2500 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

A first-in-human phase I study of the CDK4/6 inhibitor, LY2835219, for patients with advanced cancer.

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Background: Cyclin dependent kinases 4 and 6 (CDK4/6) act with D-type cyclins to inactivate the retinoblastoma (Rb) tumor suppressor protein and enable cell cycle progression from G1 to S phase. LY2835219 is a selective inhibitor of CDK4/6 that shows antitumor activity in preclinical models of human cancer and also distributes efficiently to the brain. We performed a phase 1 study to evaluate safety, pharmacokinetics, pharmacodynamics, and antitumor activity of LY2835219. **Methods:** 3+3 dose escalation was followed by expansions in 5 tumor types (brain metastases permitted): non-small cell lung cancer (NSCLC), glioblastoma, breast cancer, melanoma, and colorectal cancer. LY2835219 was taken orally every 12 or 24 hours (in escalation) and every 12 hours (in expansions) on days 1-28 of a 28-day cycle. **Results:** 55 patients (pts) received LY2835219. In escalation, 33 pts received LY2835219 on 1 of 2 schedules: 50, 100, 150, 225 mg every 24 hours (Q24H) or 75, 100, 150, 200, 275 mg every 12 hours (Q12H). On the Q24H schedule, the maximum tolerated dose (MTD) was not identified. On the Q12H schedule, the MTD was 200mg Q12H with dose limiting toxicity of G3 fatigue at 200 mg (1/6 evaluable pts) and 275 mg (2/3 evaluable pts). At 200mg Q12H, the mean C_{max} and $AUC_{0\text{-}24hr}$ at steady state were 285 ng/mL and 5502 ng-hr/ml, respectively. In skin, LY2835219 induced pharmacodynamic inhibition of both Rb phosphorylation and topoisomerase IIα expression. In the ongoing expansions, 22 pts have received LY2835219. Across the study, the most common related adverse events were diarrhea (52%, including 5% G3), nausea (30%, 4% G3), fatigue (21%, 7% G3), vomiting (18%, 2% G3), and neutropenia (16%, 7% G3). 15 pts have reached $\geq$4 cycles for stable disease or better with 3 pts achieving 8, 16, and 26 cycles. One pt with ovarian cancer had a durable CA-125 response with $>$50% decrease for 16 cycles. One pt with KRAS mutant NSCLC had a 27% decrease by RECIST. One pt with $CDKN2A^{-/-}$ NRAS mutant melanoma had a confirmed partial response. Early clinical activity has been observed in ovarian cancer, NSCLC, breast cancer, and melanoma. **Conclusions:** LY2835219 shows acceptable safety and early clinical activity as a single agent for patients with advanced cancer. Clinical trial information: NCT01394016.

A phase I first-in-human study of PRI-724 in patients (pts) with advanced solid tumors.

Anthony B. El-Khoueiry, Yan Ning, Dongyun Yang, Sarah Cole, Michael Kahn, Marwan Zoghbi, Jennifer Berg, Masamoto Fujimori, Tetsuhi Inada, Hiroyuki Kouji, Heinz-Josef Lenz; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; University of Southern California, Los Angeles, CA; PRISM Pharma Co, Yokohama, Japan

Background: PRI-724 is a first-in-class modulator of Wnt signaling that inhibits the CREB binding protein and β-catenin interaction. In pre-clinical models, PRI-724 (active metabolite C82) increases p300/β-catenin binding and promotes stem cell differentiation thereby eliminating tumor initiating cells and increasing sensitivity to cytotoxic or targeted drugs. **Methods:** PRI-724 was given as a continuous infusion X 7 days q 2 wks. There was an initial accelerated dose escalation with one pt per dose level and a plan to revert to a 3+3 escalation after 640 mg/m2 unless a dose limiting toxicity (DLT) or 2 moderate toxicities occurred earlier. Eligibility criteria: adequate bone marrow function, AST/ALT <5XULN, total bilirubin<1.5 mg/dL. Survivin/BIRC5 expression was measured by immunomagnetic RT-PCR on circulating tumor cells (CTC). **Results:** 18 pts treated; median age: 53 years (38-71); 12 (67%) males; median number of prior therapies: 3 (1-5). There was one DLT of grade 3 hyperbilirubinemia. Grade 3 AEs were limited to hyperbilirubinemia in 2 pts, one of which did not meet DLT criteria. Grade 2 AEs were: diarrhea (2pts; 11%), bilirubin elevation (2 pts; 11%), hypophosphatemia (2pts; 11%), nausea (1pt; 6%), fatigue (1pt; 6%), anorexia (1pt; 6%), thrombocytopenia (1 pt; 6%) and alkaline phosphatase elevation (1pt; 6%). There was no MTD at the doses tested. The recommended phase 2 dose was 905 mg/m2 based on the incidence of AEs at 1280 mg/m2 and the plateau in pK parameters. The median Cmax and AUC 0-t for C-82 at 905 mg/m2/day were 887 ng/mL and 262787 h*ng/mL. Median elimination T ½ was 7.35 h. 3 pts with colon cancer had stable disease for 8, 10 and 12 weeks. Survivin expression in CTCs decreased in 72% of pts on C1D8 and 61% on C2D8. There was an inverse relationship between C82 plasma concentration and survivin expression on C1D8 (Spearman correlation coefficient $r = -0.72$; $p=0.001$). **Conclusions:** PRI-724 had an acceptable toxicity profile. Downregulation of survivin expression in CTCs may serve as a pharmacodynamic marker of drug-on-target effect. Studies combining PRI-724 with chemotherapy are ongoing. Clinical trial information: NCT01302405.

Dose mg/m²/day	No. of pts	No. of evaluable for dose escalation	DLT
40	1	1	0
80	1	1	0
160	1	1