteines were mutated to serines, leaving the only cysteine at 45 for the simple and cost-effective synthesis of a single isoform of pegylated human arginase. Different forms of PEG moieties were evaluated for the selection of a drug candidate (PT01), followed by extensive characterization. **Results:** Converting Cys at 168 and 303 to serine impacted least on enzymatic activity (with cobalt cation). Pegylation with different sizes and shapes showed that 20 and 40 kDa (linear and branched) had similar PK/PD profile without damaging enzymatic activity. Therefore, arginase modified with a linear 20 kDa PEG was chosen as the candidate. A single 0.4 mg/kg IV dose of PT01 in rats induced 4 days of near complete plasma arginine depletion, while 6–7 days of depletion between 1.2 and 2 mg/kg. Plasma arginine levels were reversible. First-order clearance of both plasma PT01 concentration and activity suggested a terminal half-life of about 20 hours. *In vitro* assay showed very potent cytotoxicity at sub-nM level against various cell lines of breast, prostate, and pancreas in origins. In two mouse cancer models (hard-to-cure pancreas and castration-resistant prostate), weekly infusion at 5 and 10 mg/kg induced significant tumor growth inhibition of 44-67%. All mice experienced dose-dependent but rapidly reversible weight loss following each weekly dose. **Conclusions:** A novel single isoform of pegylated human arginase was created, showing excellent enzymatic activity, PK/PD profiles, and cytotoxicity *in vitro*. Mouse xenograft models showed good tumor growth inhibition activity with tolerable toxicity as manifested on transient weight loss during therapy.

3091 **Poster Session (Board #83), Sat, 8:00 AM-11:00 AM**

A phase Ib study of prexasertib, a checkpoint kinase (CHK1) inhibitor, and LY3023414, a dual inhibitor of class I phosphatidylinositol 3-kinase (PI3K) and the mammalian target of rapamycin (mTOR) in patients with advanced solid tumors.

David S. Hong, Kathleen N. Moore, Johanna C. Bendell, Daniel D. Karp, Judy Sing-Zan Wang, Susanna Varkey Ulahannan, Melissa Lynne Johnson, Raid Aljumaily, Scott Hynes, Sophie Callies, Rodney Decker, Elizabeth LaBell, Michele Niland, Xuejing Aimee Wang, Aimee Bence Lin, Manish R. Patel; The University of Texas MD Anderson Cancer Center, Houston, TX; Stephenson Cancer Center at the University of Oklahoma HSC and Sarah Cannon Research Institute, Oklahoma City, OK; Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; Florida Cancer Specialists and Sarah Cannon Research Institute, Sarasota, FL; Stephenson Cancer Center, Oklahoma City, OK; Stephenson Cancer Center, University of Oklahoma HSC; Sarah Cannon Research Institute, Nashville, TN; Eli Lilly and Company, Indianapolis, IN; Florida Cancer Specialists, Sarasota, FL

Background: Prexasertib inhibits CHK1, a kinase involved in DNA repair and replication. LY3023414 inhibits PI3K/mTOR signaling, implicated in the development of malignant disease. Prexasertib + LY3023414 has resulted in enhanced antitumor activity in triple negative breast cancer (TNBC) in vitro models. **Methods:** This Phase 1b study in patients (pts) with solid tumors assessed escalating doses of prexasertib (60-105 mg/m^2 IV every 14 days [q14d]) and LY3023414 (100-200 mg orally twice daily [BID]). Dose escalation ceased once the maximum tolerated dose of each monotherapy was reached. An initial expansion cohort (Arm E) explored prexasertib 105 mg/m^2 q14d + LY3023414 200 mg BID. Subsequent expansion cohorts evaluated prexasertib 105 mg/m^2 q14d + LY3023414 150 mg BID in pts with solid tumors with PIK3CA mutations (Arm E2) or TNBC (Arm E3). **Results:** Fifty pts were enrolled (escalation: n = 13; Arm E: n = 9; Arm E2: n = 15; Arm E3: n = 13). No dose-limiting toxicities (DLTs) were observed during escalation however DLT-equivalent toxicities were observed in 2 pts in Arm E (anemia, neutropenia, thrombocytopenia, oral mucositis, abdominal pain, fatigue). Due to toxicity, a reduced dose of LY3023414 (150 mg BID) was assessed in Arm E2/E3. In the 28 patients treated in Arms E2/E3, common treatment-related adverse events (any grade; grade $\geq$3) were: leukopenia/neutropenia (82%; 79%), thrombocytopenia (46%; 36%), nausea (46%; 0%), stomatitis (39%, 4%), vomiting (36%; 0%), and anemia (29%; 18%). Febrile neutropenia was reported in 25% of pts. Dose reductions in Arm E2/E3 were common. In escalation, 2 pts achieved a partial response (PR) and 3 pts achieved stable disease (SD). In Arm E, 78% of pts achieved SD. Of the pts evaluable at the time of data transfer, PRs were achieved in 1 pt with an unknown primary (Arm E2) and 2 pts with TNBC (Arm E3). Each agent's pharmacokinetic profile was consistent with prior monotherapy data. **Conclusions:** Prexasertib + LY3023414 showed preliminary efficacy in heavily pretreated pts with solid tumors but was associated with toxicity, suggesting supportive care may be required. Clinical trial information: NCT02124148.

3092 **Poster Session (Board #84), Sat, 8:00 AM-11:00 AM**

Preclinical testing of ultra-rapid FLASH total abdominal irradiation demonstrates survival benefit and decreased gastrointestinal toxicity compared to conventional external beam radiation.

Karen Levy, Marjan Rafat, Emil Schueler, Joshua Thomas Eggold, Jinghui Wang, Keriann Casey, Albert Koong, Peter Maxim, Billy W. Loo, Erinn Rankin; Stanford University, Stanford, CA; Vanderbilt University, Nashville, TN; Stanford Univ Medcl Ctr, Stanford, CA; Stanford University School of Medicine, Stanford, CA; Stanford Cancer Institute, Stanford, CA

Background: Total abdominal irradiation (TAI) is not widely used in the treatment of ovarian cancer due to high abdominopelvic toxicity. Ultra-rapid FLASH irradiation has been shown to spare the lung, skin and brain from radiation toxicity in preclinical models. Conventional radiotherapy delivers a dose-rate of 3-4 Gy/minute, while our small animal FLASH system uses a linear accelerator to generate a dose-rate of 200 Gy/second. Our data demonstrates that use of FLASH-TAI in a preclinical model protects against death from irradiation and confers gastrointestinal (GI) protection when compared to conventional external beam irradiation. Ongoing studies are evaluating the potential for tumor control in an ID8 mouse model of ovarian cancer. **Methods:** Female C57BL/6 mice received TAI using FLASH and conventional (CONV) radiation at increasing doses: 8.5 Gy, 10.5 Gy and 12 Gy. Unirradiated controls and irradiated cohorts were analyzed at 5-days and 12 months post-irradiation. Normal tissue toxicity was determined by measuring total body weights, stool counts, laboratory analysis, histological analysis, immunohistochemistry, immunofluorescence microscopy and survival. **Results:** Solid stool production was preserved in FLASH mice, whereas a 50-63% decrease was observed in the CONV cohorts. Histology demonstrated that FLASH preserves small intestinal architecture. TUNEL analysis demonstrated an increase in apoptosis throughout the small intestine of only the CONV cohort. Exploratory necropsy of all surviving cohorts at 12 months post-irradiation was notable for secondary transmural proximal duodenal adenocarcinomas within the radiation field in 25% of only the aged CONV cohorts. There was no laboratory evidence of long-term hematopoietic, liver or kidney toxicity at 12 months. Survival analysis was notable for death of all 12 Gy CONV mice by 9 days post-irradiation whereas 75% of the 12 Gy FLASH mice were alive at 11 months. **Conclusions:** FLASH protects against death from TAI, improves small intestine epithelial integrity following TAI, protects against radiation-induced apoptosis and may protect from secondary gastrointestinal tumors in the radiation field. Our discovery that FLASH is a safe strategy to deliver effective doses of total abdominal radiation potentially identifies a new opportunity to utilize FLASH-TAI for treatment of ovarian peritoneal metastases.

3093 **Poster Session (Board #85), Sat, 8:00 AM-11:00 AM**

First-in-human imaging of nanoparticle entrapped docetaxel (CPC634) in patients with advanced solid tumors using ^{89}Zr-Df-CPC634 PET/CT.

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Background: CPC634 is a nanoparticle entrapping docetaxel designed to improve tumor accumulation and tolerability compared to conventionally administered docetaxel by taking advantage of the presumed enhanced permeability and retention (EPR) effect. In vivo imaging with zirconium-89 (^{89}Zr)-desferal (Df)-CPC634 will provide valuable information on its biodistribution and will quantify tumor retention. **Methods:** Patients with solid tumors not amenable to standard therapy received 37 MBq, 0.1-2mg of ^{89}Zr-Df-CPC634 tracer and whole body PET/CT scans were obtained at 2, 24 and 96h post-injection (p.i.). Patients were administered CPC634 (60mg/m^2) two weeks later followed by a second tracer injection and scans at 24 and 96h p.i. Biodistribution was quantified by delineating organs of interest and calculating mean %ID/kg. Visual tumor retention was defined as focal uptake in tumor lesions exceeding local background and quantified as standardized uptake peak values (SUV_{peak}) in volumes of interest. **Results:** Five patients were included. Biodistribution of ^{89}Zr-Df-CPC634 showed significant retention in healthy liver, and spleen compared to lung (respectively 2.54, 1.61 and 0.56 mean %ID/kg at 96h p.i.), supporting apparent opsonization of nanoparticles in cells of the reticuloendothelial system. Visual retention was observed in 16/37 evaluable tumor lesions with the highest intensity at 96h p.i, compatible with the assumed EPR effect. Tumor retention showed intra- and interpatient heterogeneity, with a mean %ID/kg of 3.43 [1.14-9.32]. Pre-administering unlabeled CPC634 did not change the mean tumor retention of ^{89}Zr-Df-CPC634 (at 96h p.i. mean 3.50 %ID/kg [1.64-9.97]), however, four additional lesions were visible in comparison to tracer only. **Conclusions:** The biodistribution of ^{89}Zr-Df-CPC634 was consistent with a prolonged exposure of nanoparticle containing docetaxel. ^{89}Zr-Df-CPC634 showed high retention in tumors confirming the EPR effect of these nanoparticle in humans, and supporting their further development for tumor targeting of therapeutic agents. A Phase II efficacy study in platinum resistant ovarian cancer (NTC03742713) is currently ongoing. Clinical trial information: NCT03712423.

3094 **Poster Session (Board #86), Sat, 8:00 AM-11:00 AM**

A first-in-human phase I/II trial of SRA737 (a Chk1 Inhibitor) in subjects with advanced cancer.

Elizabeth Ruth Plummer, Rebecca Sophie Kristeleit, Elena Cojocaru, Noor Md Haris, Louise Carter, Robert Hugh Jones, Sarah Patricia Blagden, T.R. Jeffry Evans, Hendrik-Tobias Arkenau, Debashis Sarker, Sarah Danson, Stefan N. Symeonides, Harriet Walter, Joanita Ocen, Manreet Randhawa, Mark Marion Kowalski, Ines Verdon, Andrew Dye, Udai Banerji; Northern Centre for Cancer Care, Newcastle-upon-Tyne, United Kingdom; University College London Hospitals, London, United Kingdom; Gustave Roussy, Arcueil, France; Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne, United Kingdom; The University of Manchester, Manchester, United Kingdom; Velindre Cancer Centre, Cardiff, United Kingdom; University of Oxford, Oxford, United Kingdom; University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Sarah Cannon Research Institute, Cancer Institute, University College London, London, United Kingdom; King's College Hospital, Institute of Liver Studies, London, United Kingdom; Sheffield Experimental Cancer Medicine Centre, Weston Park Hospital, Sheffield, United Kingdom; Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh, United Kingdom; University of Leicester, Leicester, United Kingdom; South West Wales Cancer Centre, Swansea, United Kingdom; Sierra Oncology, Inc., Brisbane, CA; Sierra Oncology Inc., Vancouver, BC, Canada; Drug Development Unit-The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

Background: SRA737 is a potent, highly selective and orally-bioavailable inhibitor of checkpoint kinase 1 (Chk1). SRA737-01 was designed to investigate the safety and tolerability of continuous, daily dosing with SRA737 and to evaluate preliminary efficacy in expansion cohorts of prospectively-selected genetically-defined subjects with advanced tumors. **Methods:** The escalation phase employed an accelerated titration design starting at 20 mg administered orally in 28-day cycles. Incremental 100% dose escalations in single-subject cohorts were followed by a rolling-6 design once SRA737-related $\geq$ Grade 2 toxicity was observed during Cycle 1. The expansion phase enrolled subjects prospectively selected by next-generation sequencing with: high grade serous ovarian, colorectal, metastatic castration-resistant prostate, non-small cell lung, and head and neck cancers. **Results:** In escalation, 18 subjects received SRA737 in 9 dose level cohorts, from 20 to 1300 mg QD; median treatment duration 62.5 days (range 1 to 226). Of these subjects, 3 experienced dose limiting toxicity (DLT; inability to receive 75% of the planned dose); 2 at 1300 mg QD due to gastrointestinal intolerability and 1 at 500 mg BID due to thrombocytopenia. The maximum tolerated dose (MTD) was established at 1000 mg QD or 500 mg BID. The C_{max} and $AUC_{0\text{-}24}$ at 1000 mg QD were 2391 ng/mL and 26795 ng•h/mL respectively and the C_{min} (411 ng/mL) exceeded that determined in preclinical models to be effective. Doses $\geq$ 300 mg QD also exceeded this level. Of 462 subjects prospectively screened for genetic alterations associated with Chk1 sensitivity, 93 were enrolled in expansion across all tumor types. Overall, the most commonly reported treatment-emergent adverse events were diarrhea (70%), nausea (64%), vomiting (51%), and fatigue (47%); the majority were of mild to moderate severity. **Conclusions:** In this first-in-human trial of SRA737 monotherapy, the MTD was 1000 mg/day and based on overall tolerability and PK, the recommended Phase 2 dose is 800 mg/day. The successful enrollment of prospectively-selected genetically-defined subjects will allow response data to be correlated with genomic profiles hypothesized to confer sensitivity to Chk1 inhibition. Clinical trial information: NCT02797964.

3095 **Poster Session (Board #87), Sat, 8:00 AM-11:00 AM**

A phase I/II first-in-human trial of oral SRA737 (a Chk1 inhibitor) given in combination with low-dose gemcitabine in subjects with advanced cancer.

Udai Banerji, Elizabeth Ruth Plummer, Victor Moreno, Joo Ern Ang, Amy Quinton, Yvette Drew, Tatiana Hernández, Desamparados Roda, Louise Carter, Alejandro Navarro, Rebecca Sophie Kristeleit, Hendrik-Tobias Arkenau, Debashis Sarker, Daniel E. Castellano, Harriet Walter, Patricia Roxburgh, Sarah Patricia Blagden, Alan Anthoney, Ines Verdon, Robert Hugh Jones; Drug Development Unit-The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Northern Centre for Cancer Care, Newcastle-upon-Tyne, United Kingdom; START Madrid - FJD, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; Royal Marsden Hospital and The Institute of Cancer Research, Sutton, United Kingdom; Velindre Cancer Centre, Cardiff, United Kingdom; Newcastle University, Northern Institute for Cancer Research, Newcastle-upon-Tyne, United Kingdom; Hospital Fundación Jiménez Díaz, Madrid, Spain; Instituto de Investigación Sanitaria INCLIVA, Valenica, Spain; The University of Manchester, Manchester, United Kingdom; Vall d'Hebron University Hospital/Vall d´Hebron Institute Oncolgy (VHIO), Barcelona, Spain; University College London Hospitals, London, United Kingdom; Sarah Cannon Research Institute, Cancer Institute, University College London, London, United Kingdom; King's College Hospital, Institute of Liver Studies, London, United Kingdom; Medical Oncology Service, Hospital Universitario 12 de Octubre, Madrid, Spain; University of Leicester, Leicester, United Kingdom; University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; University of Oxford, Oxford, United Kingdom; St James's Institute of Oncology, St. James's University Hospital, West Yorkshire, United Kingdom; Sierra Oncology Inc., Vancouver, BC, Canada

Background: SRA737 is a potent, highly selective and orally-bioavailable inhibitor of checkpoint kinase 1 (Chk1). SRA737-02 was designed to investigate the safety, tolerability and preliminary activity of SRA737 in a novel combination with sub-therapeutic doses of gemcitabine (low dose gemcitabine; LDG) utilized to potentiate SRA737's activity by induction of replication stress in subjects with advanced solid tumors. **Methods:** Phase 1 dose escalation investigated cohorts of 3 to 6 subjects receiving escalating doses of SRA737 for 2 days after LDG administration on days 1, 8, 15 of 28-day cycles. Phase 2 expansion cohorts explored the hypothesis that LDG strongly synergizes with SRA737 in subjects with genetically-defined tumors hypothesized to be sensitive to Chk1 inhibition: urothelial, high grade serous ovarian, small cell lung, soft tissue sarcoma, and cervical or anogenital cancers. **Results:** A total of 55 subjects received SRA737 in 13 dose escalation cohorts at doses of 40 to 600 mg SRA737 combined with LDG doses of 50 to 300 mg/m^2. No protocol-defined dose limiting toxicities (DLTs) have been observed. The pharmacokinetic profile of SRA737 revealed an $AUC_{0\text{-}24}$ and C_{max} of 3550 ng•h/mL and 548 ng/mL at 150 mg SRA737. At this dose, the C_{min} (52 ng/mL) exceeded that determined in preclinical models to be effective. Enrollment into expansion cohorts was initiated at 500 mg SRA737 plus 100 mg/m^2 LDG with intra-patient dose escalation permitted to 250 mg/m^2 LDG. Approximately 80 subjects were planned and 82 have been treated. Median treatment duration was 51 days (range 1 to 358). The most common treatment-emergent adverse events were nausea (53%), vomiting (45%), fatigue (40%), diarrhea (38%), and anemia (28%); the majority were of mild to moderate severity. Proof-of-concept clinical activity has been seen in tumor types such as anal, cervical, and rectal. **Conclusions:** The combination of LDG and SRA737 has been well tolerated. This first-in-human clinical study provides proof-of-concept that sub-therapeutic LDG effectively potentiates SRA737. This novel replication stress-targeted therapy warrants further evaluation in genetically pre-defined solid tumors. Clinical trial information: NCT02797977.

3096 **Poster Session (Board #88), Sat, 8:00 AM-11:00 AM**

Nanoparticle entrapped docetaxel (CPC634) enhances intratumoral docetaxel exposure compared to conventional docetaxel (Cd) in patients with solid tumors.

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Background: Failure or resistance to chemotherapy may be caused by sub-therapeutic intratumoral drug levels. Nanomedicine aim to improve intratumoral drug exposure. CPC634 is a nanoparticle entrapping docetaxel. We hypothesized that CPC634 increases intratumoral docetaxel exposure. **Methods:** In this randomized cross-over study we assessed intratumoral and plasma pharmacokinetics (PK) of docetaxel after intravenous administration of CPC634 and conventional docetaxel (Cd). The study was powered to identify an 25% increase in intratumoral docetaxel exposure of CPC634 relative to Cd. Patients ($\geq$18 years) were randomized to receive 75 mg/m^2 CPC634 in cycle 1 and Cd in cycle 2 or *vice versa*. After drug administration, patients underwent tumor biopsies during both cycles. Total docetaxel was determined for both drugs and released docetaxel for *CPC634* in tumor tissue and in plasma with a validated LC-MS/MS method. PK data were analyzed with mixed model analysis. **Results:** Sixteen evaluable patients were included. Intratumoral PK revealed a 323% (95% CI: 148,621) higher total docetaxel ($p < 0.001$) for CPC634. Released docetaxel for CPC634 was comparable to total docetaxel levels for Cd (95% CI: -35-,67) ($p = 0.43$). Plasma released docetaxel for CPC634 exhibited an 89% (95% CI: 86, 91) lower ($p < 0.001$) peak plasma concentration (C_{max}) and 81% (95% CI: 46, 125) higher ($p < 0.001$) area under the curve (AUC) relative to Cd. **Conclusions:** CPC634 resulted in higher intratumoral total docetaxel and comparable released docetaxel levels relative to total docetaxel for Cd. CPC634 had a favorable plasma PK profile with a lower C_{max} and prolonged higher systemic exposure relative to Cd. These results indicate that CPC634 could improve intratumoral docetaxel exposure compared to Cd. Additional studies assessing the intratumoral exposure to CPC634 (NCT0371243) and a phase II efficacy study of CPC634 in patients with platinum resistant ovarian cancer (NCT03742713) are currently ongoing.

3097 **Poster Session (Board #89), Sat, 8:00 AM-11:00 AM**

A phase I study of the APE1 protein inhibitor APX3330 in patients with advanced solid tumors.

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Background: APX3330 is an orally administered anti-cancer, anti-CIPN agent targeting the APE1 protein. APE1 maintains NFkB, STAT3, AP-1 and HIF-1a in a reduced form, acting as a regulator of transcription factors. A dual function protein, APE1 also plays a role in protecting against oxidative DNA damage in neurons. APX3330 is a highly selective inhibitor of APE1 redox function in tumors that enhances the neuronal protection function of APE1. **Methods:** We report on study NCT03375086 evaluating APX3330 in patients with incurable malignancies. Eligibility required adequate organ function, PS 0-2 and tumors not amenable to curative therapy. 1° and 2° objectives included determining the recommended phase 2 dose (RP2D), the safety and PK/PD profiles of APX3330 and reporting any RECIST anti-tumor activity. Patients received APX3330 b.i.d, in 21-day cycles. AE evaluation included 1 pt/cohort until the occurrence of $\geq$ G2 toxicity at which time the study proceeded in a 3+3 design. Additional patient were also recruited in cohorts in order to attain PK/PD and biopsy samples. **Results:** Between 2/18 and 8/18, 19 subjects (13M, 6F) with median age of 69 y started therapy. Dose (mg/d) escalation and number of patients treated (n) per each cohort proceeded as follows: 240 mg (1), 360 (4), 480 (2), 600 (6) and 720 (6). APX3330 was well tolerated at dose levels from 240-600 mg/d. The most frequent treatment-related adverse event (all grades) was G1 fatigue. A G3 rash occurred in two subjects at the 720 mg level defining 600 mg/d as the RP2D for further development. Six subjects had disease stabilization for $\geq$ 4 cycles, and of these, four subjects with the following diagnosis, RECIST response and days on study included: (CRC, PR, 356), (Endometrial, SD, 316), (Melanoma, SD, 245), (Prostate, SD, 246). Final PK and PD data, including proteomic, transcriptome, APE1 serum levels and CTC analyses are pending and will be reported at the conference. **Conclusions:** APX3330 is an orally administered inhibitor of APE1. This phase I study identified 600 mg PO daily as the RP2D for further development. RECIST evaluation identified signs of clinical activity in this un-selected population of patients with advanced cancer. PD analyses indicate APX3330 mediated targeting of the APE1 protein. Clinical trial information: NCT03375086.

3098 **Poster Session (Board #90), Sat, 8:00 AM-11:00 AM**

A phase I, open label, multicenter dose escalation study of AZD2811 nanoparticle in patients with advanced solid tumors.

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Background: Aurora kinase B (AURKB) represents a potential target for therapy in solid and hematological malignancies. AURKB inhibitor AZD1152 (barasertib) was previously investigated in solid tumor pts in a phase I setting. AZD2811-nanoparticle (np) is a novel, encapsulated slow release AURKB inhibitor offering several advantages over AZD1152 (Ashton S et al., Sci Transl Med 2016). We report the completed dose-escalation safety, pharmacokinetics (PK), preliminary activity and defined maximum tolerated dose (MTD) of AZD2811-np in pts with advanced solid tumors (NCT02579226). **Methods:** Adult pts with advanced solid tumors received AZD2811-np IV on Day 1 (D1) and 4 (D4) Q4 week (wk) in six cohorts 15-200 mg/infusion without the use of g-csf in cycle 1. D1 Q4wk and Q3wk schedules were investigated up to 600 mg/infusion (including cohorts with mandatory g-csf prophylaxis on day 8). A standard 3+3 design was used. PK was assessed in cycle 1. **Results:** 50 pts were recruited into 12 cohorts. D1, D4 Q4wk schedule: 24 pts (15, 25,38, 50, 100 mg/infusion (n=3/cohort), 200 mg/infusion (n=9)). All cohorts were tolerated. Transient grade 4 neutropenia was observed in 7/9 pts at 200 mg/infusion, including 1 DLT (gr4 $>$ 7 days) D1 Q4wk: 200 mg(n=3) was tolerated. D1 Q3wk: 23 pts were evaluated (200/400 mg (n=3,7), and 400/600/500 mg with mandatory g-csf (n=3/5/6)). 400 mg without g-csf was not tolerated (1 gr3 mucosal inflammation & 1 gr4 neutropenia $>$ 7 days). 600 mg with g-csf was not tolerated (gr3 febrile neutropenia & gr3 fatigue). 25/50 pts experienced AE $\geq$gr 3 (21 considered AZD2811-np-related, 19 neutropenia-related, no deaths within-DLT period). AZD2811-np caused transient gr1/2 fatigue, nausea, diarrhoea and mucosal inflammation. AZD2811 total blood PK appears dose proportional with a $t_{1/2}$ of 30-50 hours irrespective of schedule. Released AZD2811 concentrations ~1% of total. 14 pts (28%) had disease stabilisation. 1 prostate ca. pt had a confirmed partial response (PR) (continued tx to 451 days). **Conclusions:** The MTD for AZD2811-np is 500 mg D1 Q3wk. AZD2811-np is now being investigated in a small cell lung cancer expansion. Clinical trial information: NCT02579226.

3099 **Poster Session (Board #91), Sat, 8:00 AM-11:00 AM**

FGFR2: A pan-genomic target.

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Background: *FGFR2* genomic alterations (GA) have been described in a variety of solid tumors and emerged as biomarkers for investigational agents undergoing clinical trials. **Methods:** 201,766 primarily relapsed/refractory malignancies were evaluated with a hybrid-capture based sequencing assay Tumor mutational burden (TMB) was determined on 0.8-1.1 Mbp of sequenced DNA and reported as mut/Mb. Microsatellite instability (MSI) was determined on 114 loci. PD-L1 expression was determined by IHC (Dako 22C3 antibody). **Results:** *FGFR2* GA were detected in 2,993 (1.5%) cases featuring short variant (SV) mut (42%), copy number changes (27%), rearrangements/fusions (28%) and multiple GA (3%). The most frequent SV GA were S252W, N549K, C382R, P253R, Y375C, K659E and R664W. A small cohort (2%) of tumors featured the V564I and V564L GA that are associated with resistance to TKI drugs. The *FGFR2*-altered cases were 69% female/31% male with median age of 61 yrs. Most frequent GA in *FGFR2* altered cancers: *TP53* (47%), *PIK3CA* (22%), *PTEN* (20%), *ARID1A* (18%), *CDKN2A/2B* (18/14%) and *MYC* (12%). FGFR2 SVs most common in endometrial, breast carcinomas (ca) and CUP. *FGFR2* amplification most common in breast, gastro-esophageal and lung ca. *FGFR* rearrangement/fusions most common in cholangioca (37%), CUP (15%), pancreatobiliary (12%) and breast ca (6%). The *FGFR2-BICC1* was the most frequent fusion followed by fusions with TACC2, AHCYL1, CCDC6, VCL, and KIAA1217. MSI-High status present in 6.8% of evaluable *FGFR2* altered cases (63% in endometrial ca). Median TMB was 3.5 mut/Mb with 21.8% featuring $\geq$ 10 mut/Mb and 12.0% featuring $\geq$ 20 mut/Mb. Only 63% of MSI-High *FGFR2* mut tumors had TMB $\geq$ 20 mut/Mb. 12.7% FGFR2 mut+ had $>$ 1% PD-L1 staining with 3.4% $>$ 50% staining. 29% of PD-L1 IHC+ cases in NSCLC. *FGFR* mut ca's responding to anti-FGFR2 therapies will be presented. **Conclusions:** *FGFR2* GA are most frequent in cholangioca, breast, GI tract, lung ca and CUP, with enrichment of *FGFR2* fusions in biliary tract ca. Cases with *FGFR2* GA typically do not feature other kinase driver GA and are associated with mut in the MTOR/PIK3CA/AKT pathways. Finally, in contrast with RTK driver GA in *EGFR* (5.7%) and *ERBB2* (7.9%), at 12.0%, across all tumor types, *FGFR2* mut cancers may have higher frequency of TMB $\geq$ 20 mut/Mb suggesting potential immunotherapy responsiveness.

3100 **Poster Session (Board #92), Sat, 8:00 AM-11:00 AM**

A randomized phase 0 trial of the mitochondrial inhibitor ME344 or placebo added to the antiangiogenic (Aa) bevacizumab in early HER2-negative breast cancer (E-HERNEBC).

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Background: We have shown that when Aas induce vascular normalization (VN), tumors escape upregulating mitochondrial metabolism. Mitochondrial inhibition with ME344 induced synergy with various Aas. We also found that VN could be traced by showing a 10% decrease in tumor FDG-PET SUV from day (d) 0 to d8 of Aa. We studied the activity of adding ME344 or placebo to Bev (Ki67 decrease) in E-HERNEBC in a phase 0 randomized trial. As a secondary objective we measured the activity of the combination in patients (Pts) showing VN according to FDG-PET. **Methods:** Untreated E-HERNEBC Pts with T > 1cm, any N, M0 underwent a baseline FDG-PET (d1) and received a single dose of Bev (15mg/kg) prior to randomization (1:1) to arm A (FDG-PET on d8 followed by ME344 10 mg/kg IV on d8, d15 and d21) or Arm B (FDG-PET on d8 followed by placebo on d8, d15 and d21). Tumors were biopsied on d0 and 28. A 40 Pts sample size was powered to detect a 30% relative difference between arms in digitally acquired Ki67 decrease from d0 to d28 (alpha 0.05, beta 0.2). **Results:** Arm A: 20 Pts; Arm B: 21 Pts. Baseline characteristics were in arm A vs B: age 58.4(41.5-75.3) vs 53.6(39-82.8); T1(30%)/T2(60%)/T3(10%) vs T1(52%)/T2(48%)/T3(0%); N0(80%)/N1(20%) vs N0(81%)/N1(19%); ER+(75%)/TNBC(25%) vs ER+(71.4%)/TNBC(28.6%); Ki67 31.6% (3.6%-70%) vs 25.2% (1.2% - 81.5%). PET-SUV decreased > 10% from d0 to d8 in 6/20 (arm A) and 6/21 (arm B) Pts. Two G3 adverse events (blood pressure) were reported (1/arm) and deemed related to Bev. Results of the primary endpoint: table. **Conclusions:** ME344 showed significant biologic activity, enhancing the effect in Ki67 decrease vs placebo when added to Bev in E-HERNEBC. The activity was greater in TNBC. A trend for greater activity in patients experiencing VN according to FDG-PET was observed. Clinical trial information: NCT02806817.

All Patients	Arm A	Arm B	P value
Absolute Ki67 change Day 1 to Day 28	-13.3	-1.1	0.0107
Relative Ki67 change Day 1 to Day 28	-23.9%	+186%	< 0.01
Relative Ki67 change D1 to D28 in patients with VN by FDG-PET	-33.4%	+11.8%	0.09
Relative Ki67 change D1 to D28 in patients without VN by FDG-PET	-18.8%	+168%	NS
Patients by receptor	Arm A - TNBC	Arm A – HR+	
Absolute Ki67 change Day 1 to Day 28	-39.8	-5.5	< 0.01
Relative Ki67 change Day 1 to Day 28	-73.6%	-8.7%	< 0.01

3101 **Poster Session (Board #93), Sat, 8:00 AM-11:00 AM**

Patient-derived organoid (PDO), a new personalized therapy selection tool for prompt clinical decision making in metastatic gastrointestinal (mGI) cancer patients.

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Background: PDO is a promising translational tool that recapitulates the biology and drug response of donor cancer patient. However, an unmet need is to have PDO drug-screening data available for treatment decision making in clinic. We conducted a pilot study to determine whether PDO testing results will be available at critical treatment decision points in metastatic GI cancer patients. **Methods:** Metastatic GI cancer patients undergoing core-needle biopsy were eligible. Tumor cells isolated from $\leq$4 fresh biopsy tissues were grown in a Matrigel-based culture. PDO response to anti-cancer drugs were evaluated; and when available, correlated with donors' clinical response to the same agent(s). PDO response was defined as IC50 $<$ 0.1 $\times$ published Cmax of the drug clinically; stable as IC50 between 0.1 to 10 $\times$ Cmax. Radiographic response was per RECIST criteria. **Results:** We enrolled 27 refractory metastatic GI cancer patients (9 colorectal [CRC], 9 pancreas, and 9 biliary tract). Median lines of therapy were 4, 2, and 2; the success rate of organoid establishment was 89%, 44%, and 55%, respectively. The median time from biopsy to availability of drug-testing data was 64 days (range: 24 to 93 days). The median time from biopsy to next CT re-staging in donors was 64 days. The established PDOs shared histological and genomic features with donor clinical tissue. PDO and clinical responses to the same agent(s) were correlated in 2 CRC donors including (1) $BRAF^{V600E}$-mutated PDO responded to vemurafenib + panitumumab, as did the donor who had partial response (PDO drug-testing data were available 55 days post-biopsy, 23 days prior to restaging scan); (2) *KRAS/FGF*-dual amplified PDO had stable disease status to regorafenib, as did the biopsied lesion from the donor (73 days post-biopsy, 5 days post-scan). **Conclusions:** We showed the feasibility of completing PDO drug sensitivity testing in metastatic GI cancer patients within a short time that could impact clinical decision making, particularly in CRC. PDO drug response showed correlation with clinical response. With further refinement, PDO can be a powerful tool for personalizing cancer therapy in metastatic GI cancer patients.

3102 **Poster Session (Board #94), Sat, 8:00 AM-11:00 AM**

Molecular biology and treatment strategies for non-V600 BRAF-mutant NSCLC.

Marcelo Vailati Negrao, Victoria M. Raymond, Richard B. Lanman, Patrick Kwok Shing Ng, Rebecca Nagy, Kimberly Banks, Viola Weijia Zhu, Bianca E Amador, Emily Roarty, Young Kwang Chae, Jeffrey Melson Clarke, Jeffrey Crawford, Sai-Hong Ignatius Ou, David R. Gandara, John Heymach, Trever Grant Bivona, Caroline Elizabeth McCoach; Department of Thoracic / Head and Neck Medical Oncology - The University of Texas MD Anderson Cancer Center, Houston, TX; Guardant Health, Inc., Redwood City, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA; Department of Thoracic and Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; Duke University Medical Center, Durham, NC; Duke Cancer Institute, Duke University Medical Center, Durham, NC; Chao Family Comprehensive Cancer Center, University of California, Orange, CA; University of California, Davis, Sacramento, CA; University of California San Francisco, San Francisco, CA

Background: *BRAF* alterations (alts) account for ~4% of non-small cell lung cancers (NSCLC) with 50% being non-V600 alts. Because these alts are functionally heterogeneous and have a poorly characterized genomic landscape, determining appropriate treatment strategies is a challenge. **Methods:** The Guardant360 clinical database was queried for NSCLC patients (pts) with *BRAF* alts. Alts were categorized by clonality, type and class (1 and 2: *BRAF* monomer and dimer signaling; 3: requires co-occurring upstream RAS-mediated signaling). Functionality and drug screen assays were performed in Ba/F3 cells. Pts with non-V600 mutations were analyzed for sensitivity to *MEK* +/- *BRAF* inhibitors (M+Bi). **Results:** 306 unique BRAF alts were identified and the majority were observed once (233/306; 76%). Amplifications (806/1663; 48.5%) and missense alts (795/1663; 47.8%) were the most common occurrences. Missense alts were predominantly clonal (58%), and of known functionality (428/795; 54%). All class 1-2 alts were activating in Ba/F3 cells, while class 3 alts were found to have variable functionality (activating: 4/9). Functionality was correlated with clonality as demonstrated by class 1-3 alts having higher clonality compared to variants of unknown significance (VUS) (1: 56%; 2: 54%; 3: 45%; VUS: 38%; $P<0.01$). Drug screens for G469V and L597R alts showed resistance to first generation *BRAF* inhibitors (IC50 $\geq$100nM), but sensitivity to M+Bi (IC50 0.02-36nM). Growth inhibition was more pronounced for dabrafenib + trametinib (D+T) (IC50 $<$0.1nM) compared to encorafenib + binimetinib (IC50 8-35nM) and vemurafenib + cobimetinib (IC50 2-36nM). *BRAF* D594G mutation (class 3) was not activating in Ba/F3 cells. Three pts with non-V600 alts were treated with M+Bi. G469V and D594G had rapid disease progression (PFS 2 and 4 mos respectively), while pt with L597R has ongoing partial response (PFS 8+ mos). **Conclusions:** *BRAF* alts show correlation between clonality and functionality, which provides important clinical information given the numerous VUS in the *BRAF* non-V600 setting. Drug screens reveal non-V600 alts may be sensitive to M+Bi and suggest D+T is the most active combination. Clinical data supports that some non-V600 BRAF mutations may be sensitive to M+Bi.

3103 **Poster Session (Board #95), Sat, 8:00 AM-11:00 AM**

The Circulating Cell-free Genome Atlas (CCGA) Study: Size selection of cell-free DNA (cfDNA) fragments.

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Background: Detection of somatic copy number aberrations in individuals with cancer via cfDNA whole-genome sequencing (WGS) is challenging at low tumor fractions. Given that tumor-derived cfDNA fragments are shorter than those from healthy tissues, this exploratory analysis evaluated the potential effect of size selection on the ability to detect cancer. **Methods:** CCGA WGS libraries were *in silico* and *in vitro* size selected to estimate the change in tumor fraction by tumor types (breast, lung, and colorectal [CRC]) and stage (I-III vs IV). *In silico* analyses used clinically evaluable training set samples with WGS assay results (n = 1422: 560 non-cancer [NC], 862 cancer [C] stages I-IV); classification (cancer/non-cancer) performance was estimated using fragments within the 90-150 bp range. *In vitro* analyses used a subset of samples (n = 93: 28 NC, 65 C stages I-IV), including C cases sampled within a range of tumor fractions; tumor fraction was also measured at each progressive removal of maximum-length fragments (intervals of 10 bp: 150 bp down to 50 bp). **Results:** *In silico* and *in vitro* analyses, respectively, resulted in median 2.00±0.58-fold (at 6.91±2.64X depth) and 2.00±0.52-fold (at 23±4.45X depth) increases, in overall tumor fraction (compared to non-size-selected 36X depth). This was consistent across tumor types (*in silico:* 1.78±0.73 breast, 2.00±0.58 CRC, 2.00±0.41 lung; *in vitro:* 2.00±0.82 breast, 2.51±0.52 CRC, 2.53±0.94 lung) and stages (*in silico:* 2.00±0.74 I-III, 1.78±0.52 IV; *in vitro:* 2.00±0.55 I-III, 1.68±0.29 IV). Tumor fraction increased with initial fragment length titrations, but not following size selection to shorter lengths ($<$ 140 bp). Classifier trained on *in silico* size-selected data had increased sensitivity at 98% specificity compared to those trained on non-size-selected data ($p < 1e\text{-}5$). **Conclusions:** *In silico* and *in vitro* size selection consistently increased tumor fraction across cancer types and stages, and this increase was maximized by tuning the length range of size selection. Relative to full-depth data, classification performance improved significantly. These data suggest that size selection targeting cfDNA under 140 bp may enhance cfDNA-based cancer detection. Clinical trial information: NCT02889978.

3104 **Poster Session (Board #96), Sat, 8:00 AM-11:00 AM**

First-in-human phase I trial of anti-hepatocyte growth factor (HGF) antibody (YYB101) in refractory solid tumor patients: Integrative pathologic-genomic analysis and the final results.

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Background: It has been demonstrated in vivo that HGF-MET signaling axis is a key molecular determinant in tumor invasion and there is a significant association in HGF expression and mesenchymal phenotype in addition to immune cell recruitment. We have developed a HGF neutralizing humanized monoclonal antibody antibody, YYB-101. The aim of this study was to determine the maximum tolerate dose (MTD), safety, pharmacokinetics (PK), and pharmacodynamics (PD) of YYB101, in patients with refractory solid tumors. **Methods:** YYB101 was administered intravenously at once every 2 weeks doses of 0.3, 1, 3, 5, 10, 20, 30 mg/kg, according to a 3+3 dose escalation design. Enrolled patients were planned to receive YYB101 until disease progression or intolerable toxicity. The escalation and expansion cohorts (20mg/kg) were completed. Pre-planned biomarker analysis was performed in parallel. **Results:** 39 heavily pre-treated refractory cancer patients were enrolled and received YYB101. No DLT was observed. YYB101 demonstrated dose proportional PK up to the dose of 30 mg/kg. No patients discontinued treatment because of adverse events. Based on PK analysis and toxicity data, the recommended dose was determined as 20 mg/kg. Of 39 evaluation patients, there was 1 confirmed partial response for $>$ +14months (2.5%, N = 1; 1 (of 2) sebaceous carcinoma) and 17 stable disease as best response (43.5%, N = 17; 7 (of 13) CRC, 3 (of 4) melanoma, 1 (of 2) sebaceous carcinoma, 1 (of 3) gastric, 1 (of 1) basal cell carcinoma, 2 (of 10) ovarian cancer, 1 (of 1) HCC, 1 (of 1) lung cancer). Of note, 1 sebaceous carcinoma patient who have failed to $\geq$2+ lines of chemotherapy, have been responding to YYB for 14 months. The MET and HGF expressions by immunohistochemistry (IHC) were evaluated in 19 and 17 tumor specimens, respectively. Neither protein expressions were significant predictors for treatment response to anti-HGF antibody. However, we have observed significant reduction in HGF in responders to YYB. Two long-term responders had mesenchymal signature in RNA sequencing. **Conclusions:** YYB101 has a favorable safety profile in patients with refractory solid tumors and a dose-proportional PK. Efficacy data are encouraging and phase II combination therapy with YYB101 is planned to be open in metastatic CRC patients as salvage treatment. The predictive power of mesenchymal signature in YYB responders will be defined prospectively. Clinical trial information: 02499224.

3105 **Poster Session (Board #97), Sat, 8:00 AM-11:00 AM**

Targeting the p300/CBP interactome through blockage of the CH1-domain triggers tumor regression in AR-positive and AR-negative xenograft models of castration-resistant prostate cancer (CRPC).

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Background: In advanced prostate cancer, the paralog transcription co-activators p300/CBP are often highly expressed and have been associated with disease progression and poor prognosis. While several inhibitors of the bromo- and histone acetyltransferase domains of p300/CBP have been described, past efforts to develop drug-like ligands of other regions of this attractive target have been unsuccessful. **Methods:** A rationally designed small molecule modulator of the CH1-domain of p300/CBP was tested in a panel of prostate cancer cell lines, followed by cell cycle analysis and beta-galactosidase staining. Inhibition of the p300-dependent androgen receptor (AR) related transcriptional response was determined in a luciferase reporter assay and by qPCR analysis of expression of downstream genes like prostate-specific antigen (PSA), transmembrane protease-serine 2 (TMPRSS2) and prostein (SLC45A3). In vivo effects were evaluated in cell line- and patient-derived xenograft models of CRPC. **Results:** Selective blockage of the CH1 domain of p300/CBP results in sustainable anti-proliferative effects in AR-positive and AR-negative prostate cancer cells inducing apoptosis and/or senescence. Transcriptome and gene expression analyses revealed the downregulation of various drivers of cell cycle progression as well as decreased expression of hormone-induced, AR-regulated genes. In enzalutamide-resistant xenograft models of CRPC, oral administration of the compound triggered tumor regression/ eradication at well tolerated doses. Serum PSA levels were strongly decreased in treated animals. **Conclusions:** Simultaneous inhibition of both, AR-signaling and downregulation of p300/CBP activity, may cause profound and long lasting antitumoral effects in patients with advanced prostate cancer. Future clinical investigation of this novel oral small molecule agent is warranted.

3106 **Poster Session (Board #98), Sat, 8:00 AM-11:00 AM**

The landscape of *RET* alterations from 56,970 adult patients with cancer: Clinical implications.

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Background: Activating receptor-tyrosine kinase rearranged during transfection (*RET*) mutations and fusions have been recognized as potent drivers of oncogenesis. Recent identification of highly potent and selective *RET* inhibitors holds great promise in the management of *RET*-dependent tumors. Here we present a comprehensive analysis of *RET* alterations in pan-cancer adult malignancies. **Methods:** We analyzed 59,347 samples from 56,970 patients available from AACR Project GENIE (Cancer Discov. 2017) database for the prevalence of *RET* fusions, mutations, and copy number alterations in diverse cancer types. **Results:** A total of 1414 *RET* alterations were detected, including 91 fusions (6.4%), 1166 missense mutations (82.5%), 136 truncating mutations (9.6%), and 21 in-frame mutations (1.5%). *RET* fusions were observed in 0.15% of tumor samples and were most commonly identified in non-small cell lung cancer, thyroid cancer, colorectal cancer, prostate cancer, and gastric cancer (62.6%, 18.6%, 5.5%, 4.4%, 3.3% of identified *RET* fusions, respectively). *RET* fusions were significantly co-altered with *MAPK3/ERK1* (p=0.045), *SETD2 (p*=1.36E-07*)*, and *EIF4E* (p=0.045), while there was a negative association between *RET* fusions and *EGFR* (p=0.009634*), TP53* (p=0.02267), and *KRAS* (p=2.53E-05) alterations. Most common *RET* gene upstream partners were *KIF5B, CCDC6*, and *NCOA4* (42.9%, 24.2%, 7.7% of identified *RET* fusions, respectively). *RET* missense mutations were found in 2.0% of tumor samples; 136 (11.7%) of identified missense mutations, including 8 *RET* gatekeeper V804M/L mutations, were characterized as likely oncogenic, 12 (1.0%) as likely benign, and 1018 (87.3%) as variants of unknown significance using OncoKB database. *RET* amplifications occurred in 1.5% of tested samples. **Conclusions:** While *RET* fusions represent extremely rare events in multiple cancers, *RET* missense mutations occur in 2% of malignancies. Most *RET* missense variants are described as variants of unknown significance, limiting the impact of precision oncology for the majority of patients with *RET* alterations. Further functional characterization of *RET* variants is warranted. MAPK pathway co-alterations in patents with *RET* fusions may present a strategy for future therapeutic combinations.

3107 **Poster Session (Board #99), Sat, 8:00 AM-11:00 AM**

Host transcriptomic signatures associated with dysbiosis in a preclinical model of lung cancer.

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Background: Enrichment of the lower airway microbiota with oral commensals has been associated with transcriptomic changes affecting several inflammatory pathways associated with non-small cell lung cancer (NSCLC) development and progression. Using a mouse model of NSCLC, we evaluated the effects of lower airway dysbiosis on tumor progression and host transcriptomics. **Methods:** Preclinical model of lung cancer was constructed by introducing luminescence-tagged Kras mutated cells into C57/B6 mice, causing lung cancer to develop. Lower airway dysbiosis was induced by weekly intratracheal challenge with either PBS or *Veillonella parvula* in wild type and lung cancer mice. Experiments were repeated twice to evaluate for survival as well as lower airway host response using flow cytometry and RNA sequencing (HiSeq). Sequence data was processed using a validated mouse gene expression signature matrix with cibersort from https://cibersort.stanford.edu and DESeq using FDR correction. **Results:** In wild type mice, lower airway dysbiosis with *Veillonella* did not affect the survival, weight gain or airway lumen diameter. Among lung cancer mice, dysbiosis led to increased mortality, weight loss, and tumor burden. Multiple transcriptomic signatures were identified among the dysbiosis groups (both in WT and lung cancer mice). Unsupervised hierarchical clustering of immune cell profiles using cibersort on whole transcriptome showed near perfect separation between the four experimental conditions. Amongst the most differentially enriched immune cell subsets, we identified that lung dysbiosis upregulates genes annotated to Th1 and Th2 cells ($p < 0.01$, $q < 0.2$). Using flow cytometry, we identified that PD-1, IL-17, and ROR-gamma are differentially expressed in CD4+ cells in dysbiosis conditions, and these patterns are consistent in whole RNA transcriptome. **Conclusions:** Transcriptomic signatures reveal immune profiles associated with dysbiosis, an experimental condition associated with worse outcomes in lung cancer. This investigation provides novel insights into how disruption of the lower airway microbiome may contribute to the pathogenesis of NSCLC.

3108 **Poster Session (Board #100), Sat, 8:00 AM-11:00 AM**

Prediction of olaparib sensitivity for variants of unknown significance in homologous repair genes.

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Background: the recent use of PARP inhibitors in clinical practice gives very interesting outcome for ovary tumors with *BRCA1* or *BRCA2* mutation but also in other tumors with homologous repair deficiency. Nevertheless, no hotspot mutations are present, consequently, more than 85% of observed variants have unknown significance, blocking the use of PARP inhibitor. **Methods:** Exome analysis was performed on a cohort of 27 patients treated with olaparib. After bioinformatics analyses, variant interpretation was performed by interrogating different databases. For variants of unknown significance (VUS), PROVEAN software and allelic frequency normalized with tumor cellular content were used to classify VUS as potentially benign or potentially deleterious. **Results:** Among the 27 patients analyzed, 16 harbored already classified variants (3 benign and 13 pathogen variants) and 11 had VUS. The first Progression Free Survival (PFS) analysis showed that benign variants did not respond to olaparib with a median survival of 62 days, whereas pathogenic variants had a median of 109 days. Surprisingly, VUS had a median of 136 days, suggesting that some of them could be classified as potentially deleterious. On the subset of 11 patients with VUS, we applied PROVEAN prediction classifying 5 variants as benign and 6 variants as deleterious, with a median PFS of 54 days and 140 days (p=0.3235), respectively. With the second prediction, based on variant allelic frequency, we obtained PFS of 73.5 months for benign variants and 210 days for deleterious ones (p=0.29). By combining both predictions, we classified as benign, VUS predicted benign with both predictions, and as deleterious, VUS predicted as deleterious with at least one prediction. Consequently, we perfectly discriminated benign from deleterious variants with a median PFS of 36 days for predicted benign and 177 days for predicted deleterious (p=0.0084). From all patients, PFS were significantly different (p=0.0003) between benign (n=6, 56 days) and deleterious variants (n=21, 140 months). **Conclusions:** Our work tends to show that VUS of homologous repair genes could be predicted as benign or deleterious, and could increase the number of patients eligible for a treatment by PARP inhibitors. The number of patients needs to be increased in order to validate our prediction algorithm.

3109 **Poster Session (Board #101), Sat, 8:00 AM-11:00 AM**

Cell-specific upregulation of lung "cancer signature genes" in the small airway epithelium of asymptomatic smokers.

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Background: Most lung cancers are derived from the small airway (6^{th} -23^{rd} generations) epithelium (SAE). While a pathogenic mutation in a driver gene is critical to transform a SAE cell to a malignant cell, single cell analysis of lung cancers has demonstrated that individual cancer cells have transcriptional alterations in many "cancer signature genes" (Lambrechts D et al, Nature Med 2018; 24:1277) that are not driver genes, but likely support the malignant state. Based on the concept that dysregulation of many of these genes facilitate the malignant state, we hypothesized that, with the stress of smoking, some of these cancer-supporting transcriptional modifications occur long before the random hit with a driver mutation, providing a soil for the driver mutation. **Methods:** To assess this hypothesis, we applied drop-seq single cell transcriptome analysis to assess SAE recovered by fiberoptic bronchoscopy and brushing of n = 3 healthy non-smokers and n = 3 healthy smokers. Using unsupervised clustering, 11 cell types were identified including major SAE cell types (basal, intermediate, club, mucous and ciliated), rare epithelial cells (ionocyte, neuroendocrine and undefined NCL^{hi}) and rare immune/inflammatory cell (Tcell, mast, antigen presenting). **Results:** Comparison of smokers and nonsmokers showed that smoking significantly altered the transcriptome (n = 426 genes upregulated, n = 572 genes downregulated) in different SAE cell types; 21% -56% of smoking-upregulated genes in the major SAE cell population are identified as "cancer signature genes", where a number have cell-specific smoking regulated patterns within individual cell types including HSPB1 in mucous cells, ADH7 in ciliated, LAMB3 in basal and intermediate cells, MIF intermediate and club cells, ALDH3A1 in all main SAE cell types. **Conclusions:** These data support the concept that cigarette smoking, long before the development of cancer, reprograms specific SAE cells to provide the biological soil to support driver genes to function.

3110 **Poster Session (Board #102), Sat, 8:00 AM-11:00 AM**

Clinical, pathological and genetic predictors of patient-derived xenograft (PDX) engraftment in *EGFR*-mutated lung adenocarcinoma (LUAD).

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Background: PDX are useful preclinical models to study drug response and resistance. Different specimen types have been used to generate PDX models including histological (surgery and CT-guided biopsy) and cytological preparations (EBUS and pleural effusions). We hypothesize that engraftment is not stochastic and is affected by many factors including sample type and tumor pathological and molecular properties. To improve sample selection and cost-effectiveness of PDX experiments, we investigated clinical, histological and genetic correlates of engraftment in *EGFR*-mutated LUAD. **Methods:** We assessed PDX engraftment from 96 surgical resections, 13 CT-guided biopsies, 21 EBUS and 14 pleural effusions of *EGFR*-mutated LUAD. Sixty-five samples, including 6 engrafted (XG) and 54 non-engrafted (noXG) were evaluated by exome sequencing. **Results:** Engraftment was successful in 9/96 (9%) surgical resections, 6/13 (46%) CT-guided biopsies, and 0/35 cytological samples. Biopsies taken at time of treatment failure (compared to treatment naive biopsies) correlated with greater engraftment ($p=0.007$, AUC = 0.68). Multivariable regression analysis of clinical variables at the time of sampling identified advanced (vs early) stage ($p = 0.003$) and histological (vs cytological) preparations ($p < 0.001$) as the strongest predictors of engraftment (AUC = 0.79). Among tumor histologic features, solid (vs lepidic, acinar and papillary) pattern was associated with greater engraftment ($p < 0.001$). Presence of *EGFR*-T790M ($p = 0.004$) and *TP53* ($p = 0.009$) mutations were associated with greater engraftment; all XG samples carried *TP53* mutations. *EGFR*-Ex19del ($p = 0.076$) showed a trend towards engraftment whereas *EGFR*-L858R ($p = 0.086$) trended towards non-engraftment. **Conclusions:** Advanced stage, post-therapy tumors, T790M+ and TP53+ *EGFR*-mutated LUAD samples obtained for histological processing are more likely to engraft as PDXs. Despite low engraftment rates, these models are useful to study novel therapeutic strategy and elucidation of resistance mechanisms.

3111 **Poster Session (Board #103), Sat, 8:00 AM-11:00 AM**

Integrative analyses of signaling and DNA damage repair pathways in patient-derived xenograft (PDX) models from NCI's patient-derived models repository (PDMR).

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Background: Patient-derived xenografts (PDXs) are increasingly being used in translational cancer research for preclinical drug efficacy studies. The National Cancer Institute (NCI) has developed a Patient-Derived Models Repository (NCI PDMR; pdmr.cancer.gov) of PDXs with clinical annotation, proteomics, and comprehensive genomic datasets to facilitate these studies. Here, we present an integrative genomic, transcriptomic, and proteomic analysis of critical signaling and DNA damage repair pathways in these PDX models, which represent 9 common and multiple rare tumor histologies. **Methods:** 304 PDX models from 294 patients were established from various solid tumor histologies from patients with primary or metastatic cancer. Whole Exome Sequencing, RNA-Seq and Reverse Phase Protein Array (RPPA) were performed on 2-9 PDXs per model across multiple passages. An integrative workflow was applied on multiple data sets to detect pathway activation. **Results:** We profiled 10 signaling and 5 DNA repair pathways in the PDMR dataset. We observed that: (i) a large fraction (40%) of PDX models have at least 1 targetable mutation in the RTK/RAS and/or PIK3CA pathways; (ii) 131 models (45%) have putative driver and oncogenic mutations and copy number variants (CNVs) in the WNT, TGFRb , NRF2 and NOTCH pathways. In addition, 17% of PDX models have targetable mutations in DNA damage repair pathways and 20 PDMR models have a DNA mismatch repair defect (MSI-H). We confirmed activation of the signaling pathways in a subset of PDX models by pathway enrichment analysis on gene expression data from RNASeq and phosphoprotein-specific antibody binding data from RPPA. Activation of DNA repair processes was confirmed by enrichment of relevant mutational signatures and loss of heterozygosity in these PDX models. **Conclusions:** Genomic analysis of NCI PDMR models revealed that a large fraction have clinically relevant somatic alterations in key signaling and DNA damage repair pathways. Further integrative analyses with matched transcriptomic and proteomic profiles confirmed pathway activation in a subset of these models, which may prioritize them for preclinical drug studies.

3112 **Poster Session (Board #104), Sat, 8:00 AM-11:00 AM**

Genomic somatic alterations of human epidermal growth factor-2 (HER2) gene: A pan-cancer analysis.

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Background: Human epidermal growth receptor 2 (HER2) is a well-known oncogenic drive gene with multiple targeted therapeutic options. In this study, we aim to assess the landscape of HER2 alterations in solid tumors and evaluate the feasibility of circulating tumor DNA (ctDNA) tested by next-generation sequence (NGS) as a tool to detect HER2 alterations. **Methods:** Alterations of HER2 by NGS (Illumina NextSeq 500) were queried in 3D Medicines database. The mean depth of tissue and circulating tumor DNA (ctDNA) test was 500X and 5000X, respectively. 11,013 patients tested using tumor tissue and 6,970 patients tested using ctDNA were included in this analysis. **Results:** Of 11,013 patients tested using tumor tissue, any HER2 and known or likely deleterious HER2 mutations were identified in 739 (6.7%) and 531 (4.8%) patients, respectively. Of 531 patients who carried known or likely deleterious HER2 mutations, 263 (49.5%) had HER2 amplification and 259 (48.8%) had single nucleotide variations (SNVs). Across all tumor types, breast cancer was found to have the highest frequency of HER2 amplification (14.9%, 48/323), followed by gastric cancer (6.6%, 31/470) and biliary tract cancer (5.8%, 33/571). Moreover, 11% (8/73) of duodenal cancer, 4.5% (7/154) of urothelial cancer, 3.8% (18/470) of gastric cancer, 3.1% (142/4555) of lung cancer, 2.9% (17/571) of biliary tract cancer, 2.8% (44/1562) of colorectal cancer and 2.7% (9/323) of breast cancer carried known or likely deleterious HER2 SNVs. Of 6970 patients tested using ctDNA, any HER2 and known or likely deleterious HER2 mutations were identified in 592 (8.5%) and 277 (4.0%) patients, respectively. In the ctDNA cohort, 15.7% (36/230) of breast cancer and 3.1% (5/161) of biliary tract cancer carried HER2 amplification. However, 11.6% (20/173) of gastric cancer had HER2 amplification tested by ctDNA which was higher than that tested using tissue. Furthermore, 5.6% (13/230) of breast cancer, 4.5% (2/44) of urothelial cancer, 3.4% (6/173), 2.5% of biliary tract cancer and 2.0% (94/4586) lung cancer harbored known or likely deleterious HER2 SNVs in ctDNA cohort. **Conclusions:** HER2 alterations existed across tumor types and the landscape of genomic alterations in HER2 gene varied according to different type of tumor. In addition, ctDNA can be used as a potential tool to detect HER2 alterations.

3113 **Poster Session (Board #105), Sat, 8:00 AM-11:00 AM**

A randomized, multicenter clinical trial to determine the efficacy and safety of pegfilgrastim (GEMA BIOTECH) compared to pegfilgrastim (Roche) for prevention of chemotherapy induced neutropenia in patients with breast cancer.

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Background: Peg-Neutropine, GEMA BIOTECH SAU biosimilar Peg-Filgrastim, is the first Peg-Filgrastim approved in LATAM for prevention of febrile neutropenia in patients treated with myelosuppressive chemotherapy. **Methods:** Study population: women with stage 2, 3 or 4 of breast cancer scheduled to receive 4 or 6 cycles of chemotherapy (with Taxane) at 3 weeks interval. Stratification was based on breast cancer stage. Study drug was administered subcutaneously in a 6 mg dose. The study was blind to the assessors. The primary endpoint was Duration of Severe Neutropenia (DSN, Absolute Neutrophil Count-ANC $<$ 500/mm3) in the first cycle of chemotherapy. Secondary endpoints were incidence of severe neutropenia (SN), other efficacy measures, and incidence of ADRs. The non-inferiority margin for DSN was estimated in less than 1 day. **Results:** A total of 120 subjects were randomized 1:1, 58 were treated with Peg-Neutropine and 62 with Peg-Filgrastim (Roche). *Efficacy:* SN was developed in 52/283 (18,4%) cycles with Peg-Neutropine in 27 patients and 48/297 (16,2%) cycles with Peg-Filgrastim (Roche) in 20 patients (p=0,4836). In the first cycle, 16 patients with Peg-Neutropine and 11 patients with Peg-Filgrastim (Roche) developed SN. In per protocol analysis mean DNS in the first cycle was 0,78 $\pm$ 1,53 days for Peg-Neutropine group and 0,53$\pm$1,25 for Peg-Filgrastim (Roche) group (95% IC for the difference -0,26; 0,76). Per ITT analysis the mean DSN was 0,90$\pm$1,79 for Peg- Neutropine group and 0,50$\pm$1,21 for Peg-Filgrastim (Roche) group, (95% IC for the difference -0,15; 0,95). For all the efficacy secondary endpoints the differences were not statistically significant. *Safety*: 7 ADRs were developed by 3 subjects with Peg-Neutropine and 31 ADRs were developed by 10 subjects with Peg-Filgrastim (Roche). The most common reaction was myalgia, and other ADRs were arthralgia, asthenia, bone pain and acid sensitive syndrome. **Conclusions:** Based on the non-inferiority margin established we conclude that Peg-Neutropine is biosimilar to Peg-Filgrastim (Roche). Clinical trial information: NCT03404752.

3114 **Poster Session (Board #106), Sat, 8:00 AM-11:00 AM**

Development and clinical validation of Lantern Pharma's AI engine: Response algorithm for drug positioning and rescue (RADR).

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Background: The Response Algorithm for Drug positioning and Rescue (RADR) technology is Lantern Pharma's proprietary Artificial Intelligence (AI)-based machine learning approach for biomarker identification and patient stratification. RADR is a combination of three automated modules working sequentially to generate drug- and tumor type-specific gene signatures predictive of response. **Methods:** RADR integrates genomics, drug sensitivity and systems biology inputs with supervised machine learning strategies and generates gene expression-based responder/ non-responder profiles for specific tumor indications with high accuracy, in addition to identification of new correlations of genetic biomarkers with drug activity. Pre-treatment patient gene expression profiles along with corresponding treatment outcomes were used as algorithm inputs. Model training was typically performed using an initial set of genes derived from cancer cell line data when available, and further applied to patient data for model tuning, cross-validation and final gene signature development. Model testing and performance computation were carried out on patient records held out as blinded datasets. Response prediction accuracy and sensitivity were among the model performance metrics calculated. **Results:** On average, RADR achieved a response prediction accuracy of 80% during clinical validation. We present retrospective analyses performed as part of RADR validation using more than 10 independent datasets of patients from selected cancer types treated with approved drugs including chemotherapy, targeted therapy and immunotherapy agents. For an instance, the application of the RADR program to a Paclitaxel trial in breast cancer patients could have potentially reduced the number of patients in the treatment arm from 92 unselected patients to 24 biomarker-selected patients to produce the same number of responders. Also, we cite published evidence correlating genes from RADR derived biomarkers with increased Paclitaxel sensitivity in breast cancer. **Conclusions:** The value of RADR platform architecture is derived from its validation through the analysis of about ~17 million oncology-specific clinical data points, and ~1000 patient records. By implementing unique biological, statistical and machine learning workflows, Lantern Pharma's RADR technology is capable of deriving robust biomarker panels for pre-selecting true responders for recruitment into clinical trials which may improve the success rate of oncology drug approvals.

3115 **Poster Session (Board #107), Sat, 8:00 AM-11:00 AM**

A modeling and simulation study of less frequent dosing of nivolumab 480 mg.

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Background: Nivolumab was originally approved at 3 mg/kg q2w. However, there is abundant evidence that doses as low as 0.1 mg/kg q2w are effective, and a randomized trial in RCC demonstrated equivalence across a dose range of 0.3-10 mg/kg q3w. Modeling and simulation have been used to amend the labeled dosage to 240 mg q2w or 480 mg q4w, with the latter yielding an estimated steady-state trough concentration (C_{trough}) of ~50 ug/mL. Given the high cost of nivolumab and the lack of a dose-response relationship, we hypothesized that less frequent dosing of 480 mg would maintain therapeutic serum concentrations. The objective of this study was to use modeling and simulation to develop alternative dosing strategies. **Methods:** A simulation model was built from a published population pharmacokinetic model, incorporating time-dependent clearance. Various alternative dosing schedules were simulated, beginning with the third dose (doses 1 and 2 were 480 mg at wk 1 and 5). We conservatively chose 4.5 mg/mL as the target concentration (TC), slightly above the mean simulated C_{trough} at 0.3 mg/kg q3w (4.1 ug/mL), although even lower levels are likely efficacious. The simulated dose schedules were q8w, q10w, q12w and q14w, beginning with the third dose. Simulations were performed on 50 simulated patients, with each simulation replicated 5 times. **Results:** The simulated C_{trough} following doses 2-4 are presented in the table below. Dosing q12w should maintain TC in $>$ 70% of patients, and q14w dosing should achieve TC in $>$ 55% of patients. **Conclusions:** Modeling and simulation provide evidence that nivolumab can be effectively dosed q8-14w (after the first 2 doses), resulting in a potential 70% cost savings. As responding patients generally have a 35-45% decrease in clearance over the first 6 months of treatment, even less frequent dosing may be required for subsequent doses. Randomized trials of this interventional pharmacoeconomic strategy are indicated. Similar opportunities may exist for other checkpoint inhibitors.

Dose	q8w	q10w	q12w	q14w
2	19.9 (18.2 – 21.7)	13.4 (12.0 – 14.9)	9.0 (7.9 – 10.3)	6.1 (5.4 – 6.9)
3	18.5 (16.8 – 20.3)	11.6 (10.4 – 12.9)	7.4 (6.5 – 8.4)	4.8 (4.2 – 5.4)
4	18.3 (16.6 – 20.1)	11.3 (10.1 – 12.7)	7.2 (6.3 – 8.2)	4.7 (4.0 – 5.4)

*values represent geo mean (95% CI)

3116 **Poster Session (Board #108), Sat, 8:00 AM-11:00 AM**

Correlation between *NDRG1* gene polymorphism and neuropathy (N) in metastatic breast cancer (MBC) patients (pts) enrolled in the PAINTER study (Polymorphism And INcidence of Toxicity in ERibulin treatment).

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Background: MBC is an incurable disease and therefore treatment focuses mainly on prolonging pts survival and improving quality of life. Eribulin (E) is a microtubule inhibitor that increased overall survival in pretreated pts. E peripheral N is reported in 13.9-35% of cases. PAINTER main objective was to survey tolerability of E in real life in MBC, while secondary endpoints were to investigate the relationships between specific genetic polymorphisms and incidence and severity of peripheral N. **Methods:** This is a multicenter, interventional, single-arm, phase IV study, that enrolled pts who received E after taxanes and antracyclines (dose 1.4 mg/m^2 day 1, 8 every 21 days). PAINTER study follow-up is still ongoing. Genomic DNA was isolated from whole blood samples (Maxwell whole blood DNA kit. Promega). 15 SNPs (Single Nucleotide Polymorphisms) were genotyped by Taqman specific assays. For SNPs analysis, we selected pts with avaliable clinical data and who completed E treatment. N was evaluated by medical examination. The associations between peripheral N (any grade) and the selected polymorphisms were evaluated with Fisher exact test. **Results:** From May 2014 to June 2018, 180 pts were enrolled in the PAINTER study from 20 Italian hospitals and 135 were analysed for the present report. Pts and tumor characteristics were as follow: median age 62 years (31-85), ductal carcinoma 78.5%, visceral disease 70.4%, luminal type 62.6%, Her2 positive 20.3%, triple negative 17.1%, previous median treatment lines for MBC 5 (0-18), previous N reported in 17.8% of pts (sensory 87.5%, motor 12.5%). N (all grades) were reported in 33.4% of patients (G3-G4: 3%). Among the selected SNPs, one allelic variant (rs2233335 G/G versus G/T or T/T) in *NDRG1* gene had a statistically significant association with N (p 0.0010). **Conclusions:** The data reported demonstrate for the first time that the allelic variant rs2233335 (G/T and T/T) in *NDRG1* gene correlates with E induced N. These data, if corroborated, will allow a tailored treatment with E. Clinical trial information: NCT02864030.

rs2233335 Allelic variant	G1-2-3 Neurotoxicity n (%)	G0 n (%)	G1 n (%)	G2 n (%)	G3 n (%)
G/G	4/24 (16.7)	20 (22.2)	1 (3.7)	1 (7.1)	2 (50.0)
G/T	14/60 (23.3)	46 (51.1)	10 (37.0)	3 (21.4)	1 (25.0)
T/T	27/51 (52.94)	24 (26.7)	16 (59.3)	10 (71.4)	1 (25.0)

3117 **Poster Session (Board #109), Sat, 8:00 AM-11:00 AM**

Concomitant intake of abiraterone and food to increase pharmacokinetic exposure: Real-life data from a therapeutic drug monitoring program.

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Background: Abiraterone acetate is registered for the treatment of metastatic castration resistant prostate cancer. Pharmacokinetic (PK) exposure has been linked to efficacy, since patients with $C_{min} \geq$ 8.4 ng/mL have a significantly longer progression free survival compared to patients with a C_{min} below this threshold (7.4 vs. 12.2 months, p = 0.044) (Carton, 2017). At the recommended fixed dose of 1000 mg QD administered in a modified fasting state, 35% of patients do not reach this efficacy threshold (Carton, 2017), providing a strong rationale for therapeutic drug monitoring (TDM). Since a clinically relevant food effect has been established, concomitant intake of abiraterone and food could offer a cost-neutral solution in case of low exposure (Chi, 2015). This study aims to evaluate whether PK-guided abiraterone dosing is feasible and results in an increased proportion of patients with concentrations above the target. **Methods:** Patients starting regular treatment with abiraterone were included. PK sampling occurred 4, 8 and 12 weeks after start of treatment, and every 12 weeks thereafter. Abiraterone concentrations were measured and C_{min} was calculated. In case of $C_{min} < 8.4$ ng/mL and acceptable toxicity, a PK-guided intervention was advised. As a first step, concomitant intake of abiraterone and a light meal or a snack was advised. **Results:** In total, 35 patients were included, of which 18 patients (51%) had at least one $C_{min} < 8.4$ ng/mL. These patients were advised to take abiraterone concomitantly with food, after which C_{min} increased significantly from 5.6 (47%) ng/mL [mean (CV%)] to 40.6 (110%) ng/mL (p = 0.006) without additional toxicities. This intervention led to adequate exposure in 15 patients (83%). Seventeen patients had all C_{min} levels $\geq$ 8.4 ng/mL, in these patients mean C_{min} was 31.5 (65%) ng/mL. **Conclusions:** TDM of abiraterone was applied in clinical practice and proved to be feasible. Concomitant intake with food resulted into a significant increase in C_{min} and offers a cost-neutral opportunity to optimize treatment for patients with low PK exposure. Up to 100 patients will be included to evaluate the effect of PK-guided abiraterone dosing on treatment efficacy. Clinical trial information: NL6695.

3118 **Poster Session (Board #110), Sat, 8:00 AM-11:00 AM**

A phase I dose-escalation study of two cycles carboplatin-olaparib followed by olaparib monotherapy in patients with advanced cancer.

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Background: The PARP-inhibitor olaparib has single-agent activity in BRCA mutated breast and ovarian cancer. Preclinical studies show synergistic effects when combining PARP-inhibitors and platinum drugs in BRCA1/2 mutated cancer cell models. A formulation change from olaparib capsules to tablets initiated a new dose finding study of olaparib tablets BID continuously with carboplatin. **Methods:** Patients were included in a 3+3 dose-escalation schedule in the following dose-levels: olaparib 25mg BID and carboplatin AUC 3 d1/d22, olaparib 25mg BID and carboplatin AUC 4 d1/d22, olaparib 50mg BID and carboplatin AUC4 d1/d22, olaparib 75mg and carboplatin AUC 4 d1/d22 and olaparib 100mg BID and carboplatin AUC 4 d1/d22. After two cycles patients continued olaparib 300mg BID as monotherapy. Primary objective was to assess the Maximum Tolerable Dose (MTD). Secondary objectives were to investigate the preliminary response rate, pharmacodynamics and systemic exposure. **Results:** In total 24 patients were included with breast cancer (n = 18), ovarian cancer (n = 3), melanoma (n = 1), colorectal cancer (n = 1) and esophageal cancer (n = 1). Nineteen out of 24 patients had a germline BRCA mutation (79%). Most common AEs were nausea (46%), fatigue (33%) and platelet count decrease (33%). The majority of AEs (83%) were grade 1/2 in severity. Because two dose-limiting toxicities (consisting of $\geq$ 7 days dose delay of cycle 2 or missing $\geq$ 5 doses of olaparib due to hematologic toxicity) occurred in dose-level 4, dose-level 3 (olaparib 75mg and carboplatin AUC 4; n = 6 patients) was determined to be the MTD. Fourteen out of 24 patients (56%) had a partial response as best response, according to RECIST 1.1. Systemic exposure of the olaparib tablet formulation appeared comparable to the previous capsule formulation with an olaparib tablet $AUC_{0\text{-}14}$ of 16.3 μg/ml*h at MTD. PARP activity in PBMCs was decreased by 98.7% $\pm$ 0.14% at day eight compared to day one for dose-level 3. **Conclusions:** Olaparib tablets 75mg BID and carboplatin AUC 4 for two cycles preceding olaparib monotherapy is a feasible and tolerable treatment schedule with encouraging clinical antitumor activity. Clinical trial information: NCT02418624.

3119 **Poster Session (Board #111), Sat, 8:00 AM-11:00 AM**

Boosting pazopanib exposure by splitting intake moments: A prospective pharmacokinetic study in cancer patients.

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Background: Pazopanib is approved for the treatment of renal cell carcinoma (RCC) and soft tissue sarcoma (STS). Due to high (40-70%) interpatient variability in pharmacokinetic (PK) exposure, 16-20% of patients do not reach the 20 mg/L exposure threshold related to prolonged progression free survival (20 weeks versus 52 weeks, respectively) with the currently used fixed dose of 800 mg QD (Suttle, 2014; Verheijen, 2017). PK simulations showed that, due to non-linear absorption of pazopanib, splitting the intake (400 mg BID) leads to an increase in C_{min} and $AUC_{0\text{-}24h}$ of 75% and 59%, respectively (Yu, 2017). This study aimed to show whether switching patients from an 800 mg QD to a 400 mg BID dose schedule will lead to a significant increase in PK exposure. **Methods:** We performed a prospective PK trial (NL6137) in which PK sampling at the 800 mg QD dose schedule occurred at day 1, after which the intake moments were split into 400 mg BID during one week, followed by PK sampling at day 8. Paired samples t-tests were used to assess differences in C_{min}, C_{max} and $AUC_{0\text{-}24h}$ between these two dose schedules. To detect an increase in PK exposure of 50% (2-sided $\alpha = 0.05$ and $\beta = 0.20$), 10 evaluable patients were needed. **Results:** Eleven patients (6 RCC and 5 STS) have been included, of whom ten were evaluable for PK analyses. Using the 800 mg QD dose schedule mean C_{min}, C_{max} and $AUC_{0\text{-}24h}$ were 26.7 mg/L (coefficient of variation (CV%) 44.7), 46.1 mg/L (CV% 37.1) and 809 mg h/L (CV% 42.1), respectively. Switching to 400 mg BID resulted in an increase of both C_{min} and $AUC_{0\text{-}24h}$ to 40.7 mg/L (CV% 37.0, $p = 0.013$) and 1059 mg h/L (CV% 33.1, $p = 0.068$), respectively, while C_{max} did not significantly change (56.5 mg/L, CV % 33.2, $p = 0.185$). One patient (9%) experienced grade 3 diarrhea after splitting intake moments, leading to treatment interruption. This strategy could potentially save up to 2000 USD/patient/month compared to conventional dose increments. **Conclusions:** This study demonstrates that boosting pazopanib exposure by splitting intake moments leads to a significant increase in $C_{min,}$ of 52%, with acceptable tolerability. Therefore, this new dose schedule offers a safe and cost-neutral opportunity to optimize treatment for patients with low PK exposure. Clinical trial information: NL6137.

3120 **Poster Session (Board #112), Sat, 8:00 AM-11:00 AM**

Long-term follow-up of pharmacokinetics (PK) and immunogenicity of the anti–PD-1 antibodies nivolumab (Nivo) and pembrolizumab (Pembro) in real-world practice.

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Background: The PD-1 blockers Nivo and Pembro are widely used to treat patients (pts) with various types of cancer, but their PK and immunogenicity have not been adequately characterized in clinical practice. Here we report the first long-term follow-up of PK and anti-drug antibodies (ADAs) of Nivo and Pembro, correlated with efficacy and safety. **Methods:** We included 147 pts receiving Nivo (n = 98) or Pembro (n = 49) between May 2016 and Jan 2019. Plasma samples were longitudinally collected before each infusion and after discontinuation for as long as samples were obtainable. Drug concentrations were measured by ELISA (LLOQ: 0.0125 μg/mL), and ADAs were evaluated by bridging ELISA. **Results:** Median (range) follow-up was 6.0 (0.1-38.7) mo, and 1718 samples were analyzed. ADAs were confirmed at baseline or at last sample for both Nivo (2 [2.2%] and 4 [4.5%] pts, respectively) and Pembro (2 [4.2%] and 3 [6.7%] pts). Of the 4 baseline ADA-positive pts, 3 experienced drug-induced fever after initial infusion. Pts developing ADAs at last sample had earlier progression than ADA-negative pts (median PFS: 46 vs. 119 days, log-rank $P = 0.0827$). Persistent drug exposure until ~1 y beyond discontinuation was observed for both drugs. In 1 Nivo-treated pt with delayed adrenal insufficiency 8.6 mo after discontinuation, Nivo was still detectable (0.2 μg/mL). In 71 and 41 efficacy-evaluable pts receiving Nivo and Pembro, respectively, mean trough levels in the early period (~cycle 6) were significantly higher in pts achieving response than in pts with progressive disease at first assessment (Nivo: 43.5 vs. 31.0 μg/mL, $P = 0.0107$; Pembro: 30.6 vs. 22.1 μg/mL, $P = 0.0174$). **Conclusions:** Our findings provide insight into the etiological mechanism of late-onset adverse events associated with PD-1 blockers. Moreover, ADA may potentially influence clinical outcomes, and it may be possible to optimize dose in certain pts with lower drug exposure for improved efficacy, warranting further investigation. Clinical trial information: UMIN000033036.

	Nivo (n = 98)	Pembro (n = 49)
Cancer type, n		
NSCLC/MPM	21/2	37/0
SCCHN	21	0
Gastric cancer	21	0
RCC/ Urothelial carcinoma	18/0	0/10
MEL	15	2

3121 **Poster Session (Board #113), Sat, 8:00 AM-11:00 AM**

Accumulation of active metabolite M-2 predicts overall survival (OS) of chemorefractory metastatic colorectal cancer patients treated with regorafenib (REGO).

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Background: TEXCAN, a prospective phase II GERCOR study of treatment with REGO in chemorefractory metastatic colorectal cancer (mCRC) patients (NCT02699073) included a prospective pharmacokinetic (PK) ancillary study aiming to investigate correlations between OS and concentrations (C) of REGO and its active metabolites M-2 and M-5. **Methods:** 55 patients were included, with the same inclusion/exclusion criteria as CORRECT (NCT01103323), and treated orally with 160 mg REGO daily for 3 weeks on and 1 week off. 34 patients had PK samples at C1D15 and 26 at C2D15 for Cmin. REGO, M-2 and M-5 Cmin were measured by LC-MS/MS. PK analyses studied the link between OS and PK parameters: Cmin of REGO, M-2 and M-5 at C1 and accumulation of pharmacological active metabolites between C1 and C2, assessed by the C2/C1 ratio of M-2 or M-5 Cmin concentrations. **Results:** REGO, M-2 and M-5 Cmin [median (Q1-Q3)] were respectively 1.99 (1.03-2.73), 1.44 (0.89-2.49) and 1.61 (0.79-2.37) mg/L at C1D15 and 1.90 (1.10-2.76), 1.29 (0.77-2.24) and 1.17 (0.45-2.42) mg/L at C2D15. C2/C1 M-2 ratio and M-5 ratio medians were 0.82 (0.50-1.78) and 0.75 (0.41-1.93), respectively. Univariate analyses showed a major OS benefit in patients with C2/C1 M-2 ratio $\geq$median vs $<$ median (12.6 vs 4.0 months respectively, hazard ratio = 0.35, 95% confidence interval 0.14-0.86, p-value = 0.023) but not for C2/C1 M-5 ratio $\geq$median. Multivariate analyses, including the CORRECT REGOSCORE groups, showedan independent 66% reduction in death risk in the group of patients with C2/C1 M-2 ratio $\geq$median. The C2/C1 M-2 ratio correlated with C1 REGO+M-2+M-5 (Csum) (0.53, p-value = 0.006). Restricted Cubic spline analysis showed an increased OS benefit as the C2/C1 M-2 ratio rises and when C1 Csum ranged between 2.5 and 5.5 mg/L. PK parameters were not associated with toxicities. **Conclusions:** M-2 accumulation between C1 and C2 is independently associated with improved OS in mCRC patients treated by REGO. M-2 accumulates and OS is favorable when C1 REGO+M-2+M-5 sum ranged between 2.5 and 5.5 mg/L. These results may lead to develop individual REGO dosage modification strategies based on PK monitoring. Clinical trial information: NCT02699073.

3122 **Poster Session (Board #114), Sat, 8:00 AM-11:00 AM**

Larotrectinib efficacy and safety in adult TRK fusion cancer patients.

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Background: A broad range of pediatric and adult malignancies harbor TRK fusions involving the NTRK1, NTRK2, and NTRK3 genes. The highly-selective TRK inhibitor, larotrectinib, has previously shown a high overall response rate (ORR) and a favorable safety profile in patients (pts) with TRK fusion cancer. To better delineate efficacy in adults, as pediatric pts have a particularly high ORR, here we report updated efficacy and safety data from the adult subset of pts with TRK fusion cancer treated with larotrectinib. **Methods:** Adult pts (aged 18 or older) with TRK fusion cancer detected by local testing in 2 larotrectinib clinical trials (NCT02122913 and NCT02576431) were analyzed. Larotrectinib was administered 100 mg PO BID until disease progression, withdrawal, or unacceptable toxicity. Disease status was assessed by both investigator (INV) and independent assessment (IRC) using RECIST v1.1. **Results:** As of July 30, 2018, 83 adults (median age: 57 y, range 20–80 y) with TRK fusion cancer had been treated. Cancer types included salivary gland (23%) and thyroid cancer (19%), soft tissue sarcoma (14%), lung cancer (13%), colon cancer and melanoma (7% each), GIST (5%), and bone sarcoma, cholangiocarcinoma, and appendiceal, breast, and pancreas cancer (≤2% each). TRK fusions involved NTRK1 (40%), NTRK2 (2%), and NTRK3 (57%). 77% of pts had received prior systemic therapy (median lines: 2, range 0–10). In 74 pts evaluable per INV, the ORR was 76% with 9% CR, 57% confirmed PR, 9% PR pending confirmation, 12% SD, 11% PD, and 1% not determined; 9 pts were non-evaluable (NE) due to lack of post-baseline assessment. In 65 pts evaluable per IRC, the ORR was 68% with 17% CR, 51% PR, 15% SD, 12% PD, and 5% NE. With a median follow up of 17.2 and 17.5 mo per INV and IRC, respectively, the median duration of response had not been reached (ranges identical: 1.9+ to 38.7+ months). At data cutoff, 63% remained on treatment; 30% had discontinued due to disease progression. Adverse events were mostly grade 1–2. **Conclusions:** Larotrectinib demonstrated robust tumor-agnostic efficacy and a favorable safety profile in adult pts with TRK fusion cancer. These results support testing for TRK fusion cancer in pts with advanced solid tumors, regardless of site of primary diagnosis. Clinical trial information: NCT02122913 and NCT02576431.

3123 **Poster Session (Board #115), Sat, 8:00 AM-11:00 AM**

Phase 1b study of selinexor, a first-in-class selective inhibitor of nuclear export (SINE) compound, in combination with doxorubicin in patients (pts) with locally advanced or metastatic soft tissue sarcoma (STS).

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Background: Selinexor is a first-in-class SINE compound with single-agent activity in STS. We undertook this study to determine the safety, tolerability and efficacy of selinexor in combination with doxorubicin in pts with incurable STS. **Methods:** This phase 1b study was conducted using a bayesian model (modified toxicity probability index). Patients with locally advanced or metastatic STS received selinexor at either 60 or 80mg weekly PO plus doxorubicin (75mg/m^2 IV q21 days, max 6 cycles). Pts with stable disease (SD) or better (per RECIST 1.1 criteria) after 6 cycles of combination treatment received selinexor monotherapy until disease progression or unacceptable toxicity. Disease assessments were made with standard imaging after every 2 cycles. **Results:** 24 pts (19F/5M, ECOG 0/1: 12/12, median age 58.5 years [range 34-74]) were enrolled. Disease subtypes included leiomyosarcoma (n = 6), malignant peripheral nerve sheath tumor (n = 3) and other sarcomas (n = 15). Three pts at 60mg selinexor and 21 pts at 80mg selinexor were treated. The most common G3 drug related adverse events were hematological, neutropenia n = 13 (54%), anemia n = 6 (25%). There were 4 dose-limiting toxicities (2 febrile neutropenia, 1 vomiting and 1 unresolved fatigue) all at the 80mg dose level, but does not satisfy criteria for maximum tolerated dose. Two patients had clinically significant and relevant drop in ejection fraction, presenting with cardiac symptoms. Of the 24 evaluable pts 4 (17%) had a partial response, 16 (67%) had SD as best response and SD $>$ 16 weeks was seen in 13 pts (54%). PK analysis of selinexor did not demonstrate changes compared to single agent profile. The estimated median PFS and OS are 5.5 (95% CI:4.1-7.0) and 9.4 (6.6-13.8) months. **Conclusions:** Our initial data demonstrate that the combination of selinexor at 80mg with doxorubicin is tolerable and is associated with clinical benefit. Longer term follow up of available patients will be needed to understand toxicity profile. Clinical trial information: NCT03042819.

3124 **Poster Session (Board #116), Sat, 8:00 AM-11:00 AM**

A phase I study of a novel MDM2-P53 antagonist APG-115 in Chinese patients with advanced soft tissue sarcomas.

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Background: APG-115 is a novel and orally active small-molecule MDM2 inhibitor. APG-115 alone or in combination with chemotherapeutic, targeted or IO agents have shown potent antitumor activities in multiple human xenograft tumor models and human cancer patient derived xenograft (PDX) models. **Methods:** The patients with advanced solid tumors were enrolled in this study in China (CTR20170975). The study objectives were to assess safety, pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activity of APG-115. The patients received APG-115 (ranging 100–200 mg) orally QOD for first 21 days of a 28-day-cycle, until disease progression. Antitumor response assessment was performed every 8 weeks per RECIST v1.1. Archived tumor tissues were collected for analyses of MDM2 and TP53 before treatment. **Results:** As cut-off on Jan 4 2019, total 13 patients (9 soft tissue sarcomas (STSs), 2 adenoid cystic carcinomas (ACCs) and 2 osteosarcomas) were treated in 3 cohorts of APG-115 (100mg, 150mg, 200mg). The median number of prior systemic anticancer therapies was 2 (range 0-4). Two DLTs were observed in one patient at 200mg including thrombocytopenia and febrile neutropenia. The most common TEAEs (≥50% of pts) included: anemia, thrombocytopenia, vomiting, hypercholesterolaemia, and leukopenia. SAEs occurred in 7 patients (54%), four of which were treatment related. The most common Grade 3 or 4 TRAEs were anemia (38.5%), thrombocytopenia (38.5%), leukopenia (30.8%), and neutropenia (23.1%). One partial response was observed in a liposarcoma patient with MDM2-amplification and TP53-wild type at the 150mg cohort, 5 patients (3 STSs, 2 ACCs) had SD as the best overall response. PK analyses indicated an approximately dose proportional increase in Cmax and $AUC_{0\text{-}t}$ following a single or multiple oral administration across dose levels. Preliminary PD data showed that serum MIC-1 increase was exposure dependent within the dose range tested. **Conclusions:** Preliminary data suggested that APG-115 had promising anti-tumor activity in treatment of patients with MDM2-amplification and TP53-WT liposarcoma. Safety profile and PD effect were consistent with other MDM2 inhibitors. Dosing regimen optimization are ongoing. Clinical trial information: CTR20170975.

3125 **Poster Session (Board #117), Sat, 8:00 AM-11:00 AM**

A phase I study of a novel IAP inhibitor APG-1387 as a monotherapy or in combination with pembrolizumab in treatments of patients with advanced solid tumors.

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Background: APG-1387 is a novel, bivalent small molecule IAP (inhibitor of apoptosis proteins) inhibitor. It has shown strong antitumor activities in multiple human xenograft cancer models. APG-1387 also acts as host immune modulator, supporting the notion that APG-1387 in combination with anti-PD1 antibody for cancer therapy. **Methods:** This study consists of two parts (NCT03386526). Part 1 is the dose escalation study of APG-1387 including a mPC (metastatic pancreatic cancer) cohort expansion. Part 2 is the dose escalation and cohort expansion study of APG-1387 in combination with pembrolizumab. APG-1387 is administrated IV for 30 minutes once weekly in a 21-day-cycle. Pembrolizumab is administrated at 200mg IV on day1 of a 21-day-cycle. The study objectives are to assess the safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy (assessed per RECIST v1.1 every 6 weeks). **Results:** Through Jan 4, 2019, total 23 patients had been treated in 4 cohorts of APG-1387 (20mg, 30mg, 45mg, 60mg). Two DLTs were observed at 60mg including lipase increase and Bell's palsy, MTD was determined as 45mg. Nineteen of 23 patients experienced at least 1 TEAE. The most common TEAEs were nausea (21.7%), fatigue (17.4%), decreased appetite (13.0%), and abdominal pain (13.0%). Three grade 3 TEAEs including elevated bilirubin, lipase increase, and shortness of breath were documented at 45mg and 60mg. Three out of six mPC patients (one at 60mg, two at 45mg) achieved SD, one of them at 45mg has been treated $>$ 5 cycles with confirmed SD (-18%). Two patients, who were treated with APG-1387 at 20mg in combination with pembrolizumab, had no DLT observed during the first cycle. Preliminary PK data of APG-1387 showed a dose proportionality in exposure (C_{max} and AUC) over the dose range of 20-60 mg. **Conclusions:** APG-1387 was well tolerated and had manageable adverse events. The potential effects of APG-1387 alone or in combination with pembrolizumab deserve further exploration in patients with advanced solid tumors, especially in the mPC patients. Clinical trial information: NCT03386526.

3126 **Poster Session (Board #118), Sat, 8:00 AM-11:00 AM**

A phase I study of a novel MDM2 antagonist APG-115 in patients with advanced solid tumors.

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Background: APG-115 is a potent and orally active small-molecule MDM2 protein inhibitor. Binding to MDM2 protein, APG-115 restores p53 tumor suppressive function via induction of apoptosis in tumor cells retaining wild-type p53. In addition, enhanced antitumor activity was demonstrated in the syngeneic tumor models after APG-115 combined with PD-1 blockade. **Methods:** This Phase I study (APG-115-US-001) was designed to enroll the patients with advanced solid tumors in US (NCT02935907). Study objectives included to assess safety, dose limited toxicity (DLT), pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity (assessed every 8 weeks per RECIST v1.1). The patients received APG-115 orally every other day (QOD) at the designated dose (ranging from 10 to 300 mg) for first 21 days of a 28-day cycle, until disease progression. **Results:** Up until Jan 4 2019, total 28 patients were treated with APG-115 at various doses (one patient at 10mg, 20mg and 50mg, respectively; 14 patients at 100mg, 6 patients at 200mg, and 5 patients at 300mg). The median number of prior systemic anticancer therapies was 4 (range 0-15). The DLTs were observed during cycle 1, including one grade 2 thrombocytopenia at 200mg, one grade 3 thrombocytopenia at 300mg, and one grade 3 fatigue at 100mg and 300mg respectively. The most common AEs (reported in $\geq$10% of pts) included: fatigue, nausea, vomiting, diarrhea, decreased appetite, dehydration, neutrophil count decreased, white blood cell count decreased, pain in extremity, thrombocytopenia. The most common Grade 3 or 4 treatment related AEs were fatigue (10.7%), and thrombocytopenia (10.7%). Six patients had stable disease (SD) after two cycle treatments, two of them are continuing in this study. PK analyses indicated that exposure (Cmax and AUC) generally increases with the increase of dose level from 20 mg to 300 mg. **Conclusions:** APG-115 was well tolerated and had manageable adverse events. The MTD/RP2D of APG-115 monotherapy with oral administration, QOD for 21 days of a 28-day cycle for treatment of patients with advanced solid tumors was determined as 100 mg. Further evaluation of APG-115 in combination with pembrolizumab in patients with advanced solid tumors is ongoing. Clinical trial information: NCT02935907.

3127 **Poster Session (Board #119), Sat, 8:00 AM-11:00 AM**

A dose escalation pharmacokinetic (PK) and pharmacodynamic (PD) study of mTORC1/2 inhibitor XP-105 (BI 860585) as monotherapy and in combination with exemestane or paclitaxel in patients (pts) with advanced solid tumors.

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Background: Resistance to mTORC1 inhibition may develop through feedback loop leading to upregulation of mTORC2. XP-105, also known as BI 860585, is a potent dual mTORC1/2 inhibitor designed to overcome such resistance. This Phase 1 trial (NCT01938846) was performed to determine the MTD and activity of XP-105 alone or in combination with exemestane or paclitaxel in pts with advanced solid tumors. **Methods:** A 3+3 escalation design was used; Pts received XP-105 (5–300 mg/day) monotherapy or (40–220 mg/day) combined with fixed-dose exemestane 25 mg/day, or 80–160 mg/day combined with paclitaxel 60 or 80 mg/m^2/week. A reduction of pAKT/total AKT ratio was used as a PD marker of target inhibition. **Results:** 90 pts were treated (41 with monotherapy, 25 and 24 in combination with exemestane, or paclitaxel respectively). XP-105 MTD was defined as 220 mg daily for monotherapy, and 160mg daily with exemestane 25 mg/d or paclitaxel 80 mg/m^2/week. In the monotherapy arm, stable disease (SD) was reported in 8 pts (20%), with a median duration of 11 months. In the exemestane combination arm, 4 (16%) partial responses (PR) were reported. In the paclitaxel combination arm, 1 complete response (CR) and 4 PRs were reported (OR rate 21%). Disease control rate (CR/PR/SD) was 20%, 28%, and 58% in the monotherapy, XP-105/exemestane, and XP-105/paclitaxel arms, respectively. A sustained reduction in pAKT/total AKT to $<$ 50% of baseline levels was observed with XP-105 $\geq$120mg daily. Overall, XP-105 was well tolerated; in the XP-105/paclitaxel combination the most frequent drug-related AEs were diarrhea and fatigue (58.3% each), hyperglycaemia (54.2%), anaemia (50%). Grade $\geq$3 AEs were hyperglycaemia, fatigue, diarrhea, anaemia, leukopenia. No PK interaction was observed. **Conclusions:** The MTD for XP-105 monotherapy and in combination with exemestane or paclitaxel was defined as 220 mg and 160mg once daily, respectively. Combination regimens showed higher activity as compared to monotherapy with durable OR in about 20% of pts. The observed safety profile of XP-105 compared favorably to those reported from other mTOR inhibitors. Clinical trial information: NCT01938846.

3128 **Poster Session (Board #120), Sat, 8:00 AM-11:00 AM**

Cytoplasmic cyclin E independently predicts recurrence in older patients with primary breast cancer.

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Background: Primary breast cancer in the older ($>$ 70 years) population has distinct biological characteristics associated with favourable outcome, such as higher rate of estrogen receptor (ER) positivity. Due to comorbidities, older patients with primary breast cancer are more likely to die of non-breast cancer-related causes compared to their younger counterparts. Biomarkers that may influence treatment strategy therefore require interpretation in the specific biological and clinical context of older women. Cyclin E regulates cell cycle transition from G1 to S phase, and its deregulation is implicated in breast cancer pathogenesis. Tumour-specific isoforms of cyclin E localise to the cytoplasm. Expression of cytoplasmic cyclin E (c-cyclin E) is linked with poor clinical outcome. We now present multivariate analysis of breast cancer-specific survival (BCSS) by c-cyclin E and clinical markers of disease biology from a cohort of older women. The primary outcome, BCSS, excludes deaths from competing causes and is used as a surrogate for tumour biology. **Methods:** Between 1973 and 2010, 813 older women underwent initial surgery for early breast cancer and were followed up in a dedicated clinic in Nottingham. Excised tumours from 517 of these patients were successfully incorporated into a tissue microarray (TMA). Expression of c-cyclin E was assessed by IHC using an assay developed at MDACC, along with a panel of 24 biomarkers. Of these, ER, progesterone receptor (PR), human epidermal growth factor 2 (HER2) and Ki67 are in current clinical use and are analysed alongside c-cyclin E. Grade was assessed from the primary tumour. Multivariate analysis of BCSS was performed by Cox proportional hazard test. **Results:** In multivariate analysis alongside markers of disease biology currently used in the clinic (ER, PR, HER2, Ki67 and grade), c-cyclin E is the only factor that independently predicts BCSS in this cohort of older women (HR 5.0, 95% CI 2.1 – 12.0; $p< 0.001$). **Conclusions:** In the older population with primary breast cancer, c-cyclin E expression is the only independent biological marker of BCSS. Patients with low c-cyclin E expression are unlikely to die of breast cancer. These data have potential to influence treatment strategy in older patients. For example, patients with ER+, c-cyclin E negative disease plus multiple co-morbidities may be suitable for primary endocrine therapy. This hypothesis warrants prospective clinical evaluation.

3129 **Poster Session (Board #121), Sat, 8:00 AM-11:00 AM**

Clinicopathologic characteristics of *NRG1* fusion-positive cancers: A single-institution study.

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Background: *NRG1* rearrangements are oncogenic drivers across several tumor types. Chimeric proteins encoded by *NRG1* fusions activate HER3, resulting in heterodimerization with HER2 and activation of downstream signaling. Preclinical and preliminary clinical data suggest that targeting HER3 may be an effective treatment strategy for patients with *NRG1* fusion-positive tumors. We aimed to describe the clinical and genomic characteristics of patients identified at our institution with *NRG1* fusions. **Methods:** We analyzed results from prospective targeted exome and/or RNA sequencing performed at Memorial Sloan Kettering between 2014-2018 involving > 30,000 samples. *NRG1* fusion-positive tumors were identified and these cases were manually reviewed. **Results:** *NRG1* fusions were detected in 24 patients. Cancer types included lung (N = 9), pancreas (N = 7), breast (N = 5), prostate (N = 1), gallbladder (N = 1), diffuse large B-cell lymphoma (N = 1), and cancer of unknown primary (N = 1). 6/9 lung cancers had mucinous differentiation. The majority of patients were Caucasian (N = 17), half were female (N = 12) and ages ranged from 24-82 years-old. Targeted exome sequencing identified the fusion in 10/23 cases tested, including 2 not confirmed by RNA. The remaining 14 were detected using RNA. Fusion partners included *CD74* (N = 6), *SLC3A2* (N = 2), *SDC4* (N = 2), *ATP1B1* (N = 2), *FOXA1* (N = 1), *SLCA4* (N = 1), *ROCK1* (N = 1), *TNKS* (N = 1), *CCND1* (N = 1), *PAK1* (N = 1), *STAU3* (N = 1), *RAD51* (N = 1), *CD44* (N = 1), *NCOR1* (N = 1), RBPMS (N = 1), and *WHSC1L1* (N = 1). Pancreas cancers were *KRAS* wild-type and lung cancers had no co-occurring alterations in *ALK*, *ROS1*, *EGFR*, *RET*, *MET*, *RAS,* or *RAF*. All tumors were microsatellite stable. A durable response was achieved with anti-HER3 antibody therapy (GSK2849330) in a patient with a *CD74-NRG1*-rearranged invasive mucinous adenocarcinoma (previously reported). Four patients treated with an irreversible small molecule HER2 inhibitor (afatinib) did not respond to treatment, suggesting direct targeting of HER3 may be superior to HER2 inhibition in patients with *NRG1* fusion-positive tumors. **Conclusions:** *NRG1* fusions occur in several tumor types and may be amenable to targeting with HER3-directed therapy.

3130 **Poster Session (Board #122), Sat, 8:00 AM-11:00 AM**

Molecular differences between lymph nodes (LNs) and distant metastases (mets) in colorectal cancer (CRC).

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Background: LNs mets are thought to occur before distant mets. However, lymphatic and distant mets arise from independent subclones of the primary tumor, suggesting that LNs are not essential intermediaries for distant mets. We aimed to comprehensively characterize the molecular profile of LN mets and to explore the differences between LN vs distant mets and primary tumors. **Methods:** Tumor samples from primary CRCs, LNs, and distant mets were analyzed using NGS (MiSeq on 47 genes, NextSeq on 592 genes), immunohistochemistry. Tumor mutational burden (TMB) was calculated based on somatic nonsynonymous missense mutations, and microsatellite instability (MSI) was evaluated by NGS of known MSI loci. **Results:** In total, 11871 tumors samples were examined, comprising primaries (N = 5862), distant (N = 5605) and LNs mets (N = 404). The most frequently mutated genes in LNs were *TP53* (72%), *APC* (61%), *KRAS* (39%), *ARID1A* (20%), and *PIK3CA* (12%). LNs showed a higher mean TMB (13 mut/MB) vs distant mets (9, $P < .0001$). TMB-high (17mut/MB) was more frequent in primaries and LNs vs distant mets (9.5% and 8.8% vs 4.2%, $P < .001$ and $P = .001$, respectively), as well as MSI-H (8.8% and 6.9% vs 3.7%, $P < .001$ and $P = .017$, respectively). TMB-high is significantly higher in LNs vs distant mets and primaries ($P < .0001$), independent of MSI-H status. Analyzing distant mets by location, LNs showed higher TMB compared to lung, liver and peritoneum mets ($P < .0001$). Overall, LNs showed significantly different rates of mutations in *APC, KRAS, PI3KCA, KDM6A,* and *BRIP1* ($P < .01$ for all comparisons) vs primaries; while presenting a distinct molecular profile compared to distant mets (*TP53* 72 vs 67%; *KRAS* 39 vs 50%; *RNF43* 7 vs 4%; *ATM* 5 vs 3%; *KDM6A* 4 vs 1%; *BRCA2* 4 vs 2%; *MSH6* 3 vs 2%; *PTCH1* 4 vs 1%; *BRCA1* 2 vs 1%; *GNAS* 2 vs 5%; $P < .05$ for all comparisons). Our cohort of 30 paired samples confirmed the molecular heterogeneity between primaries, LNs, and distant mets. **Conclusions:** This is the largest study to investigate the molecular differences between LNs mets, distant mets and primary tumors in CRC patients. Our data support the hypothesis that lymphatic and distants mets harbor different mutation profiles which suggests that they may arise from distinct subclones.

3131 **Poster Session (Board #123), Sat, 8:00 AM-11:00 AM**

Measuring phospho-MET by multiplex immunofluorescence to aid in selection of patients with MET activation in tumors.

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Background: Currently, patient selection criteria for clinical testing of MET inhibitors are limited. Robust studies selecting patients based on MET protein expression, *MET* gene amplification, or mutations have not met their efficacy goals. Development of microscopy-based assays to quantify levels of phospho-MET (pMET) in tumors has been hampered by poor antibody specificity. Here, we present the development and validation of a robust, highly specific multiplex immunofluorescence assay (IFA) that measures pY1235-MET and total MET in tumor tissue. **Methods:** This assay utilizes antibodies to pY1235-MET (NCI-23111), total MET (D1C2), and plasma membrane (PM) marker Na^+/K^+-ATPase, each conjugated to a different Alexa Fluor dye. We used tumor tissue from crizotinib-treated SNU5 xenograft models to demonstrate pY1235-MET assay fitness-for-purpose and cross-platform assay concordance with our validated pMET ELISA. In addition, this IFA was validated by phospho-peptide competition using custom tissue microarrays (TMA) derived from patients with colorectal carcinoma (CRC). Finally, we developed quantitative algorithms to assess pY1235 MET levels in the plasma membrane and nucleus using PM and DAPI masks, respectively. Patient-derived xenograft models (PDX) were obtained from NCI's Patient-Derived Models Repository (www.pdmr.cancer.gov). **Results:** The prevalence of high pY1235-MET expression in CRC patient specimens was greater than expected; of the 64 TMA cores evaluated, 29 (45%) and 19 (29%) had high pY1235-MET and total MET levels, respectively, as defined by mean marker area of $\geq 30\ \mu m^2$/cell. To address the potential utility of pY1235-MET as a diagnostic biomarker, we examined 15 CRC PDX models by pMET ELISA and IFA. Two CRC tumor models were positive for pY1235-MET expression in both assays. The pY1235-MET IFA results and gene expression data were used to select PDX models for ongoing preclinical trials of potent MET inhibitors. **Conclusions:** This novel pY1235-MET IFA will enable clinicians to address the utility of activated MET as a biomarker for patient selection and/or prediction of response in clinical trials of MET inhibitors. Funded by NCI Contract No. HHSN261200800001E.

3132 **Poster Session (Board #124), Sat, 8:00 AM-11:00 AM**

Actionable coalterations in breast tumors with pathogenic mutations in the homologous recombination DNA damage repair pathway.

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Background: Homologous recombination (HR) deficient breast tumors may have genomic alterations that suggest responsiveness to targeted therapies other than PARP inhibitors. **Methods:** Comprehensive molecular profiles of 4,647 breast tumors performed at Caris Life Sciences using 592-gene NGS (average read depth 500X) were reviewed to identify somatic pathogenic mutations in HR genes *ARID1A, ATM, ATRX, BAP1, BLM, BRCA1/2, BRIP1, CHEK1/2, FANCA/C/D2/E/F/G/L, KMT2D, MRE11, NBN, RAD50/51/51B* & *PALB2,* as well 41 markers associated with treatment response. **Results:** Overall, 17.9% of breast tumors have HR mutations (HR-MT, 831/4647). HR-MT is seen most in HER2– disease [hormone receptor (hr)+/HER2– (18.3%, n=2183), TNBC (18.2%, n=1568), hr–/HER2+ (12.9%, n=217)]. Mean TMB is higher for HR-MT tumors across subtypes (9.2 mut/Mb vs 7.6 WT, p=<0.0001) & independent of MS status. HR-MT hr–/HER2+ tumors are more likely to have PD-L1 overexpression (25% vs 13.1% hr–/HER2+ WT, p=0.10), whereas MSI is more prevalent in HR-MT HER2– (hr+/HER2– 2.3%, TNBC 1.4%, HER2+ 0%). Mutations in chromatin remodeling genes (*) are more common in HR-MT. Additional co-alterations are outlined in the Table. **Conclusions:** In breast cancer, HR-MT is associated with HER2– disease & markers of response to immunotherapy. Clinical trials combining HRD targeted agents & immunotherapy are underway & could be enriched through comprehensive molecular profiling. Mutations were identified in both HR-MT & HR WT tumors that suggest other targets for treatment.

	HR-MT (%, +/total)	HR WT (%, +/total)	p-value
PIK3CA	26.4 (217/823)	30.3 (1150/3792)	0.02
tumor PD-L1 (IHC)	13.2 (104/788)	11 (405/3677)	0.08
ESR1	8.2 (67/820)	7.9 (298/3790)	0.77
RB1	4.9 (37/754)	4.4 (150/3442)	0.51
AKT1	2.1 (17/817)	3.7 (140/3789)	0.02
ERBB2	2.8 (23/831)	2.6 (100/3812)	0.81
ARID2*	1.3 (10/796)	0.5 (20/3671)	0.03
JAK1	1.1 (9/796)	0.2 (7/3657)	0

Pathogenic mutation frequency ≤ 1%: *AR, BRAF, CCND1, CDKN2A, EGFR, ERBB3, IDH1, IDH2, JAK2, KIT, MET, MTOR, RET, SMARCB1*, SMARCE1*, SMARCA4*, SS18L1**

No mutations: *ATR, AURKA/B, BCL7A*, BCL11A/B*, CDK4/6, ERBB4, NTRK1/2/3, PBRM1*, POLE*

By IHC (HR-MT vs WT): AR 52.3 (415/794) vs 54.9 (2014/3669) [p=0.18], EGFR 28.6 (4/14) vs 32.4 (36/111) [p=0.77], cMET 11.1 (1/9) vs 5.5 (5/91) [p=0.50]

3133 **Poster Session (Board #125), Sat, 8:00 AM-11:00 AM**

HER family protein expression and activation predicts response to combination T-DM1/pertuzumab in HER2+ patients in the I-SPY 2 TRIAL.

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Background: T-DM1 (T), a conjugate of the anti-HER2 therapeutic antibody trastuzumab and the microtubule assembly inhibitor emtansine, was administered in combination with pertuzumab (P), an anti-HER2 therapeutic antibody, to HER2+ breast cancer patients in the I-SPY 2 TRIAL, and graduated in all HER2+ subtypes. Pre-specified biomarker analysis was performed to identify candidate biomarkers associated with pCR within the HER family and cell proliferation pathways in patients treated with T+P. We hypothesized that quantitative measurement and activation of HER2 and activation of its major dimerization partner, EGFR would predict response to T+P. **Methods:** In the T+P treatment arm, 49 had RPPA and pCR data. 40 RPPA endpoints including 14 total/phospho-proteins in the HER family were assessed for association with pCR using logistic regression (likelihood ratio test; $p < 0.05$). Analysis was also performed adjusting for HR status and within HR subsets. Markers were analyzed individually; multiple comparison correction (Benjamini-Hochberg) was applied to all p-values. Our statistics are descriptive and do not adjust for multiplicities of other biomarkers outside this study. **Results:** Of the endpoints tested, only quantitative total HER2 expression, phospho-HER2 (Y1248 and Y877), phospho-EGFR (Y1173 and Y1068), and phospho-SHC Y317 had a positive association with response in the population as a whole, and in a model adjusting for HR status (BH $p < 0.05$). In HR subset analysis, these 5 analytes had uncorrected $p < 0.05$ regardless of HR subtype but only survived p-value correction in HR+ tumors. **Conclusions:** Quantitative measurement of HER2 protein positively associates with response to T+P in patients already identified as HER2+ by central IHC and FISH testing. Activation of HER2 and its dimerization partner, EGFR, also associate with response to T+P in HR+ patients. While our results need to be validated in larger prospective trials, they indicate that new approaches to measure more quantitatively the amount and activation state of HER2 and activated EGFR may more effectively identify patients that respond to HER2 targeted therapies than HER2 IHC and FISH alone.

3134 **Poster Session (Board #126), Sat, 8:00 AM-11:00 AM**

Pharmacodynamics of PI3K, MEK, and AKT inhibitors through isoform-specific measurements of MEK, ERK, AKT, and ribosomal protein S6 in needle biopsies.

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Background: The success of drugs targeting the MAPK or PI3K pathways in cancer has been slowed by insufficient pathway suppression or onset of resistance through rebound or cross-pathway activation. Isoform-specific measurement of key signaling molecules and a pathway convergence marker ribosomal protein S6 (RPS6), may provide valuable pharmacodynamic (PD) evidence to assess drug effectiveness. **Methods:** We developed Luminex multiplex assays to measure total and phosphorylated forms of RPS6, ERK1, ERK2, MEK1, MEK2, AKT1, AKT2, and AKT3 from a single tumor biopsy. Fit-for-purpose validation was performed with three drugs currently in clinical trials. A SW620 (KRAS G12V) model was tested with selumetinib (NSC741078, 20 mg/kg), MK2206 (NSC756656, 24 mg/kg), and two PTEN-null models (PC3 & HCC70) with AZD8186 (NSC777572, 25 & 50 mg/kg). Tumors were collected at multiple timepoints after single and repeated dosing, processed by a validated method (PMID 27001313) and data analyzed relative to vehicle control (n = 4-5/grp). **Results:** The multiplexed assays demonstrated satisfactory analytical performance. Treatment of the SW620 model with a single dose of selumetinib suppressed pERK1/2 ($>$ 90%), MEK1/2 (50%) and pRPS6 (40-60%) up to 4 h (last time point tested) which was reversed by 24 h. AKT inhibitor, MK2206, suppressed pAKT1/2 (75%) and pAKT3 (50%) 2 h post-dose with reversal at 24 h but did not significantly suppress pRPS6, implying limited downstream modulation. Dosing selumetinib for 21 days had no added effect on pERK isoforms. In both PTEN-null models, AZD8186 suppressed all pAKT isoforms by 40-75% up to 4 h post-dose. The pAKT remained suppressed at 7 h in HCC70 but both pAKT and pRPS6 rebounded by 7 h in PC3. The basal pERK1/2 levels were low and unaffected by AZD8186 in PC3 and HCC70. **Conclusions:** We established the fitness of PD assays to provide critical evidence regarding the duration of on-target effects, timeline of biomarker reversal and effectiveness of pathway suppression for three distinct classes of drugs. The PD assays are ready for an ongoing clinical trial of AZD8186 and to support clinical development of FGFR inhibitors. Funded by NCI Contract HHSN261200800001E.

3135 **Poster Session (Board #127), Sat, 8:00 AM-11:00 AM**

Machine learning methods with salivary metabolomics for breast cancer detection.

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Background: Saliva is non-invasively accessible and informative biological fluid which has high potential for the early diagnosis of various diseases. The aim of this study is to develop machine learning methods and to explore new salivary biomarkers to discriminate breast cancer patients from healthy controls. **Methods:** We conducted a comprehensive metabolite analysis of saliva samples obtained from 101 patients with invasive carcinoma (IC), 23 patients with ductal carcinoma in situ (DCIS) and 42 healthy controls, using capillary electrophoresis and liquid chromatography with mass spectrometry to quantify hundreds of hydrophilic metabolites. Saliva samples were collected under 9h fasting and were split into training and validation data. Conventional statistical analyses and artificial intelligence-based methods were used to access the discrimination abilities of the quantified metabolite. Multiple logistic regression (MLR) model and an alternative decision tree (ADTree)-based machine learning methods were used. The generalization abilities of these mathematical models were validated in various computational tests, such as cross-validation and resampling methods. **Results:** Among quantified 260 metabolites, amino acids and polyamines showed significantly elevated in saliva from breast cancer patients, e.g. spermine showed the highest area under the receiver operating characteristic curves (AUC) to discriminate IC from C; 0.766 (95% confidence interval [CI]; 0.671 – 0.840, $P < 0.0001$). These metabolites showed no significant difference between C and DICS, i.e., these metabolites were elevated only in the samples of IC. The MLR yielded higher AUC to discriminate IC from C; 0.790 (95% CI; 0.699 – 0.859, $P < 0.0001$). The ADTree with ensemble approach showed the best AUC; 0.912 (95% CI; 0.838 – 0.961, $P < 0.0001$). In the comparison of these metabolites in the analysis of each subtype, seven metabolites were significantly different between Luminal A-like and Luminal B-like while, but few metabolites were significantly different among the other subtypes. **Conclusions:** These data indicated the combination of salivary metabolomic profiles including polyamines showed potential ability to screening breast cancer in a non-invasive way.

3136 **Poster Session (Board #128), Sat, 8:00 AM-11:00 AM**

The Cancer Molecular Screening and Therapeutics Program (MoST): Actionable mutation frequencies in a population with rare and less common cancers.

Subotheni Thavaneswaran, Mandy L. Ballinger, John Grady, Mark Cowley, Anthony Joshua, Lucille Sebastian, Emily Collignon, Audrey Silvestri, Maya Kansara, Mark Pinese, Katrin Marie Sjoquist, Wendy Hague, Chee Khoon Lee, John Simes, David Morgan Thomas; Garvan Institute of Medical Research, University of New South Wales (Faculty of Medicine), Darlinghurst, NSW, Australia; Garvan Institute of Medical Research, University of New South Wales, Darlinghurst, NSW, Australia; Garvan Institute of Medical Research, Darlinghurst, NSW, Australia; Kinghorn Cancer Centre, St Vincent's Hospital, Sydney, NSW, Australia; The NHMRC Clinical Trials Centre, The University of Sydney, Camperdown, Australia; NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia; NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia; Australia New Zealand Gynaecological Oncology Group, Camperdown, Australia; Chris O'Brien Lifehouse, Camperdown, Australia

Background: Personalizing therapy will arguably have no greater impact than on patients (pts) with rare (< 6 per 100,000 population) or less common cancers (6-12/100,000). MoST combines a molecular screening platform and biomarker-driven treatments for pts with advanced cancer, with a particular focus on rare and less common cancers (RLC). **Methods:** Molecular screening was performed using in-house and commercial panels on archival tumor tissue. A Molecular Tumor Board by consensus reported on pathogenic variants with potential therapeutic actionability. Tiers of actionability were defined as: Tier 1–eligible for a MoST substudy; Tier 2–clinical evidence of efficacy in any cancer type, Tier 3—preclinical evidence. The clinical and molecular characteristics of the first 1,000 pts are presented here. **Results:** Pts were recruited from Sept 2016 to Dec 2018. A report was issued in 94% of cases in a median of 7.7 weeks from consent. In 6%, there was insufficient tissue. The median age at cancer diagnosis was 35 years (range 4-85 years), and 49% were male. Pts had a median of 2 lines of prior systemic therapy (0-11), and a median baseline ECOG performance status of 0 (range 0-3). 82% of pts had RLCs. A total of 2642 pathogenic variants were reported, of which 1144 (43%) were deemed therapeutically actionable. 651(57%) of actionable variants (AVs) occurred in RLC (Table). Most commonly, AVs were found in the cell cycle, homologous recombination repair (HR) and fibroblast growth factor (FGF) pathways. 559(66%) of pts had at least one AV identified, 30% tier 1, 63% tier 2 and 6% tier 3, including 66% of RLC. In 30% of cases, a tumor mutational burden >11 mutations/ megabase was reported. **Conclusions:** Here we report a high frequency of AVs in RLC, providing a rational basis for assessing the potential of personalized therapy in a population with a historically unmet need for effective treatment. Clinical trial information: ACTRN12616000908437.

Variant counts by gene.

	Cell cycle	HR	PTCH1/ SMO	FGF	PIK3CA	MTOR	EGFR	MMR	HER2/ 3	KIT/ PDGFR	BRAF	AR	RET	ALK	ROS1	NF1	NTRK	MET	BCL2	AKT, AR, EZH2, etc.
Tier 1	242	180	6	78	51	33	37	31	40	25	20	0	4	7	4	30	2	13	9	88
RLC (n= 688)	48	58	2	26	22	11	7	10	15		10	3	1			3	1	4		24
Common (n=154)																				

3137 **Poster Session (Board #129), Sat, 8:00 AM-11:00 AM**

The whole genome landscape of adult metastatic sarcoma.

Eric Yang Zhao, Xiaolan Feng, Erin D. Pleasance, Tony L. Ng, Jasleen Grewal, Nissreen Mohammad, Sara Kristina Taylor, Christine E. Simmons, Amirrtha Srikanthan, Shahrad Rod Rassekh, Rebecca Deyell, Yaoqing Shen, Emma Titmuss, Howard John Lim, Daniel John Renouf, Karen A. Gelmon, Stephen Yip, Steven J. M. Jones, Marco A. Marra, Janessa J. Laskin; Canada's Michael Smith Genome Sciences Centre, Vancouver, BC, Canada; BC Cancer, Victoria, BC, Canada; Department of Pathology & Laboratory Medicine, Vancouver General Hospital, Vancouver, BC, Canada; Department of Pathology and Laboratory Medicine, The University of British Columbia, Vancouver, BC, Canada; BC Cancer, Kelowna, BC, Canada; BC Cancer, Vancouver, BC, Canada; Princess Margaret Cancer Centre, Toronto, ON, Canada; British Columbia Children's Hospital, Vancouver, BC, Canada; British Columbia Cancer Vancouver, Vancouver, BC, Canada; BC Cancer Agency, Vancouver, BC, Canada

Background: Metastatic sarcomas represent a heterogeneous, difficult to treat family of cancers with poor median overall survival of 18 months. While global sequencing initiatives have catalogued genomic variation among primary sarcomas, metastatic sarcoma is less well understood. Genome-guided targeted therapy has made promising advances but is difficult to study in sarcomas due to heterogeneity and low prevalence. Whole genome and transcriptome analysis (WGTA) can help elucidate sarcoma oncogenesis, metastasis, and potential therapeutic targets. **Methods:** Using whole genome (80X) and transcriptome (200M read) sequencing of 43 metastatic sarcomas across 19 subtypes, we analyzed structural variants (SV), copy-number variants (CNV), mutation signatures, gene expression, and the immune microenvironment. All prior treatments were retrieved through chart review. **Results:** 17 patients (40%) attempted WGTA-informed therapy, of which 8 (47%) were classified as responders. Metastatic sarcomas demonstrated recurrent CNVs, with 17p11-p12 amplification in 42% of cases. Some recurrent expression outliers were associated with potential targets (e.g. *MYOCD*, *PMP22*, *COPS3*) while others (e.g. *ADORA2B*) have not been previously observed in sarcoma. Discovery of oncogenic fusions refined diagnoses in two cases with atypical histology. Clustering by mutation signatures distinguished histological subtypes, and two signatures were novel in sarcoma: (1) a strong base excision repair signature associated with *NTHL1* loss and (2) a cisplatin-associated signature exclusive to platinum-treated cases. Frequent homologous recombination deficiency was observed and was associated with response to ifosfamide in three leiomyosarcomas. Of four immunotherapy-treated cases, the only responder demonstrated outlier CIBERSORT immune infiltration score, which did not correlate with PD-L1 expression. **Conclusions:** This is the first in-depth WGTA of metastatic sarcoma. We found recurrent and potentially targetable CNVs, expression outliers, mutation signatures, and immune markers. Our results suggest that clinical translation is promising using actionable insights obtained through WGTA.

3138 **Poster Session (Board #130), Sat, 8:00 AM-11:00 AM**

Mutation and treatment profiles of patients with concurrent EGFR and ALK actionable mutations (muts).

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Background: Actionable muts in *EGFR* and *ALK* define two molecular subtypes sensitive to EGFR-TKIs and ALK-TKIs, respectively. Although generally mutually exclusive, they did co-exist in some cases. However, when and how do they co-exist are not well understood. **Methods:** Pts with concurrent actionable muts in *ALK* and *EGFR* were selected from our database. Their mutation profiles and treatment histories were analyzed. PFS was estimated using Kaplan-Meier method. **Results:** Among 341 *ALK*-positive (*ALK*-pos) and 3804 *EGFR*-positive (*EGFR*-pos) pts, 9 (2.6% of *ALK*-pos, 0.2% of *EGFR*-pos) had concurrent *EGFR* and *ALK* actionable muts, including 3 EX19Indel + *EML4-ALK*, 2 EX19Indel + *STRN-ALK*, 2 L858R + L1152R, 1 L858R + *EML4-ALK*, and 1 G719C + S768I + *STRN-ALK*. All 9 pts had lung cancer. One pt with EX19Indel + *EML4-ALK* was treatment naïve. The other 8 pts have taken $\geq$ 1 EGFR-TKIs. The mPFS of these pts on first-generation EGFR-TKIs was 22 mo (95% CI: 11 - NR). Except for 1 pt who progressed on Gefitinib and subsequently on Osimertinib had a T790M+C797G, the other 7 EGFR-TKI resistance pts had no common known resistance muts. 3 pts ordered NGS tests before taking EGFR-TKIs. None of them had ALK muts at that time. Later, 1 pt (19Indel) gained an *STRN-ALK* after 15 mo on Osimertinib, 1 pt (L858R) gained an *EML4-ALK* after 5 mo on Gefitinib, and 1 pt (L858R) gained an L1152R after 10 mo on Afatinib. Therefore, ALK muts were likely developed as resistance mechanisms during EGFR-TKIs therapies in these 3 pts. Unfortunately, with no information on *ALK* status before EGFR-TKI therapies, we can not tell if the ALK muts were also developed during and conferred resistance to EGFR-TKI therapies in the other 5 pts. Both *STRN-ALK* and *ALK* L1152R were recorded 4 times in our database, and they concurred with *EGFR* actionable muts in 3 and 2 of the 4 records, respectively. **Conclusions:** *ALK* and *EGFR* actionable muts concurred at a relatively low frequency in our pts. In some cases, *ALK* muts were developed during EGFR-TKI therapies. Developed either together or sequentially, some combinations of *EGFR* and *ALK* muts, such as L858R with L1152R and EX19Indel with ALK fusion, may form more easily or may be preferable than other combinations for the development or evoluation of tumors.

3139 **Poster Session (Board #131), Sat, 8:00 AM-11:00 AM**

A prognostic 10-miRNA risk score (10-miRNA RS) in predicting neoadjuvant chemotherapy sensitivity of luminal breast cancer.

Chang Gong, Luyuan Tan, Na You, Kai Chen, Weige Tan, Zhenluan Tian, Wenjing Zhong, Wanyi Lin, Zhigang Yu, Zhihua Li, Wenbo Zheng, Qiang Liu, Erwei Song; Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; Department of Statistical Science, School of Mathematics and Computational Science & Southern China Research Center of Statistical Science, Sun Yat-sen University, Guangzhou, China; Department of Breast Surgery, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; Department of Breast Surgery,The Second Affiliated Hospital of Shandong University, Jinan, China; Prevention and Cure Center of Breast Disease, Key Laboratory of Breast Disease, the Third Hospital of Nanchang City, Nanchang, China; Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

Background: The 10-miRNA risk score is a prognostic 10-gene expression signature specifically developed in luminal breast cancer associated with relapse-free survival. Since high-risk patients identified by10-miRNA RS had worse prognosis but better outcome with chemotherapy than low-risk patients (Gong C et al, *EBioMedicine. 2016*), this model may facilitate personalized therapy-decision making for luminal breast cancer patients. Therefore, we seek to validate whether high-risk group are more sensitive to chemotherapy than low-risk group by assessing the predictive value of 10-miRNA RS for pathological complete response (pCR) in patients receiving neoadjuvant chemotherapy (NAC). **Methods:** The 10-miRNA gene expression and clinicopathological data were prospectively gathered from 251 pretreated biopsy-diagnosed luminal breast cancer patients from 4 breast cancer centers. Formalin-fixed paraffin-embedded tissues from basal line biopsy were used for the detection of 10-miRNA expression to calculate the RS. The correlation between pCR and the 10-miRNA RS classification were identified. **Results:** In this prospective, multicenter study, the overall pCR rate was 13.6% (34/251). The 10-miRNA RS of the pCR group was significantly higher than the non-pCR group ($P = 0.015$). Fifty-one percent of patients were classified as low-risk according to the 10-miRNA RS classification and 49% as high-risk with a RS cut-off point of 2.144. The 10-miRNA RS classification was associated with a pCR rate of 9.4% in the low-risk group and 17.8% in the high-risk group ($P = 0.041$). The correlation between the pCR and the 10-miRNA RS classification was significant in subgroup analysis stratified by molecular subtypes (8% *vs.* 13.2% in luminal B_1; 14.7% *vs.* 30.1% in luminal B_2; no pCR was observed in all 13 luminal A subtype). In multivariate analysis, the 10-miRNA RS remained significantly associated with pCR and independent from subtype, ki67 and other clinicopathological characteristics. **Conclusions:** 10-miRNA RS clearly defined that high-risk patients are more sensitive to chemotherapy which leads to a higher pCR rate in NAC patients. Thus, 10-miRNA RS is not only a prognostic factor but an effective method in determining whether a patient would undergo surgery or receive NAC prior to surgery. Clinical trial information: ChiCTR-DDD-17013651.

3140 **Poster Session (Board #132), Sat, 8:00 AM-11:00 AM**

Prediction of biomarker status, diagnosis and outcome from histology slides using deep learning-based hypothesis free feature extraction.

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Background: Recently, histological pattern signatures obtained from diagnostic H&E images have been found to predict mutation, biomarker status or outcome. We report here on a novel deep learning based framework designed to identify and extract predictive histological signatures. We have applied this framework in 3 experiments, predicting specifically the microsatellite status (MSS) of colorectal cancer (CRC), breast cancer (BC) micrometastasis in Lymph nodes (LN) and Pathologic Complete Response (pCR) in BC diagnostic biopsies. **Methods:** Our deep learning based algorithm was trained on histology images at 20X magnification. Algorithms were trained for binary classification for each of the three cohorts. We used 75% of the images for training and test our algorithm on the remaining 25% of the images. Cohort details are as follows: MSS for CRC: 94 patients' H&E stained tissue images from the Roche internal CRC80 dataset (MSS n =24; MSI n = 70) were used. BC LN: 270 patients' H&E stained tissue images from the CAMELYON16 dataset (LN(+) n = 110 ; LN(-), n =160) were used. pCR for BC: 225 patients' H&E stained tissue images from the Tryphaena Study BO22280, neoadjuvant, Trastuzumab/Pertuzumab chemotherapy combination trial. (pCR=111, non-pCR n=114). **Results:** We report and assess algorithm performance on each of the cohorts by Area Under the Curve (AUC). Prediction of MSS in the CRC80 status yielded AUC 0.9. Prediction of LN invasion on CAMELYON16 dataset yielded AUC 0.85. Prediction of pCR on the Tryphaena cohort yielded an AUC of 0.8. **Conclusions:** We present a new approach to generate predictive signatures based on conventional diagnostic H&E images and a novel machine learning framework. The CRC80 and CAMELYON16 cohorts served as a confidence building experiments with predictive features well known by clinicians and visually confirmed. The predictive algorithm for pCR in the Tryphaena cohort yielded both response prediction and the high predictive value FOVs. These included tissue patterns which have not until now been considered to influence on the prediction of pCR.

3141 **Poster Session (Board #133), Sat, 8:00 AM-11:00 AM**

MET exon 14 skipping analogs: Rare but potentially clinically actionable.

Rebecca Feldman, Michelle Ellis, Jeffrey Swensen, Wolfgang Michael Korn, Zoran Gatalica; Caris Life Sciences, Phoenix, AZ

Background: The DpY motif within the exon 14 juxtamembrane domain of the *MET* receptor gene is critical for Cbl-mediated negative regulation. Splicing alterations that delete this residue, known as exon 14 skipping mutations (ex14sk mt), lead to prolonged MET protein stability and oncogenic signaling. Specific mt at the Y1021 (aka 1003) residue are thought to lead to similar effects as ex14sk, but due to their rarity, their role in NSCLC is unknown. We sought to identify and characterize non-ex14sk mt that include/surround Y1021. **Methods:** Retrospective review of molecular profiles for non-ex14sk mt that include/surround the DpY motif (Y1021) in *MET*. Two NGS platforms were included: MiSeq (2014-2017; n=2865) and NextSeq (2017-2019; n=6084). Immunohistochemistry (IHC) of cMET (SP44) and co-occurring alterations (EGFR, KRAS, ALK, ROS) were also reviewed. **Results:** Of 8,949 NSCLC patients with successful NGS of *MET* gene by either platform, 13 cases or 0.2% were identified to have an alteration within the amino acids of interest. Eleven cases included substitutions at Y1021 (5 phenylalanine, 4 histidine and 3 arginine) and the remaining two cases included small insertion-deletions p.E1017_Y1021delinsH and p.D1020_Y1021delinsV, the latter was later excluded as it co-harbored an ex14sk mt. **Conclusions:** Similar to patients with ex14sk mt, substitutions and small indels at Y1021 exhibit Clinicopathological features such as previous smoking history and older age, mutual exclusivity with oncogene drivers and MET protein overexpression. The rarity of these analogous ex14sk mt suggests deletions of exon 14 provide cellular advantages beyond Cbl-mediated ubiquitinylation of MET. Although rare, the impact of these mt on efficacy of Met-directed therapy deserves further exploration.

Case	Smoking Hx	Sex/Age	Histology	Stage	protein change	cMET IHC	Staining Pattern
1		M/82	adc		p.Y1021F	2+ 90%	
2	Former	F/84	adc	III	"	2+ 10%	
3		F/85	adc	IV	"		
4		F/80	adc	IV	"	3+ 100%	membranous/cytoplasmic
5		M/83	other	IV	"	2+ 100%	membranous/cytoplasmic
6		F/71	adc		p.Y1021H	2+ 5%	
7		F/77	adc		"	3+ 100%	
8	Former	M/79	mixed	IV	"	3+ 100%	membranous
9	Former	M/81	adc	IV	"		
10	Former	M/83	adc	IV	p.Y1021N	3+ 100%	
11	Former	F/69	adc	IB	"	1+ 100%	cytoplasmic
12	Never	F/84	adc		p.E1017_Y1021delinsH	2+ 80%	membranous

3142 **Poster Session (Board #134), Sat, 8:00 AM-11:00 AM**

Effects of immune architecture on response to adjuvant capecitabine in triple-negative breast cancer (FinXX trial).

Saranya Chumsri, Karama Asleh, Heather Ann Brauer, Douglas Hinerfeld, Jennifer M. Kachergus, Susanna Lauttia, Henrik Lindman, Torsten Nielsen, Heikki Joensuu, E. Aubrey Thompson; Mayo Clinic, Jacksonville, FL; The University of British Columbia, Vancouver, BC, Canada; NanoString Technologies, Inc., Seattle, WA; Nanostring Technologies, Seattle, WA; University of Helsinki, Helsinki, Finland; Uppsala University Hospital, Uppsala, Sweden; University of British Columbia, Vancouver, BC, Canada; Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland

Background: Recent studies have demonstrated a benefit of adjuvant capecitabine, particularly in triple negative breast cancer (TNBC) patients with residual disease after neoadjuvant chemotherapy. However, biomarkers to predict which patients are more likely to benefit from capecitabine are needed. **Methods:** The nanoString Breast Cancer 360 (BC360) and PanCancer Immunoncology (IO360) panels were used to quantify mRNA expression in TNBC samples in the FinXX trial. FinXX is a phase III trial which randomized high risk patients to receive either 3 cycles of docetaxel followed by 3 cycles of cyclophosphamide, epirubicin, and fluorouracil (Arm A: T+CEF) vs. 3 cycles of docetaxel plus capecitabine followed by 3 cycles of cyclophosphamide, epirubicin, and capecitabine (Arm B: TX+CEX). Gene signature scores were analyzed using prespecified algorithms developed by nanoString. Digital Spatial Profiling was carried out using GeoMX platform. **Results:** A total of 111 TNBC patients in FinXX trial were included (57 in Arm A and 54 in Arm B) with 10.2 years median follow up. There were 7 cancer- and immune-related gene signatures identified by BC360 and IO360 panels that were significantly associated with improved recurrent free survival favoring an addition of capecitabine. These include cytotoxic cell signature (HR 0.37, 95%CI 0.15-0.92, p 0.03), endothelial signature (HR 0.18, 95%CI 0.04-0.83, p 0.03), mast cell signature (HR 0.43, 95%CI 0.21-0.88, p 0.02), PDL2 gene (HR 0.29, 95%CI 0.09-0.99, p 0.05), immunoproteasome (HR 0.34, 95%CI 0.13-0.89, p 0.02), exhausted CD8 (HR 0.29, 95%CI 0.09-0.97, p 0.04), and PD1 (HR 0.44, 95%CI 0.20-1.02, p 0.05). **Conclusions:** Analysis of RNA abundance signatures strongly suggests that there are important immune features that are associated with benefit from capecitabine in TNBC. However, analysis of RNA extracted from whole tumor sections lacks spatial discrimination. We anticipate that a more detailed, spatially-defined analysis of protein abundance, using the novel NanoString GeoMX platform, will provide more insights and define specific immune features associated with improved outcome. Additional results of GeoMX will be reported at the meeting. Clinical trial information: NCT00114816.

3143 **Poster Session (Board #135), Sat, 8:00 AM-11:00 AM**

Vascular endothelial growth factor A (VEGF-A) amplification and long-term response to ramucirumab (ram) in metastatic gastric cancer (mGC): The VERA study.

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Background: The anti-VEGFR-2 monoclonal antibody ram, alone or with paclitaxel, is a cornerstone of second-line treatment of mGC. Even if about half patients do not benefit from ram, no predictive biomarkers have been identified so far. In TCGA, *VEGF-A* amplification was found in 7% of cases, almost exclusively in chromosomal instability subtype. We hypothesize that *VEGF-A* amplification in tumor cells could lead to autocrine/paracrine stimulation of tumor growth beside angiogenesis, potentially identifying a patients' subgroup with exceptional responses to ram. **Methods:** VERA was a multicentric, prospective study based on a translational hypothesis. mGC patients were included according to the following criteria: 1) complete (CR) or partial response (PR) to single-agent ram; 2) $>$6 months PFS to single-agent ram; 3) $>$10 months PFS to paclitaxel+ram. According to a Fleming single-stage design, hypothesizing a prevalence of *VEGF-A* amplification of 1% and 15% among all-comers and exceptional responders, 20 exceptional responders were required to reject the null hypothesis of low prevalence of *VEGF-A* amplification, with alpha- and beta- errors of 0.05 and 0.10, respectively. *VEGF-A* amplification (defined as $>$10% tumor cells with $\geq$10 *VEGF-A* copies, variably sized signal clusters or a ratio of *VEGF-A* gene to centromere of $\geq$2) was centrally assessed through fluorescent in situ hybridization on pre-treatment FFPE tumor tissue. **Results:** At 7 Italian Centers, we included 20 patients satisfying the 1st (n=1), 2nd (n=2), or 3rd (n=17) criterion. Clinical-pathological features were: M/F, 11/9; median age 63 years; gastric/GEJ, 17/3; intestinal/diffuse, 14/6, HER2+/HER2-, 4/16. Median PFS and overall survival to ram-based treatment were 15.6 and 25.7 months, with best response: CR/PR/SD, 0/10/10. VERA met its primary endpoint, revealing 3/20 (15%) tumors with *VEGF-A* amplification (1 case presenting big clusters, 1 small clusters and 1 with $>$10% tumor cells with $\geq$10 *VEGF-A* copies). **Conclusions:** Validation analyses of first- and second-line randomized trials could confirm *VEGF-A* amplification as a biomarker of long-term response to ram-based treatment in mGC patients, advancing treatment personalization.

3144 **Poster Session (Board #136), Sat, 8:00 AM-11:00 AM**

Reassignment of HER2 status for subgroups of breast cancer according to the 2018 updated American Society of Clinical Oncology and College of American Pathologists guidelines: The impact of combined immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) reflex testing in a large national reference laboratory.

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Background: Updated ASCO/CAP Guidelines for HER2 testing in breast cancer have been most impactful on the resolution of certain challenging groups of FISH results. We review the change in assignment of HER2 status in a large series of breast cancers referred to a large national reference laboratory for FISH testing since the introduction of the 2018 updated guidelines. **Methods:** Patient samples submitted to the Mayo Clinic Cytogenetics Laboratory (N = 2208) were analyzed by FISH. Samples with Group 2, Group 3, or Group 4 FISH results were reflexed to immunohistochemistry (IHC) in our central laboratory; FISH slides for those cases with equivocal 2+ IHC results were re-scored in the regions of invasive cancer showing more intense membranous staining. A subset of 202 samples with Group 4 FISH results were also reflexed to the previously employed reflex FISH assay (HER2/D17S122), and these were also re-analyzed according to the new reflex IHC/FISH process. **Results:** 382 of 2208 breast cancer samples tested (17.3%) had FISH results categorized as Group 2 (N = 17, 0.8%), Group 3 (N = 34, 1.5%), or Group 4 (N = 331, 15%) and required reflex IHC testing, and of those, 75% were 2+ equivocal and required targeted re-analysis of the FISH slide according to the 2018 updated guidelines. Re-analysis of the FISH slide resulted in switching between Groups 1-5 in 19.4% of cases, but HER2 status was changed by FISH re-scoring in only 7.7% of cases re-scored (1.0% of all samples), generally due to only minor shifts in HER2 copy number and HER2/control ratios between the initial and IHC-guided reflex FISH scores. In the subset of 202 cases tested by both reflex methods, the previously employed HER2/D17S122 reflex probe set was positive in 123 cases (60.9%), whereas reflex IHC/FISH was positive in only 10 cases (7.9%). Including positive reflex IHC (0.4%) and positive reflex FISH results (2.1%), the overall assignment of positive HER2 status on our series of 2208 cases was 11.5%. **Conclusions:** Overall rates of HER2 positive FISH results have declined under the most recent ASCO/CAP guideline update as a consequence of new recommendations for reflex testing for Groups 2-4. This change is largely due to reassignment of Group 2 and Group 4 results as negative in the absence of positive IHC.

3145 **Poster Session (Board #137), Sat, 8:00 AM-11:00 AM**

BRCA1 genetic variant to predict survival in metastatic colorectal cancer (mCRC) patients (pts) treated with FOLFIRI/bevacizumab (bev): Results from phase III TRIBE and FIRE-3 trials.

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Background: BRCA muts in CRC are associated with a higher tumor mutation burden irrespective of microsatellite instability, which highlights the possibility of using PARP-inhibitors(i) in CRC in the future. Early phase studies have shown that combination of PARP-i with oxaliplatin or irinotecan enhances tumor lysis in CRC. In this study, we investigated the influence of mutations in the Homologous Repair Pathway genes on survival outcomes among mCRC pts treated with oxaliplatin or irinotecan-based regimens. **Methods:** The impact of selected SNPs within 4 genes (BRCA1, BRCA2, RAD51, BARD1) on OS/PFS was analyzed through the OncoArray, a custom array manufactured by Illumina, on genomic DNA from blood samples of 431 pts enrolled in 2 randomized trials. TRIBE FOLFIRI/bev arm (n = 215, mPFS/OS: 9.7/26.2 mo) served as discovery cohort, FIRE-3 FOLFIRI/bev arm (n = 107, mPFS/OS: 11.5/31.4 mo) as validation and TRIBE FOLFOX/bev arm (n = 109, mPFS/OS: 10.8/26 mo) as control. **Results:** Significant associations were found among carriers of BRCA1 rs8176318 SNP, where C > A base change is known to reduce BRCA1 expression among CRC cells. In the discovery cohort, pts with A/A had shorter OS (22.4 vs 27.3 mo, P = .009) and PFS (7.5 vs 10.5 mo, P = .0006) compared to carriers of any C allele in both univariate and multivariate analysis. Same results were observed in pts with left-sided CRCs (PFS-7.5 vs 11 mo, P = .005; OS- 25.6 vs 32.3, P = .034) and among males (PFS- 7.5 vs 10.3 mo, P = .008; OS-25.7 vs 31.3 mo, P = .008) in both uni and multivariate analysis. These results were also seen in the validation cohort: A/A carriers in left-sided CRCs had poor OS (26.1 vs 36.0 mo, P = .027) and PFS (9.5 vs 11.7 mo, P = .002. Males with A/A genotype also had poor OS (24.7 vs 32.5 mo, P = .028) and PFS 96.9 vs 12.2 mo; P = .0002). In the control cohort, A/A genotype carriers had poor tumor response in overall (P = .011) and left-sided disease (P = .034). These outcomes were independent of KRAS mutation status. No significant relationship was observed among females with mCRC. **Conclusions:** This is the first study to report that BRCA1 mut influence survival outcomes among mCRC pts, particularly among males and those with left-sided disease. Prospective trials are warranted to assess the utility of routine BRCA mut testing and the role of PARP-i in improving survival outcomes in this pt population.

TPS3146 **Poster Session (Board #138a), Sat, 8:00 AM-11:00 AM**

First-time in-human study of VMD-928, an allosteric and irreversible TrkA selective inhibitor, in patients with solid tumors or lymphoma.

Vincent Chung, Ling Wang, Margaret S. Fletcher, Erminia Massarelli, Karen L. Reckamp, Mihaela C. Cristea, Nikeeta Prajapati, Aruna Parikh, Roger Lewis Whiting, Maggie Wang, Jay Wu; City of Hope, Duarte, CA; VM Oncology, Fremont, CA; MedAssessment, Inc, San Clemente, CA; City of Hope Comprehensive Cancer Center, Duarte, CA; VM Oncology, LLC, Fremont, CA

Background: Tropomysin receptor kinase A (TrkA) is a protein encoded by the NTRK1 gene. NTRK fusions involving the kinase domain are oncogenic for multiple tumor types and larotrectinib was recently approved for advanced solid tumors harboring NTRK gene fusions. Larotrectinib, an ATP-competitive, reversible pan-TrkA/B/C inhibitor, has shown impressive response rates in patients harboring these fusions; however, resistance can develop due to acquired ATP-site mutations. This has been previously identified in other oncogenic driver kinases such as ALK and EGFR treated with ATP-competitive kinase inhibitors. A newly approved allosteric ALK/EGFR inhibitor brigatinib was able to clinically overcome acquired resistance of many ATP-competitive ALK/EGFR inhibitors (1). Also, irreversible EGFR inhibitors such as afatinib (ATP-competitive) were active against tumors resistant to first-generation inhibitors (2), although their efficacy can be compromised by acquired ATP-site mutations (3). VMD-928 is the first oral small-molecule TrkA (NTRK1) selective inhibitor with dual allosteric and irreversible mechanisms of action. It inhibits TrkA non-competitively at an allosteric (non-ATP) site and has no resistance in vitro to acquired ATP-site mutations such as G667C. VMD-928 in vitro has little or no activity against 348 other kinases including TrkB (NTRK2) and TrkC (NTRK3). We are conducting the first time in human phase 1 trial of oral VMD-928, a novel allosteric and irreversible TrkA selective inhibitor.
Methods: This is an open label, Phase 1 study investigating the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of oral VMD-928 in adults with advanced solid tumors or lymphoma (NCT03556228). In part 1 of the study, an accelerated titration scheme will be utilized to determine the recommended phase 2 dose and evaluate PK / PD of VMD-928. In part 2, expansion cohorts including patients with thymic, pancreatic, triple-negative breast carcinoma, or solid tumors with TrkA alterations will be accrued to further evaluate safety and efficacy. Part 3 of the study will characterize the biologically active dose. The study is open and accruing patients at City of Hope. Clinical trial information: NCT03556228.

TPS3147 **Poster Session (Board #138b), Sat, 8:00 AM-11:00 AM**

A first-in-human study of, NUC-7738, a 3'dA phosphoramidate, in patients with advanced solid tumors or lymphoma (NuTide 701).

Hagen P Schwenzer, Stefan N. Symeonides, Elizabeth Ruth Plummer, Gareth P Bond, Sarah Patricia Blagden; University of Oxford, Oxford, United Kingdom; Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh, United Kingdom; Northern Centre for Cancer Care, Newcastle-upon-Tyne, United Kingdom; Ludwig Institute, Oxford, United Kingdom

Background: Nucleoside analogs form the backbone therapy for both hematological and solid malignancies. However, their clinical effectiveness is severely limited by key cellular resistance mechanisms linked to increased breakdown, impaired activation and transport. NUC-7738 is a phosphoramidate transformation of cordycepin (3'-deoxyadenosine; 3'-dA), a derivative of adenosine that was first isolated from *Cordyceps sinensis.* The cytotoxic effect of 3'-dA is largely attributed to intracellular generation of the triphosphate metabolite, 3'-dATP, terminating DNA and RNA synthesis. Although 3'-dA has shown potent anti-tumor activity in non-clinical studies, it has not been successful in clinical studies mainly because of rapid enzymatic degradation by adenosine deaminase. NUC-7738 is not a substrate for adenosine deaminase and has been designed to bypass the key resistance pathways which have limited the clinical effectiveness of cordycepin. **Methods:** NuTide:701 is a two-part, first-in-human Phase I study in patients with advanced solid tumors and lymphoma who have exhausted all standard treatment options. The primary objective is to determine the RP2D and schedule of NUC-7738. Secondary objectives include safety, PK/PD and anti-tumor activity. Part 1, in patients with advanced solid tumors, will establish the RP2D and dose administration schedule of NUC-7738 for Part 2. Part 2 will further evaluate the selected RP2D and designated dosing schedule in an expansion cohort of patients with advanced solid tumors or lymphoma. The study initiated in Q1 2019. Clinical trial information: NCT03829254.

TPS3148 **Poster Session (Board #139a), Sat, 8:00 AM-11:00 AM**

Trial in progress abstract phase I trial of 5-aza-4'-thio-2'-deoxycytidine (Aza-TdC) in patients with advanced solid tumors.

M. Cecilia Monge B., Geraldine Helen O'Sullivan Coyne, Richard Piekarz, Naoko Takebe, Ashley Bruns, Arjun Mittra, Sabrina Sharmin Khan, Jerry M. Collins, Larry Anderson, Lamin Juwara, Brandon Miller, Robert J. Kinders, Larry Rubinstein, Alice P. Chen, James H. Doroshow; National Cancer Institute, National Institutes of Health, Bethesda, MD; Developmental Therapeutics Clinic/Early Clinical Trials Development Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD; Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD; Developmental Therapeutics Clinic/Early Clinical Trials Development Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, MD; National Cancer Institute, Bethesda, MD; Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD; National Cancer Institute/Division of Cancer Treatment and Diagnosis, Rockville, MD; National Cancer Institute/Division of Cancer Treatment and Diagnosis/Developmental Therapeutics Program/Office of the Associate Director, Frederick National Laboratory for Cancer Research, Frederick, MD; NCI at Frederick, Bethesda, MD; Frederick National Laboratory for Cancer Research, Frederick, MD; 1050 Boyles Street, Frederick, MD; Biometric Research Branch, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD; Center for Cancer Research, Bethesda, MD

Background: The nucleoside analog 5-aza-4'-thio-2'-deoxycytidine (Aza-TdC) inhibits DNA methyltransferase 1 (DNMT1), a methyltransferase involved in methylation-mediated silencing of tumor suppressor genes. Attenuation of DNA methylation via DNMT1 inhibitors results in reactivation of silenced tumor suppressor genes and can lead to tumor growth arrest and apoptosis. The DNMT1 inhibitors decitabine and 5-azacytdine are currently FDA-approved for use in myelodysplastic syndromes and are also used in patients with acute myeloid leukemia. Relative to these compounds, Aza-TdC exhibits enhanced stability and incorporation into DNA and has shown improved preclinical antitumor activity in both leukemia and solid tumor xenograft models. This study seeks to evaluate the safety and maximum tolerated dose (MTD) of oral Aza-TdC in patients with advanced solid tumors. Secondary study objectives include assessing objective response by RECIST 1.1, pharmacokinetic (PK) analysis, and examining re-expression of tumor suppressor genes inhibited by methylation in circulating tumor cells (CTCs). **Methods:** Patients are treated with Aza-TdC on days 1-5 and 8-12 of each 21-day cycle. The study follows Simon accelerated titration design 3, with 100% dose increments and 1 patient per dose level. Accelerated titration will continue until 1 patient experiences a dose-limiting toxicity (DLT) or 2 patients experience drug-related grade 2 toxicity at any dose level, after which, a 3 + 3 dose escalation design will be used. Blood samples are collected for PK and CTC analyses. An MTD expansion cohort is planned, in which tumor biopsies will be collected for further pharmacodynamic assessments. Patients included in this study must be $\geq$18 years old and have histologically documented solid tumors that have progressed on standard therapy and for which there is no other standard therapy available. Dose level 3 has been completed without any DLTs; enrollment to dose level 4 began in February 2019. Funded by NCI Contract No. HHSN261200800001E. Clinical trial information: NCT03366116.

TPS3149 **Poster Session (Board #139b), Sat, 8:00 AM-11:00 AM**

Update on the Drug Rediscovery Protocol: Expanded use of existing anticancer drugs in patients with a known molecular profile.

Jade Maxime van Berge Henegouwen, Louisa Rose Hoes, Hanneke van der Wijngaart, Daphne Liselotte Van Der Velden, Alwin Huitema, Edwin P.J.G. Cuppen, Elly J. Lugtenburg, Filip Yves Francine Leon De Vos, Haiko Bloemendal, Katrien Grunberg, Henk M.W. Verheul, Hans Gelderblom, Emile E. Voest; Leiden University Medical Center, Department of Medical Oncology, Leiden, Netherlands; Netherlands Cancer Institute, Division of Molecular Oncology, Amsterdam, Netherlands; Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam, Netherlands; Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, Netherlands; Hartwig Medical Foundation, Amsterdam, Netherlands; Erasmus MC Cancer Institute, Department of Hematology, Rotterdam, Netherlands; University Medical Center Utrecht, Division of Medical Oncology, Utrecht, Netherlands; Meander Medical Center, Division of Medical Oncology, Amersfoort, Netherlands; Radboud University Medical Center, Division of Pathology, Nijmegen, Netherlands; Department of Medical Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam and Center for Personalized Cancer Treatment, Rotterdam, Netherlands

Background: With the emergence of large-scale genetic tumor profiling and the increasing availability of approved targeted therapies, precision medicine has become crucial in cancer treatment. However, for many cancers the relative contribution of either tumor type or genetic aberration to drug sensitivity often remains unknown. Since drug access is generally limited to the on-label indication and outcome of off-label use is not systematically collected in clinical practice, innovative trials facilitating drug access, whilst systematically analyzing treatment outcomes, are urgently needed. **Methods:** The Drug Rediscovery Protocol (DRUP) is an ongoing, prospective, non-randomized, multi-drug, and pan-cancer trial, in which patients with advanced cancer, who have exhausted all standard of care treatment options, are treated with either targeted or immunotherapy matched to their genetic tumor profile. All submitted patients are reviewed and enrolled in multiple parallel cohorts, preceded by a baseline tumor biopsy for whole genome sequencing to confirm previously identified variants and for exploratory biomarker analyses. Each cohort is defined by a study drug, histologic tumor type, and molecular tumor profile. Efficacy is analyzed per cohort: 8 patients in stage I and 16 more in stage II if ≥ 1 response is observed in the first stage. Primary endpoints include objective response rate, stable disease at 16 weeks, and grade ≥ 3 adverse events. Since the start of recruitment in September 2016, 870 patients have been submitted for review and 365 patients (42%) have started treatment in one of 101 opened cohorts. Eight cohorts have graduated to the second stage, two cohorts completed accrual in either their first or second stage, and one cohort was closed due to a registered indication. Twenty-two different study treatments (i.e. immunotherapy, monoclonal antibodies, and PARP/small molecule inhibitors), provided by 11 different pharmaceutical companies, are currently available in DRUP. Data sharing with similar trials such as TAPUR and CAPTUR enables to achieve completion of slow accruing cohorts and affirm conclusions. Clinical trial information: NCT02925234.

TPS3150 **Poster Session (Board #140a), Sat, 8:00 AM-11:00 AM**

A phase I clinical study to evaluate the safety, tolerability, pharmacokinetics (PK), and antitumor activity of FN-1501 monotherapy in patients with advanced solid tumors.

Gary Edward Richardson, Ulka N. Vaishampayan, Lin Lin, Viviana Bozon, Ai-Min Hui, Stephen K. Williamson; Monash University, Cabrini Hospital, Malvern, Australia; Wayne State University, Detroit, MI; Shanghai Fosun Pharmaceutical, Shanghai, China; Shanghai Fosun Pharmaceutical, Billerica, MA; University of Kansas Cancer Center, Kansas City, KS

Background: Receptor tyrosine kinases (RTK), a group of transmembrane proteins, are responsible for growth factor signaling transduction in normal cellular functions. Abnormal RTK functions are associated with human tumorigenesis. FMS-like tyrosine kinase 3 (FLT3) belongs to the type III receptor tyrosine kinase family and plays a well-established role in normal growth and differentiation of hematopoietic precursor cells. FLT3 mutations have been reported to occur in approximately 30% newly diagnosed AML patients. The internal tandem duplications mutation (FLT3/ITD) is the major mutation and correlated with more aggressive progress and poor prognosis. FN-1501 is an inhibitor of various tyrosine kinases such as cyclin-dependent kinase 4/6(CDK4/6), platelet-derived growth factor receptor (PDGFR), KIT protein, anaplastic lymphoma kinase (ALK) and RET protein, particularly potent on FLT3. The preclinical data generated from biochemical, cell based and animal in vivo studies suggest that FN-1501 as a single agent could offer cancer patients clinical benefit by inhibiting multiple tyrosine kinases including FLT3, PDGFR, KIT, ALK, and RET. **Methods:** This is a Phase1, open label, multicenter, dose-escalation study that will evaluate the safety, pharmacokinetics (PK), and preliminary efficacy of FN-1501 in up to 33 cancer patients with solid tumors. There is a dose escalation phase that will be followed by an expansion cohort. The dose escalation phase utilizes a standard "3 + 3" design where doses of FN-1501 will be escalated up to the Maximum-Tolerated Dose (MTD) or until the Recommended Phase 2 dose (RP2D) is identified. Once the MTD or RP2D dose is identified, an expansion cohort including patients with hematologic malignancies will be enrolled to further evaluate the safety and efficacy of FN-1501. Key exploratory analyses will include an evaluation of safety and efficacy and levels of expression and/or amplification of FLT3 mutations. As of February 8, 2019, cohorts 1 and 2 have been completed without a dose limiting toxicity (DLT). A total of 11 patients have been treated. Enrollment to cohort 3 is on-going. Clinical trial information: NCT03690154.

TPS3151 **Poster Session (Board #140b), Sat, 8:00 AM-11:00 AM**

Basket of baskets (BoB): A modular, open label, phase II, multicenter study to evaluate targeted agents in molecularly selected populations with advanced solid tumors.

Irene Brana, Christophe Massard, Richard D. Baird, Frans Opdam, Richard F. Schlenk, Luigi De Petris, Claudio Vernieri, Elena Chavarria, Elena Garralda, Ruud van der Noll, Ana Vivancos, Lodewyk F. A. Wessels, Jose-Ezequiel Martin, David Tamborero, Rodrigo Dienstmann, Gerrit A. Meijer, Susana Muñoz, Alejandro Piris-Giménez, Fabien Calvo, Jordi Rodon, Cancer Core Europe; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Gustave Roussy Cancer Campus and University Paris-Sud, Villejuif, France; University of Cambridge, Cambridge, United Kingdom; NKI-AVL, Amsterdam, Netherlands; National Center of Tumor Diseases Heidelberg, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany; Dep of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; Hospital Universitari Vall d'Hebron, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; The Netherlands Cancer Institute, Antoni Van Leeuwenhoek Hospital, Amsterdam, Netherlands; Cancer Genomics Lab and Molecular Pathology Lab, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Department of Molecular Carcinogenesis, Netherlands Cancer Institute, Amsterdam, Netherlands; CRUK Cambridge Centre, Cambridge, United Kingdom; Karolinska Institutet, Stockholm, Sweden; Oncology Data Science Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Netherlands Cancer Institute, Amsterdam, Netherlands; Vall d'Hebron University Hospital, Barcelona, Spain; Fundacio Privada Institut Oncologica Vall Hebron, Barcelona, Spain; INSERM, Paris, France; Vall d'Hebron University Hospital Institute of Oncology (VHIO), Barcelona, Spain

Background: Basket trials with targeted agents can show high response rates for tumors with specific molecular profiles, granting extension of the label of some drugs. In other cases, study results were disappointing, likely due to the rarity of molecular alterations, limits in trial design and the difficulties in applying molecular tumor profiling in the clinical setting. **Methods:** Basket of Baskets (BoB), NCT03767075, aims to bridge the gap between Academic Genomics and clinical applications (ready-to market multi-marker Companion Diagnostics) by providing a sustainable and adaptable (to new technologies, markers, and therapeutic agents) platform for co-development of drug/companion diagnostic. BoB is a novel platform trial from Cancer Core Europe, a recently established sustainable European network for innovative cancer research. This protocol has two parts: (1) Part A includes a molecular profiling program for subjects with advanced solid tumors (iPROFILER), a variant annotation tool, and a molecular tumor board to select the most appropriate treatment. It also enables testing/ developing companion diagnostics linked with the therapeutic part (part B). (2) Part B includes iBASKET, a modular multi-arm basket trial for subjects with tumors harboing selected molecular alterations. Each module is focused on a certain molecular pathway or on certain molecular alterations that may confer sensitivity to the study drug or study drug combination evaluated in that module/arm. The current version of iBASKET (Module 1- Atezolizumab in genomically-selected patients) is open for enrollment for patients with advanced neoplasms bearing one of the following alterations: Arm 1A: *BRCA1* or *BRCA2*; Arm 1B: *MLH1*, *MSH2*, *MSH6, PMS2*; Arm 1C: *POLE*, *POLD1 mutations;* Arm 1D: hypermutated tumors; Arm 1E: other mutations in DNA-repair genes; Arm 1F: *PDL1 gene amplification.* All patients enrolled in Module 1 will receive single-agent atezolizumab. New Modules for genomically selected populations can be added through amendments. Our final aim is to achieve drug repurposing of treatments, co-develop multi-marker companion diagnostics and a large database of knowledge in Precision Medicine. Clinical trial information: NCT03767075.

TPS3152 **Poster Session (Board #141a), Sat, 8:00 AM-11:00 AM**

A phase I study of [^{225}Ac]-FPI-1434 radioimmunotherapy in patients with IGF-1R expressing solid tumors.

Rosalyn A. Juergens, Katherine A. Zukotynski, Daniel Juneau, Lily Krnezich, Ryan Simms, John Forbes, Eric S. Burak, John Valliant, Lauren Stafford, Thomas Armor, Istvan Molnar, Fred Saad; Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; Departments of Medicine and Radiology, McMaster University, Hamilton, ON, Canada; Centre Hospitalier de l'Université de Montréal, Université de Montréal, Montréal, QC, Canada; Fusion Pharmaceuticals Inc, Hamilton, ON, Canada; Centre Hospitalier de l'Université de Montréal/CRCHUM, Montréal, QC, Canada

Background: Type I insulin-like growth factor receptor (IGF-1R) is a transmembrane protein which is overexpressed in solid tumors including non–small cell lung, prostate, and breast cancers. [^{225}Ac]-FPI-1434 is a radioimmunoconjugate consisting of a humanized monoclonal antibody that binds to the external domain of IGF-1R, a proprietary bifunctional chelate, and an alpha-emitting radionuclide actinium-225 (Ac-225), which binds to the external domain of IGF-1R. Internalization of the conjugate and decay of Ac-225 causes tumor cell death primarily through double stranded DNA breaks. The indium-111 analog, [^{111}In]-FPI-1547, with the identical antibody and bifunctional chelate is used for patient selection, in-vivo imaging, and quantification of IGF-1R targets prior to therapy. Based on anti-tumor activity of [^{225}Ac]-FPI-1434 in preclinical models, favorable toxicology studies in cynomolgus monkeys, and prior human experience with the unconjugated antibody, the first in human clinical evaluation was initiated. **Methods:** This open-label multi-center phase I study (NCT03746431) follows a modified 3+3 dose-escalation design to characterize the safety profile, determine a maximum tolerated dose (MTD), evaluate dose-limiting toxicities (DLT), describe pharmacokinetics, derive radiation dose estimates to normal organs, and evaluate the objective response rate of [^{225}Ac]-FPI-1434 therapy in patients with IGF-1R expressing solid tumors. Eligibility requirements for therapy include: presence of at least one measurable lesion as determined by sufficient tumor uptake using SPECT/CT of an imaging analog [^{111}In]-FPI-1547; radiation dose estimates of the planned therapeutic activity within prespecified limits; and adequate bone marrow reserves, hepatic, and renal function. Dose cohorts begin with 10 kBq [^{225}Ac]-FPI-1434 per kilogram (kg) patient weight and successively increase to 20, 40, 80, and 120 kBq/kg as a single intravenous injection per patient followed by an 8-week DLT evaluation period. This trial is currently enrolling patients. Clinical trial information: NCT03746431.

TPS3153 **Poster Session (Board #141b), Sat, 8:00 AM-11:00 AM**

TROPHY-U-01: A phase II open-label study of sacituzumab govitecan (IMMU-132) in patients with advanced urothelial cancer after progression on platinum-based chemotherapy and/or anti-PD-1/PD-L1 checkpoint inhibitor therapy.

Scott T. Tagawa, Daniel Peter Petrylak, Petros Grivas, Neeraj Agarwal, Cora N. Sternberg, Chris Hernandez, Peggy Siemon-Hryczyk, Trishna Goswami, Yohann Loriot; Sandra and Edward Meyer Cancer Center, New York, NY; Yale School of Medicine, New Haven, CT; University of Washington, School of Medicine, Seattle, WA; University of Utah Huntsman Cancer Institute, Salt Lake City, UT; Weil Cornell Medicine, New York, NY; Immunomedics, Inc., Morris Plains, NJ; Institut de Cancérologie Gustave Roussy, Villejuif, France

Background: Patients (pts) with advanced urothelial cancer (UC) who progress after checkpoint inhibitor (CPI) therapy (following failure of or ineligibility for platinum-based chemotherapy) have limited options. Trop-2 is an epithelial cell surface antigen overexpressed in UC (Avellini. *Oncotarget* 2017). Sacituzumab govitecan (SG) is an antibody-drug conjugate that targets Trop-2 and delivers the active metabolite SN38 of the topoisomerase I inhibitor irinotecan to tumor cells (Starodub. *Clin Cancer Res* 2015). In a phase 1/2 trial, pts with advanced cancers received SG on days 1 and 8 of a 21-day cycle. In the UC cohort, 45 evaluable pts received SG 10 mg/kg with a median of 2 (range 1–6) prior therapies. Objective response rate (ORR) was 31%; median duration of response was 12.9 mo. Grade $\geq$3 adverse events in $\geq$5% of pts were neutropenia/neutrophil count decreased (38%), anemia (13%), hypophosphatemia (11%), diarrhea (9%), fatigue (9%), and febrile neutropenia (7%). Median progression-free survival (PFS) was 7.3 mo and overall survival (OS) 16.3 mo (Tagawa 2019 ASCO Genitourinary Cancers Symposium). These results warrant further investigation in a dedicated phase 2 trial. **Methods:** TROPHY-U-01 (NCT03547973) is a single-arm, global phase 2 trial evaluating the antitumor activity of SG (10 mg/kg on days 1 and 8 of a 21-day cycle) in 140 pts with advanced UC and measurable disease. Patients are also required to have an Eastern Cooperative Oncology Group Performance Status score of 0 or 1 and creatinine clearance $\geq$30 mL/min. The pivotal cohort (Cohort 1: progression after both platinum chemotherapy and CPI) will enroll 100 evaluable pts in a Simon 2-stage design with $>$ 90% power accounting for dropouts to exclude the null hypothesis or ORR $<$ 12%; an exploratory cohort (Cohort 2: 40 pts) includes platinum-ineligible pts who progress after prior CPI. The primary objective is ORR per RECIST 1.1, assessed by central review. Secondary objectives include response duration, PFS, and OS. Adverse events, pharmacokinetics, and tissue correlates will also be assessed. Enrollment began August 2018. Clinical trial information: NCT03547973.

TPS3154 **Poster Session (Board #142a), Sat, 8:00 AM-11:00 AM**

A phase II study for prostate cancer monitoring using ^{18}F-DCFPyL and blood-based biomarkers.

Emerson A. Lim, Akiva Mintz, Mark N. Stein, Alex J. Rai, Mahesh M. Mansukhani, David Henry Aggen, Matthew Dallos, Jessica Hawley, Hiram A Shaish, Lawrence Howard Schwartz, Charles G. Drake; Columbia University-Herbert Irving Comprehensive Cancer Center, New York, NY; Columbia University Medical Center, New York, NY; Columbia University, New York, NY; Herbert Irving Comprehensive Cancer Center, New York, NY

Background: Assessing treatment response in castrate resistant prostate cancer (CRPC), remains a challenge due to the limited sensitivity and specificity of existing imaging modalities. Understanding prostate cancer biology with tumor biopsies does not address the issue of tumor heterogeneity or cellular degradation during the decalcification process of bone biopsies. Next generation positron emission tomography (PET) imaging and circulating biomarkers might provide additional insights on treatment responses and inform clinical decision-making earlier in therapy. ^{18}F-DCFPyL (PyL) is a second-generation fluorinated PSMA PET tracer that has superior sensitivity and specificity to detect prostate cancer compared to standard imaging. Its role in assessing tumor response to therapy has not been evaluated. Circulating tumor DNA (ctDNA) in blood can provide tumor genomic information, while exosomes in serum and urine may provide data on the proteomic landscape of tumors. **Methods:** We are conducting a prospective study of 15 men with metastatic CRPC who are scheduled to start a new systemic therapy for their disease. Upon enrollment, subjects will have baseline assessments with standard cross-sectional imaging, ^{99m}Tc bone scan, and blood work. Standard scans will be performed every 8-12 weeks until progression of disease. PyL PET/CT scans and liquid biopsies (ctDNA and exosomes) will occur at baseline, 6 weeks after starting their new therapy, and at disease progression. Lesions seen on PET/CT images will be identified by a certified reader. The maximum standardized uptake value (SUV_{max}) will be measured and recorded in up to the five hottest lesions and normalized to a background SUV_{mean} measured in the liver, spleen, kidney, mediastinum, and parotid glands. Changes in the normalized SUV from baseline to the 6-week PyL PET scan will be correlated to PSA response by the Pearson's correlation coefficient. The Kaplan-Meier method will be used to evaluate progression free survival and overall survival dichotomized by the median value of SUV change. Blood for ctDNA and exosomes will be stored for future analysis. The study is open with two patients enrolled at the time of submission. One patient has completed his initial PyL PET/CT scan. Clinical trial information: NCT03585114.

TPS3155 **Poster Session (Board #142b), Sat, 8:00 AM-11:00 AM**

Clinical Trial in Progress: The FLEX Big Data Platform explores new gene expression profiles and investigator-initiated protocols in early-stage breast cancer.

Sarah Untch, Gordan Srkalovic, Adam Brufsky, Jennifer A. Crozier, Mehran Habibi, Pat W. Whitworth, Charles E. Cox, Nina D'Abreo, William Audeh, Erin Yoder, Ian Grady; Agendia, Irvine, CA; Sparrow Regional Cancer Center, Lansing, MI; University of Pittsburgh Medical Center, Division of Hematology Oncology, Pittsburgh, PA; Mayo Clinic, Ponte Vedra Beach, FL; The Johns Hopkins University School of Medicine and The Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Nashville Breast Center, Nashville, TN; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Winthrop Univ Hosp, Mineola, NY; North Valley Breast Clinic, Redding, CA

Background: Genomic signatures are revolutionizing the definition, identification, and treatment of breast cancer. To precisely stratify breast cancers into actionable subgroups, full genome expression data and matching clinical data must be aggregated into a large data set. Such a data set will accelerate research and discovery, especially for smaller patient subsets who are not as widely represented within the current body of literature. **Methods:** FLEX is a multicenter, prospective, population-based, observational trial for patients with Stage I, II, and III breast cancer. All patients with stage I to III breast cancer who receive MammaPrint, with or without BluePrint on a primary breast tumor are eligible for enrollment. The study's primary aim is to create a large scale, population-based registry of full genome expression data matched with clinical data to investigate new gene associations with prognostic and/or predictive value. Secondary objectives include utilizing the shared study infrastructure to examine and generate hypotheses for targeted subset analyses and/or trials based on full genome expression data. The design of FLEX allows targeted sub-studies and sub-analyses to be added as appendices after the initial baseline study is opened. Patients enrolled in the initial study are also eligible for inclusion in sub-studies where they meet all criteria and additional consent is not required. Additional clinical data will be collected as specified in the appendix protocols. The FLEX collaborative platform allows participating investigators the opportunity to author their own sub-study protocols, as approved by the FLEX Steering Committee of their peers. 13 sub-studies have already been identified and are under development. Eligibility: The study will enroll a minimum of 10000 patients aged $\geq$18 years with histologically proven invasive stage I-III breast cancer who signed informed consent. Enrollment began April 2017 and 1506 patients have been enrolled. Clinical trial information: NCT03053193.

TPS3156 **Poster Session (Board #143a), Sat, 8:00 AM-11:00 AM**

TiFFANY study: A multicenter phase II basket-type clinical trial to evaluate efficacy and safety of pan-FGFR inhibitor TAS-120 for advanced solid malignancies with *FGFR* alterations identified by circulating tumor DNA.

Tomoko Jogo, Yoshiaki Nakamura, Yoshito Komatsu, Ken Kato, Eiji Shinozaki, Hideaki Bando, Takeshi Kato, Tomohiro Nishina, Taito Esaki, Satoshi Fujii, Mitsuko Suzuki, Nozomu Fuse, Akihiro Sato, Shogo Nomura, Martina Lefterova, Justin Odegaard, Hiromichi Ebi, Takayuki Yoshino; Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan; Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; Department of Gastroenterology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; Aichi Cancer Center Hospital, Nagoya, Japan; 6.Department of Surgery, National Hospital Organization Osaka National Hospital, Amagasaki, Japan; National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; Department of Gastrointestinal and Medical Oncology, National Kyushu Cancer Center, Fukuoka, Japan; National Cancer Center, EPOC, Chiba, Japan; Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan; National Cancer Center, Kashiwa, Japan; Guardant Health, Redwood City, CA; Lifecode, San Francisco, CA; Division of Molecular Therapeutics, Aichi Cancer Center Research Institute/ Precision Medicine Center, Aichi Cancer Center, Nagoya, Japan; National Cancer Center Hospital East, Kashiwa, Japan

Background: Approximately 7% of advanced solid malignancies have *FGFR* gene alterations. However, standard treatment for *FGFR*-altered malignancies has not been established. Moreover, circulating tumor DNA (ctDNA) analysis has a potential to accurately identify *FGFR* alterations by assessing spatial and temporal intratumoral heterogeneity, which have shown to be associated with a poor prognosis and resistance to anti-cancer therapy. **Methods:** We are conducting an investigator-initiated multicenter phase II basket-type trial to investigate efficacy and safety of TAS-120, a highly selective covalent pan-FGFR inhibitor, for the patients with advanced solid malignancies with *FGFR* alterations identified by ctDNA analysis as a part of the Nationwide Cancer Genome Screening Project (GOZILA study, UMIN000029315). Eligibility criteria include histologically confirmed unresectable advanced or recurrent solid tumors regardless of histology of origin; ECOG PS of 0 or 1; refractory or intolerant to the standard therapies; and clonal *FGFR* alterations (*FGFR1-3* gain-of-function mutations, *FGFR1,2* amplifications and *FGFR2,3* fusions) identified by a 73-gene sequencing ctDNA panel (Guardant360). Enrolled patients will receive TAS-120 20 mg once daily, orally, in a 21 day-cycle. The primary endpoint is to clarify objective response rate (ORR) assessed by investigators per RECIST v1.1. The secondary endpoints are to evaluate progression-free survival, duration of response, time to treatment failure, disease control rate, overall survival, ORR by central determination, and incidence of adverse events. Target sample size is determined as 26 to test the null hypothesis of ORR as 5% with one-sided alpha level of 2.5% and power of 80% to detect an expected value of ORR as 25%. Furthermore, tumor tissue and ctDNA will be serially collected and analyzed to investigate the resistance mechanisms and provide clinically meaningful biomarker which may be used for identifying and implementing treatment changes. Clinical trial information: 194624.

TPS3157 **Poster Session (Board #143b), Sat, 8:00 AM-11:00 AM**

FUZE clinical trial: a phase 2 study of Debio 1347 in FGFR fusion-positive advanced solid tumors irrespectively of tumor histology.

David Michael Hyman, Lipika Goyal, Petros Grivas, Funda Meric-Bernstam, Josep Tabernero, Youyou Hu, Yulia Kirpicheva, Valerie Nicolas-Metral, Anna Pokorska-Bocci, Anne Vaslin, Claudio Zanna, Keith Flaherty; Memorial Sloan Kettering Cancer Center, New York, NY; Massachusetts General Hospital, Boston, MA; University of Washington, School of Medicine, Seattle, WA; The University of Texas MD Anderson Cancer Center, Houston, TX; Vall d'Hebron University Hospital and Institute of Oncology, Barcelona, Spain; Debiopharm International SA, Lausanne, Switzerland; Dana-Farber Cancer Institute/Harvard Medical School and Massachusetts General Hospital, Boston, MA

Background: Dysregulation of fibroblast growth factor receptor (FGFR) signaling by FGFR fusions is implicated in many cancers. 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. Preliminary data from an ongoing phase 1 trial show efficacy and tolerability in patients (pts) harboring FGFR 1-3 fusion irrespectively of tumor type. We present the design for a multicenter, basket, 2-stage, adaptive single arm Phase 2 trial investigating Debio 1347 in pts with solid tumors harboring FGFR1-3 fusion/rearrangement. **Methods:** Adults with locally advanced/unresectable or metastatic tumors with documented FGFR1-3 gene fusion/rearrangement who require systemic therapy and have progression after $\geq$1 prior standard treatment or have no satisfactory alternative treatment option are eligible. Three cohorts are included: biliary tract cancer (cohort 1), urothelial cancer (cohort 2) and all other solid tumors (cohort 3). Primary brain tumors are excluded. Other key exclusion criteria include prior treatment with FGFR1-3 selective inhibitor; clinically significant corneal/retinal disorder; history of calcium/phosphate homeostasis disorder or systemic mineral imbalance with ectopic soft tissue calcification, and symptomatic/unstable brain metastases $<$ 1 month before enrollment. Genomic screening of tumor tissue is done at local or central laboratory with post-hoc central confirmation by RNA sequencing. Eligible pts will receive Debio 1347, 80 mg PO once daily in 28-day cycles until occurrence of progression or unacceptable toxicity. Primary Endpoint is objective response rate (ORR) based on independent central review using RECIST v.1.1. The targeted sample size (N=125) will provide approximately 90% power to reject H_0: ORR $\leq$ 15% at an overall 5% significance level based on an expected ORR of 30% in at least one of the cohorts. Secondary endpoints are: duration of response, disease control rate, progression-free survival, overall survival, safety, tolerability, and quality of life. An interim analysis for futility and homogeneity will be performed after 27 evaluable pts. PK sparse sampling is performed to assess exposure-response relationships with efficacy and safety. Biomarkers of response and resistance will be explored. Accrual is opened in US, EU, Asia and Australia. Clinical trial information: NCT03834220.

TPS3158 **Poster Session (Board #144a), Sat, 8:00 AM-11:00 AM**

A phase I open label study evaluating VT1021 in patients with advanced solid tumors.

Michael Cieslewicz, Devalingam Mahalingam, Wael A. Harb, Amita Patnaik, Joyce F. Liu, Dejan Juric, Andrea J. Bullock, Lei Zheng, Kathleen N. Moore, Manish R. Patel, Robert Guttendorf, Suming Wang, Kathy Kerstein, Gregory Ivan Berk, Jing Watnick; Vigeo Therapeutics, Cambridge, MA; Northwestern University, Chicago, IL; Horizon Oncology Research, LLC, Lafayette, IN; South Texas Accelerated Research Therapeutics, San Antonio, TX; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Johns Hopkins University Hospital, Baltimore, MD; Stephenson Cancer Center at the University of Oklahoma, Oklahoma City, OK; Florida Cancer Specialists, Sarasota, FL; Aclairo Pharmaceutical Development Group, Inc, Vienna, VA; VIGEO THERAPEUTICS INC, Cambridge, MA; Gregory Berk MD PC, Dover, MA

Background: VT1021 is a cyclic pentapeptide that functions as a potent inducer of thrombospondin-1 (Tsp-1) expression in the tumor microenvironment (TME). By triggering the production of Tsp-1, VT1021 reprograms the TME from one that is immune-suppressive and tumor-promoting, to one that activates the adaptive immune system and is tumor-inhibiting. Tsp-1 reprograms the TME to: (i) induce apoptosis in tumor cells that express CD36 on their cell surface, (ii) convert macrophages from M2 to M1 polarization, which promotes phagocytosis and blunts immunosuppression and (iii) inhibit angiogenesis. Preclinical studies have shown robust anti-tumor activities of VT1021 in animal models of ovarian, pancreatic and breast cancer, including complete tumor regression and reprogramming of the immune TME. These observations led to the initiation of the first-in-human study of VT1021. **Methods:** This study is a first-in-human, Phase 1, open-label, multicenter, dose escalation (Part 1) study with dose expansion (Part 2) in advanced solid tumors. The primary objectives are to assess the safety and tolerability of VT1021, to assess dose-limiting toxicities (DLT), and to determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D). Secondary objectives include the evaluation of pharmacokinetics (PK) and pharmacodynamic (PD) effects of VT1021 in tumor and tumor microenvironment, and assessment of preliminary antitumor activity. VT1021 is administered intravenously twice weekly. DLTs will be assessed in the first cycle (Days 1-28) of the dose escalation cohort and are defined as grade 3 adverse events related to VT1021. In Part 1 of the study, 24-30 patients will be enrolled to determine the MTD and RP2D for expansion. In Part 2 of the study, 80-100 patients will be enrolled, grouped into cohorts based on disease subtypes (ovarian, pancreatic, Triple-negative breast cancers, and glioblastoma). Blood samples and biopsy samples from patients will be collected to assess PK properties and PD responses systemically as well as in the TME. No formal statistical hypothesis testing will be conducted in this study. This study is currently open for enrollment in the US. Clinical trial information: NCT03364400.

TPS3159 **Poster Session (Board #144b), Sat, 8:00 AM-11:00 AM**

Express study: A trial in progress exploring the association between low level of genomic alteration and exceptional and unexpected response to targeted therapies in patients with solid tumors.

Olivia Le Saux, Antoine Italiano, Fabrice Andre, Thomas Filleron, Dominique Spaeth, Pierre-Etienne Heudel, Laurence Albiges, Thomas Denis Bachelot, Anthony Goncalves, Jean-Yves Pierga, Fabrice Barlesi, Valerie Boige, Celeste Lebbe, Laurent Mortier, Jean-Sebastien Frenel, Olivier Tredan, Marta Jimenez, François Legrand, Charles Ferte; CH Lyon Sud, Lyon, France; Institut Bergonié, Bordeaux, France; Institut Gustave Roussy, Villejuif, France; Department of Biostatistics, Institut Claudius Regaud-IUCT, Toulouse, France; ORACLE, Centre d'Oncologie de Gentilly, Gentilly, France; Centre Léon Bérard, Lyon, France; Medical Oncology, Gustave Roussy, Université Paris-Saclay, Villejuif, France; GINECO-Centre Léon Bérard, Lyon, France; Aix-Marseille Univ, CNRS, INSERM, Institut Paoli-Calmettes, Department of Medical Oncology, CRCM, Marseille, France; Institut Curie, Paris, France; Hospital Nord Service Oncologie, Marseille, France; Digestive Oncology, Gustave Roussy, Villejuif, France; APHP Dermatology and CIC, U976, Université de Paris, Hôpital Saint-Louis, Paris, France; Université Lille, Centre Hospitalier Régional Universitaire de Lille, Lille, France; GINECO-Institut de Cancerologie de l'Ouest, Centre René Gauducheau, Saint-Herblain, France; Département d'Oncologie Médicale, Centre Léon Bérard, Lyon, France; Unicancer, Paris, France; UNICANCER R&D, Paris, France; Institut Gustave Roussy, St Maur Des Fosses, France

Background: Molecular targeted agents (MTA) resulted in breakthroughs in selected niches. It is often assumed that tumor regression is consecutive to an oncogenic de-addiction effect. An emerging hypothesis suggests that genomic instability may be associated with poor response to MTA. Indeed, the accumulation of defects in multiple oncogenes or tumor suppressor genes may result in the activation of multiple oncogenic pathways. These multiple signaling would mechanically result in a limitation of the oncogenic de-addiction process. Another hypothesis, suggests that tumor heterogeneity could also be associated with poor outcome under MTA. Such heterogeneity could also result from the genomic instability, and be appraised by bioinformatic and functional approaches. In this study, we thought to investigate whether molecular profiles reflecting a low level of genomic alterations in genes causally implicated in oncogenesis could be associated with an exceptional response (ER) to MTA. **Methods:** This is an exploratory, multicenter, multicohort, prospective trial conducted in 264 adult patients, with advanced breast, lung, colorectal, ovarian, kidney cancers and melanoma, having presented an ER to an approved MTA. ER is defined using the definition chosen by the NCI which combines the three criteria: - complete or partial response, - lasting $>$ 6 months, - and not expected in $>$ 10% of the patients in this drug – organ situation. The primary objective is to assess whether ER can be associated with a low level of genomic instability in the tumor. Low genomic instability is defined by the presence of less than the 5th quantile of genomic alterations (mutations, amplifications, deletions) to be expected in the given tumor type as per TCGA database. For each tumor type, the null hypothesis H0: $\pi = 0.05$ will be tested, against the one-sided alternative hypothesis $\pi > 0.05$. For each of the 6 cohorts, a sample size of 44 patients is necessary to achieve 80% power at $\pi = 15$ with a one-sided level 5% test. Patients presenting an ER will be identified retrospectively, in a nationwide manner, then monthly reviewed and validated for inclusion by a panel of pathology experts. As of February 2019, 75 patients have been included. The identification of molecular traits associated with ER might serve the development of predictive classifiers for precision medicine. This study also represents a unique opportunity to better understand cancer biology. Clinical trial information: NCT02701907.

TPS3160 **Poster Session (Board #145a), Sat, 8:00 AM-11:00 AM**

SGNTV-001: Open label phase 2 study of tisotumab vedotin for locally advanced or metastatic disease in solid tumors.

David S. Hong, Omid S. Tehrani, Howard Safran, Conor Ernst Steuer, Jill Lacy, Matthew H. Taylor, Thomas J. George, Reshma A. Rangwala, Shweta Jain, Leonardo Viana Nicacio, May Thet Cho; The University of Texas MD Anderson Cancer Center, Houston, TX; Karmanos Cancer Inst/Wayne State Univ, Detroit, MI; Brown University Oncology Research Group, Providence, RI; Winship Cancer Institute of Emory University, Atlanta, GA; Smilow Cancer Hospital, Yale University, New Haven, CT; Oregon Health & Science University, Portland, OR; University of Florida Health Cancer Center, Gainesville, FL; Merck & Co., Inc., North Wales, PA; Seattle Genetics, Inc., Bothell, WA; Flatiron Health, New York, NY; Barnes Jewish Hospital, St. Louis, MO

Background: Tisotumab vedotin (TV) is being developed for patients with cervical cancer and other solid tumors known to express Tissue Factor (TF). Expression of TF on tumor cells has been associated with poor prognosis in several tumor types. Four tumor types were chosen for this study based on unmet medical need and TF expression. TV is an antibody-drug conjugate composed of a TF-targeted fully human monoclonal immunoglobulin G1 conjugated via a protease-cleavable valine citrulline linker to the drug monomethyl auristatin E (MMAE). TV-mediated delivery of MMAE drives antitumor activity through cytotoxic cell killing and has been shown to induce immunogenic cell death (ICD). In preclinical studies, TV treatment resulted in potent and long-lasting tumor regression in TF-expressing xenograft models derived from a variety of solid cancers, including patient-derived xenograft models with heterogeneous TF expression. TV has shown preliminary evidence of activity in heavily pretreated patients with many TF-expressing tumor types in the GEN701 phase 1 study. **Methods:** SGNTV-001 (innovaTV 207) is a global, open label, multicenter phase 2 trial designed to assess the safety, tolerability, and activity of TV for the treatment of solid tumors. (NCT03485209; EudraCT 2017-005076-26). Patients are currently enrolling in 4 cohorts: colorectal cancer (CRC), squamous non-small cell lung cancer (NSCLC), exocrine pancreatic adenocarcinoma, and squamous cell carcinoma of the head and neck (SCCHN). Patients must have measureable disease per RECIST v1.1 that has progressed despite standard of care systemic treatment in the locally advanced or metastatic setting (up to 3 prior lines for CRC, 2 for squamous NSCLC and SCCHN, and 1 for pancreatic adenocarcinoma) and have an ECOG score of 0 or 1. The primary endpoint is investigator-determined confirmed ORR as measured by RECIST v1.1. Secondary objectives include DOR, PFS, OS, DCR, and TTR, as well as safety and pharmacokinetic parameters. The first patient was enrolled in July 2018 and the study is currently enrolling across 16 sites in the US (as of January 2019) with additional sites opening in EU countries. Clinical trial information: NCT03485209.

TPS3161 **Poster Session (Board #145b), Sat, 8:00 AM-11:00 AM**

A phase I/II multiple expansion cohort trial of MRTX849 in patients with advanced solid tumors with *KRAS* G12C mutation.

Kyriakos P. Papadopoulos, Sai-Hong Ignatius Ou, Melissa Lynne Johnson, James Christensen, Karen Velastegui, Diane Potvin, Demiana Faltaos, Richard C. Chao; South Texas Accelerated Research Therapeutics, San Antonio, TX; Chao Family Comprehensive Cancer Center, University of California, Orange, CA; Sarah Cannon Research Institute, Nashville, TN; Mirati Therapeutics, Inc., San Diego, CA

Background: RAS proteins are part of the family of small GTPases which regulate intracellular signaling pathways responsible for cell growth, migration, survival and differentiation. Oncogenic point mutations in RAS in codons 12, 13, and 61 occur in up to one-third of all human cancers and result in constitutive activation of RAS signaling, playing a key role in uncontrolled cellular growth and malignant transformation. Mutant $KRAS^{G12C}$ in particular comprises approximately 14% of lung adenocarcinoma and 4% of colon adenocarcinoma, and less commonly in certain other types of cancer. For decades, KRAS was considered undruggable due to its high affinity for GTP/GDP and the lack of a clear binding pocket. Recent discoveries have enabled the development of compounds, including MRTX849, that covalently bind to $KRAS^{G12C}$ at the cysteine at residue 12, lock the protein in its inactive GDP-bound conformation, and inhibit KRAS-dependent signal transduction. MRTX849 is a potent, orally-available, mutation-selective small molecule covalent inhibitor of $KRAS^{G12C}$. MRTX849 inhibits $KRAS^{G12C}$ signaling in cell lines harboring this mutation, and results in tumor regression in a broad spectrum of $KRAS^{G12C}$ animal models. **Methods:** This multi-center, Phase 1/2, multiple expansion cohort trial evaluates the safety, pharmacokinetics (PK), metabolites, pharmacodynamics, and clinical activity of MRTX849 in patients with advanced solid tumor malignancies with a *KRAS* (p.G12C) mutation. The study starts with an evaluation of dose and regimen of MRTX849 using a combination of the accelerated titration and modified toxicity probability interval designs, with MRTX849 initially administered once daily in a continuous regimen expressed in 3-week cycles. As potentially viable regimens are identified, Phase 1b expansion cohorts will be opened to provide greater safety and PK data for determination of the recommended Phase 2 dose (RP2D) and regimen. In Phase 2, separate cohorts of patients by histological diagnosis, including non-small cell lung cancer, colorectal, and other solid tumors, will be enrolled and evaluated for clinical activity using a predictive probability design. The study is open for enrollment, and recruitment is ongoing. Clinical trial information: NCT03785249.

TPS3162 **Poster Session (Board #146a), Sat, 8:00 AM-11:00 AM**

A phase I study of BOS172738 in patients with advanced solid tumors with RET gene alterations including non-small cell lung cancer and medullary thyroid cancer.

Patrick Schoffski, Philippe Georges Aftimos, Christophe Massard, Antoine Italiano, Christiane Jungels, Karen Andreas, Mitchell Keegan, Peter T.C. Ho; UZ Leuven, Leuven, Belgium; Institut Jules Bordet, Brussels, Belgium; Institut Gustave Roussy, Villejuif, France; Institut Bergonié, Bordeaux, France; Institut Jules Bordet, Unversité Libre de Bruxelles, Brussels, Belgium; Boston Pharmaceuticals, Cambridge, MA

Background: RET gene alterations (mutations and fusions) leading to constitutive kinase activity have been identified in various tumor types including non-small cell lung cancer (NSCLC), medullary thyroid (MTC), colon, breast and ovarian cancer. The current generation of multi-kinase inhibitors approved for treatment of such tumors, do not selectively target RET and exhibit significant off-target activity especially against vascular endothelial growth factor receptor 2 (VEGFR2), resulting in dose-limiting toxicities that prevent the full inhibition of RET in those tumors. Recently, early clinical data from a class of more selective RET inhibitors have shown promising results with a more favorable safety profile in patients with RET alterations. BOS172738 is a novel RET inhibitor with nanomolar potency against RET and approximately 300-fold selectivity against VEGFR2. This phase 1 study is assessing the safety and tolerability of BOS172738 in patients with advanced solid tumors with RET alterations. **Methods:** NCT03780517 is a phase 1, open label, multicenter, dose escalation trial to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of BOS172738, an orally dosed RET kinase inhibitor, in patients with advanced solid tumors with RET gene alterations. RET gene alteration status will be assessed locally but confirmed centrally. The study is comprised of 2 parts: in Part A (dose escalation), patients with advanced solid tumors with RET gene alterations will receive BOS172738 orally once daily in each 28-day cycle. Select patients in Part A are eligible for intrapatient dose escalation. On establishing the recommended phase 2 dose (RP2D), Part B (expansion) will enroll up to an additional 60 patients to 1 of 3 tumor type-specific cohorts. The 3 expansion cohorts will each consist of up to 20 advanced cancer patients with: 1) RET gene-fusion NSCLC; 2) RET gene-mutant MTC; and 3) other RET gene-altered advanced tumors or NSCLC/MTC with prior specific RET gene-targeted therapy. Patients in expansion cohorts will receive BOS172738 daily at the RP2D until disease progression or other discontinuation criteria have been met. The study is currently open to enrollment globally with the first patient entered in 01/2019. Clinical trial information: NCT03780517.

TPS3163 **Poster Session (Board #146b), Sat, 8:00 AM-11:00 AM**

A phase I dose-escalation and immune biomarker study of intravenous FF-10832, liposomal gemcitabine, in patients with advanced solid tumors.

Erkut Hasan Borazanci, Gerald Steven Falchook, Atif Abbas, Catherine A. Wheeler, Gary Maier, Mary Johansen, Paula Sedivy, Ruth Ann Subach, Shiraj Sen, Suzanne Fields Jones, Tadaaki Ioroi, Takeshi Matsumoto, Takeaki Suzuki, Timothy Madden, Erika Paige Hamilton; HonorHealth Research Institute, Scottsdale, AZ; Sarah Cannon Research Institute, Denver, CO; FUJIFILM Pharmaceuticals U.S.A., Inc, Cambridge, MA; FUJIFILM Pharmaceuticals U.S.A., Inc., Cambridge, MA; FUJIFILM Pharmaceuticals, Cambridge, MA; Sarah Cannon Research Institute, Nashville, TN; FUJIFILM Corporation, Minato-Ku, Tokyo, Japan; FUJIFILM Pharmaceuticals U.S.A., Inc, Brookline, MA; Tennessee Oncology, PLLC and Sarah Cannon Research Institute, Nashville, TN

Background: FF-10832 (832) is a liposomal formulation of gemcitabine (GEM) that demonstrates a prolonged half-life and preferential uptake in tumor vs normal tissues and marrow in pre-clinical models. Macrophage uptake has been shown in the tumor microenvironment (TME), with subsequent GEM release in tumor cells. This relative selectivity and anti-tumor immunological changes observed in the TME may lead to decreased toxicity and increased efficacy compared to GEM. Ferumoxytol (FMX) may be a surrogate for nanoparticle penetration into tissue and is being examined as a potential correlate for activity. **Methods:** This ongoing Phase 1, 3+3 dose-escalation study of 832 will determine the safety profile, maximum tolerated dose, dose-limiting toxicities (DLT) and recommended Phase 2 dose, and will be followed by expansion. Enrollment of up to 60 patients (pts) with advanced solid tumors is planned. Pre-treatment (tx) FMX MRI scans are performed, followed by 832 administration on Days 1 &15 of each 28-day cycle until disease progression or unacceptable toxicity. In addition to standard biomarker and imaging evaluations, change in macrophage polarity, myeloid-derived suppressor cell (MDSC) and regulatory T cell populations are being investigatedin peripheral blood and tumor tissue. Clinical trial information: NCT03440450.

TPS3164 **Poster Session (Board #147a), Sat, 8:00 AM-11:00 AM**

Phase I study of procaspase activating compound -1 (PAC-1) in combination with temozolomide (TMZ) for the treatment of recurrent malignant glioma.

Martin Kelly Nicholas, Matthias Holdhoff, Richard A. Peterson, Oana Cristina Danciu, Theodore M. Tarasow, Paul J. Hergenrother, Arkadiusz Z. Dudek; University of Illinois at Chicago, Chicago, IL; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Health Partners, St. Paul, MN; Vanquish Oncology Inc, Champaign, IL; Health Partners Cancer Care Center, St. Paul, MN

Background: The caspase family of cysteine proteases play key roles in the initiation and execution of apoptosis. The activation of procaspase-3 to caspase-3 is critical in both the intrinsic and extrinsic apoptotic cascades. Procaspase-3 levels are elevated in many cancers, including glioblastoma (GBM). As a result, caspase-3 levels are abnormally low in these tumors; thus they avoid apoptosis. PAC-1 is a small molecule that directly activates procaspase-3 and induces apoptosis of cancer cells. PAC-1 has activity against a wide range of cancer cell lines, and in animal models of cancer. PAC-1 crosses the blood brain barrier and has been shown to synergize with TMZ in both canine malignant glioma and meningioma that arise spontaneously. **Methods:** This Phase I dose escalation study uses a modified- Fibonacci 3+3 design to determine the MTD of PAC-1 when combined with TMZ in patients with recurrent malignant gliomas: anaplastic astrocytoma (AA) and GBM (open to enrollment). Here, we focus on component 2 of the study. Primary objectives: to establish MTD of PAC-1 when combined with a fixed dose of TMZ, tolerability, and toxicity using CTCAE v.4. Secondary and correlative objectives: pharmacokinetics, pharmacodynamics, preliminary anti-tumor activity correlation with procaspase-3 expression in tumor tissue, radiographic response using the Response Assessment in Neuro-Oncology (RANO) criteria, and neurocognitive function using a validated test battery. Inclusion criteria: diagnosis of recurrent high grade glioma (AA or GBM), ECOG PS 0-2, adequate organ function. Exclusion criteria: received prior cytotoxic therapy in the last 3-6 weeks (duration based on prior therapy) or uncontrolled chronic illness. Administration and design, Component 2: PAC-1, orally administered, is dosed at 375-650 mg daily (up to 3 dose levels) on days 1-21 of each 28-day cycle. A fixed dose of TMZ, (150 mg/m2), is administered orally, days 8 -12 of each cycle. The study is currently enrolling patients for Component 2. Clinical trial information: NCT02355535.

TPS3165 **Poster Session (Board #147b), Sat, 8:00 AM-11:00 AM**

A window of opportunity trial of atorvastatin in p53-mutant and p53 wild type malignancies.

Mohammad Telfah, Tomoo Iwakuma, Andres Bur, Lisa Shnayder, Terry Tsue, Mazin Mazin Al-Kasspooles, John Ashcraft, Benjamin Martin, Raed Moh'd Taiseer Al-Rajabi, Anup Kasi, Qamar J. Khan, Tara L. Lin, Anwaar Saeed, Stephen K. Williamson, Prabhakar Chalise, Andrew K. Godwin, Greg Reed, Sufi Thomas, Takefumi Komiya, Joaquina Celebre Baranda; University of Kansas Cancer Center, Westwood, KS; University of Kansas Medical Center, Kansas City, KS; Univ of Kansas Cancer Hosp, Westwoo, KS; UT Health Science Center, San Antonio, TX; University of Kansas Cancer Center, Kansas City, KS; Fox Chase Cancer Center, Philadelphia, PA; University of Kansas, Kansas City, KS; Parkview Cancer Institute, Fort Wayne, IN; University of Kansas Cancer Center, Fairway, KS

Background: Mutations in p53 contribute to tumor progression. A rational approach is to destabilize mutant (m) p53. The group at the University of Kansas Cancer Center screened compounds that suppress m p53 in a preclinical model. Luciferase-based reporter assay identified statins as suppressors of m p53 expression. In vitro validation assay demonstrated atorvastatin (A) suppressed m p53 level and cell growth selectively; and depletion of mevalonic acid lead to degradation of m p53. These effects were limited to mutations in the conformation of p53, while wild-type and DNA contact mutations were not as sensitive to statin-induced degradation of p53. M p53 xenograft model confirmed that A could suppress tumor growth at a concentration that can decrease LDL level. The primary objective of this trial is to determine if A decreases the level of conformational m p53. The secondary objective is to assess the effects of A on Ki-67 and caspase-3 in conformational m p53 tumors. **Methods:** This is an open-label, window of opportunity pilot trial to see if A given for 1 to 4 weeks at a dose of 80 mg/day is sufficient to reduce the levels of conformational m p53 in the tumor tissues. Subjects with new diagnosis of malignancy with a planned surgical therapy, and subjects with previously treated AML, in between treatment regimens, are eligible. Tissues from solid tumors, and bone marrow or peripheral blood samples from AML will be used to screen for m p53 by immunohistochemistry (IHC). Subjects will receive A at 80 mg/day po for 1 to 4 weeks. Pharmacokinetics at pre-dose and 1-hour post-dose on Day 1 and on the day of surgery will be done. Mutational analysis using exome sequencing technique will be done on m p53. Using IHC, the amount of p53 in pre-treatment and post-treatment samples will be measured and compared simultaneously. The levels of Ki67 and caspace-3 will be tested and compared between pre-treatment and post-treatment samples in subjects with conformational m p53, between conformational and non-conformational m p53, and in wild-type p53 tumors. The trial is actively enrolling subjects. The results of this trial will determine further investigations on the role of atorvastatin in tumors with p53 mutations in a placebo-controlled, randomized trial. Clinical trial information: NCT03560882.

TPS3166 **Poster Session (Board #148a), Sat, 8:00 AM-11:00 AM**

A phase Ia/Ib, open label, multicenter, dose-escalation study of BI 907828 (MDM2-p53 antagonist) in adult patients with advanced or metastatic solid tumors.

Curtis Robert Chong, Todd Michael Bauer, Scott Andrew Laurie, Manish R. Patel, Noboru Yamamoto, Teffany Davenport, Junxian Geng, Neil Gibson, Markus P. Vallaster, Patricia LoRusso; Memorial Sloan Kettering Cancer Center, New York, NY; Sarah Cannon Cancer Research Institute/Tennessee Oncology, PLLC, Nashville, TN; The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada; Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; National Cancer Center Hospital, Tokyo, Japan; Boehringer-Ingelheim, Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT; Boehringer Ingelheim, Biberach an Der Riß, Germany; Boehringer Ingelheim Pharmaceuticals, Cambridge, MA; Yale Cancer Center, Yale University, New Haven, CT

Background: Inactivation of tumor protein 53 (TP53) is a central mechanism of tumors to promote survival and proliferation. The murine double minute 2 (*MDM2*) oncogene is the primary cellular negative regulator of TP53. Small molecule inhibitors of the MDM2-p53 interaction are currently being evaluated in clinical trials as new anti-cancer drugs, and clinical data published to date support the rationale to target MDM2-amplified tumors. BI 907828 is a potent MDM2-p53 antagonist that has shown efficacy in mouse models of human cancer. **Methods:** NCT03449381 is a Phase 1a/1b, open-label, multicenter, dose-escalation trial of BI 907828 in patients aged ≥18 years with advanced/metastatic solid tumors. Primary objectives of the Phase 1a (dose-escalation) part are to determine: the maximum tolerated dose (MTD) of BI 907828 based on dose-limiting toxicities (DLTs) during the first treatment cycle; the recommended dose for expansion (RDE); safety and tolerability. Patients in Arm A will receive one dose of BI 907828 every 21 days, and patients in Arm B one dose on Days 1 and 8, every 28 days. Secondary objectives include pharmacokinetics (PK), pharmacodynamics (PD) [GDF-15 induction in plasma], and preliminary anti-tumor activity. Primary endpoints are the number of patients with DLTs during the first treatment cycle, and the MTD. Phase 1a will include ≈50 evaluable patients with locally advanced or metastatic solid tumors with either a known TP53 wild type (wt) status or unknown TP53 status, regardless of MDM2 amplification status at the time of study entry. The main objectives of Phase 1b (expansion cohorts) are to assess efficacy, safety, and PK profiles at the RDE, and to determine the recommended dose for Phase 2. The primary endpoint is objective response, where best response is determined according to RECIST v1.1, or RANO criteria for patients with glioblastoma. Phase 1b will include up to 150 evaluable patients with TP53 wt tumors, assigned to four different cohorts, including non-squamous NSCLC, soft tissue sarcoma, glioblastoma, urothelial carcinoma, and solid tumors with brain metastases. As of 8th February 2019, 11 patients have been enrolled. Clinical trial information: NCT03449381.

TPS3167 **Poster Session (Board #148b), Sat, 8:00 AM-11:00 AM**

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

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Background: CDC7 is a protein with key roles in DNA replication initiation, the intra-S-phase checkpoint and M-phase completion. CDC7 is over-expressed in malignant compared to non-malignant cells, particularly those with *TP53* mutations, making it an attractive therapeutic target. LY3143921 hydrate is an orally administered ATP-competitive CDC7 inhibitor. Pre-clinical studies in colorectal cancer (CRC) and squamous non-small cell lung cancer (sqNSCLC) demonstrate favourable anti-cancer activity, particularly in squamous NSCLC and in CRC with *TP53* null and missense mutations. We hypothesise that solid tumours mutated in *TP53* will be sensitive to LY3143921 therapy. **Methods:** This is a first-in-human, phase I trial of LY3143921 hydrate (LY3143921) monotherapy given twice daily, continuously on a 21 day schedule until disease progression, patient (pt) withdrawal or unacceptable toxicity (NCT03096054). Eligible pts have histologically proven advanced/metastatic solid tumours for which no further standard therapy exists and WHO PS 0-1. Pts have regular clinical assessment and tumour imaging every 2 cycles. Phase Ia (dose escalation) is recruiting in a 3+3 design following 3 initial single patient cohorts (starting dose 30 mg OD), enriching for patients with malignancies associated with p53 mutations (CRC, sqNSCLC, high grade serous ovarian, squamous cell oesophageal, squamous cell head & neck, urothelial, pancreatic and triple negative breast cancer). Recruitment to cohort 6 (180 mg BD) is ongoing. On determination of the maximum tolerated dose (MTD) and recommended phase II dose and schedule (RP2D), 2 expansion cohorts ($\leq$ 25 pts each) of patients with CRC and sqNSCLC will be evaluated. Primary objectives: assess safety and tolerability of LY3143921, determine MTD and RP2D. Secondary objectives: evaluate preliminary efficacy and PK profile of LY3143921. All pts will have archival tumour tissue retrospectively analysed, while patients in phase Ib will also have pre- and on-treatment tumour biopsies. Evaluation of potential predictive and pharmacodynamic biomarkers including p53 mutations, phosphorylated MCM2, cyclin B1 and molecular subgroups of target tumours will be included. Clinical trial information: NCT03096054.

TPS3168 **Poster Session (Board #149a), Sat, 8:00 AM-11:00 AM**

A phase I, first-in-human, dose-escalation and dose-expansion study of the multitarget kinase inhibitor TT-00420 in patients with advanced solid tumors.

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Background: Multi-target kinase inhibitors have gained increasing attention in the past few years due to their capabilities of simultaneously targeting several hallmarks of cancer. Triple negative breast cancer (TNBC), the most aggressive type of breast cancer, is a highly heterogeneous disease composed of several subtypes with distinct genomic profiles and activating pathways. TT-00420 is a multi-target kinase inhibitor that targets Aurora A/B, receptor tyrosine kinases (RTKs) involved in angiogenesis, and other kinases involved in tumor-associated inflammation and immune escape. Preclinical studies have established signs of efficacy for TT-00420 in TNBC. Targets inhibited by TT-00420 are among the key dysregulated pathways directly involved in the tumorigenesis of TNBC. TT-00420 is efficacious against most subtypes of TNBC cell lines. This anti-TNBC activity is confirmed in both cell line derived xenograft (CDX) and patient derived xenograft (PDX) TNBC model *in vivo*, in which TT-00420 is active both as first-line and second-line treatment. TT-00420 demonstrated good oral bioavailability and pharmacokinetic properties in mice, rats and dogs, and revealed mechanism-related but manageable toxicities. The IND approval of TT-00420 was granted by the FDA on Sept. 27, 2018. **Methods:** TT420X2101 is an open-label, first-in-human, multicenter, phase I study including a dose escalation portion in adult patients with advanced solid tumors, followed by dose expansion in two parallel cohorts, TNBC cohort (N=22) and selected advanced tumor (SAT) cohort (N=22). Adverse events will be evaluated per CTCAE v5.0 criteria, and tumor responses will be evaluated per RECIST v1.1 criteria. Patients aged 18-75 with measurable target lesion(s) at baseline and ECOG status of 0 or 1 will be enrolled. Patients are treated with a single daily oral administration of TT-00420 continuously for a 28-day cycle. Dose escalation is driven by Bayesian modeling with over-dose control. Approximately 66 patients are expected to be enrolled and treated in this study. Primary endpoint is to evaluate dose limiting toxicity (DLT) and identify maximum tolerate dose (MTD), if feasible, or establish recommended dose for Dose Expansion. Preliminary efficacy and PK profile will be evaluated as well. Enrollment is currently ongoing. Clinical trial information: NCT03654547.

TPS3169 **Poster Session (Board #149b), Sat, 8:00 AM-11:00 AM**

Phase 1, open-label, dose-escalation study of M3814 + avelumab ± radiotherapy (RT) in patients (pts) with advanced solid tumors.

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Background: DNA-dependent protein kinase (DNA-PK) regulates a key DNA damage response (DDR) pathway for double-strand break (DSB) repair. DNA-PK inhibition augments DNA DSB damage generated by many antitumor therapies, including RT. DNA damage and repair impact the interaction of tumors with the immune system; combining immune checkpoint inhibitors (CPIs) with RT + DDR-targeted agents may modulate the tumor immune microenvironment, enhancing responsiveness to CPIs. M3814 (small molecule selective DNA-PK inhibitor) has demonstrated monotherapy activity in several tumor cell lines, and M3814 + RT combined with avelumab (programmed death ligand 1 mAb) significantly delayed tumor growth vs either agent alone + RT in MC38 syngrafts. This study will evaluate the clinical utility of M3814 combined with avelumab ± RT in pts with advanced solid tumors.
Methods: NCT03724890 is a 2-part first-in-man study in adult pts with advanced or metastatic solid tumors. Part A is enrolling pts with measurable/evaluable solid tumors (RECIST v1.1); Part B will enrol pts with primary or metastatic tumor(s) in the lung which is/are amenable to be irradiated. In Part A, M3814 will be given orally twice daily. In Part B, M3814 + TRT will be given once daily, 5 days/wk for 2 wk. In both parts, pts will receive avelumab iv once every 2 wk from Day 1 until disease progression/unacceptable toxicity. Part B will initiate once the Safety Monitoring Committee declares the first dose level of Part A to have acceptable safety/tolerability. Primary objectives are to define the recommended Phase 2 dose (RP2D) of M3814 when combined with avelumab (Part A) and with avelumab + TRT (Part B) via dose-limiting toxicities (DLTs) occurring during the first 3/4 (Part A/B) wk of treatment. Secondary objectives include safety/tolerability, pharmacokinetics, immunogenicity, preliminary antitumor activity (BOR, PFS, OS). Sample size for each part depends on the number of DLTs/dose levels for M3814; dose escalation will be based on a Bayesian logistic regression model with overdose control. Part A aims to include 6–24 pts (≤4 dose levels), Part B 6–18 pts (≤3 dose levels). Recruitment began in Dec 2018. Clinical trial information: NCT03724890.

TPS3170 **Poster Session (Board #150a), Sat, 8:00 AM-11:00 AM**

Leeomic: A comprehensive proteomic analysis towards discovery of predictive patterns of protein expression to ribociclib sensitivity and resistance—A compLEEment-1 Canadian correlative sub-study.

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Background: Despite developments in the treatment of advanced hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer, primary or acquired resistance eventually occurs in all cases and there is still very limited understanding of the mechanisms of resistance to therapy. LEEOMIC is a sub-study of the main CompLEEment-1 (N = 3255 patients enrolled, CLEE011A2404 v03) trial, an open-label, phase 3b study evaluating ribociclib + letrozole as first-line therapy in an expanded advanced breast cancer patient population which recruited over 250 Canadian patients. The purpose of this Canadian correlative sample collection study is to explore the mechanisms of response and resistance to ribociclib in combination with letrozole through proteomic and ctDNA analysis. **Methods:** The British Columbia Cancer Research Centre team developed a novel and optimized MS/MS platform called SP3-Clinical Tissue Proteomics (SP3-CTP) to perform in-depth proteome profiling ($>$ 8,000 proteins) from formalin fixed paraffin embedded (FFPE) material (10-micron section). SP3-CTP analysis of the proteome of the study patients who did not achieve clinical benefit (primary resistance: progression within 3 months of treatment) will be compared to the proteome of the sub-group of prolonged responders (time to progression of 22 months or more) in order to identify biomarkers that can predict response or de-novo resistance to therapy. Archival tumor biopsies (primary or metastatic) collected from the study will be submitted for proteomic analysis to identify proteomic expression levels that may serve as predictor of response. It is anticipated that over 150 samples will be collected. If available, blood samples taken at time of progression or end of treatment will also be analyzed for ctDNA for genetic profiling and to study if there is any correlation between genetic mutations and response or resistance to therapy. Currently, both tissue and blood samples are being collected and no analysis has been conducted thus far. Clinical trial information: NCT03613220.

TPS3171 **Poster Session (Board #150b), Sat, 8:00 AM-11:00 AM**

Prospective observational study for treatment resistance-related gene screening using plasma circulating tumor DNA in the third generation EGFR TKI osimertinib therapy elucidator.

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Background: Osimertinib (Osi) is a third-generation epidermal growth factor receptor (EGFR) – -tyrosine kinase inhibitor (TKI) that potently and selectively inhibits both EGFR-TKI sensitizing and EGFR T790M resistance mutations (mu). O showed superior efficacy compared with first generation EGFR-TKIs in patients (pts) with previously untreated advanced NSCLC harboring sensitizing EGFR mu in the prior phase III trial. Therefore, Osi is one of the most important standard therapies in EGFR mu positive pts. However, there are few reports about mechanisms of Osi resistance as the first line (1L) EGFR-TKI. Understanding of 1L Osi resistance mechanisms is essential to conduct future therapeutic strategy for EGFR mu NSCLC pts. We planned the analysis of the resistant mechanism by the ultra-sensitive next-generation sequence (NGS) using the circulating tumor (ct) DNA to clarify a resistant mechanism of 1L Osi. **Methods:** We prospectively collect ctDNA samples from EGFR mu positive NSCLC who will be treated with Osi as 1L. Planned enrollment is 180 cases, we estimate an analysis case at exacerbation to be 120 cases in a registration period and the observation period of for each two years. ctDNA samples are collected at treatment initiation, 3 and 12 months after Osi treatment, and disease progression. We will analyze the mechanisms of 1L Osi by the ultra-sensitive NGS using ctDNA. The key inclusion criteria are histologically or cytologically proven NSCLC, EGFR mu positive, pts treated with Osi as 1L, and written informed consent. The key exclusion criteria are patients who were deemed unsuitable for participation by an attending physician due to other conditions. The primary outcome is to clarify the incidence and ratio of Osi resistance by the ultra-sensitive NGS method using ctDNA at treatment initiation and progression disease. And key secondary endpoint is to examine how the detection quantity of the Osi resistance association mu in ctDNA at treatment initiation influences progressive disease. Clinical trial information: jRCTs031180051.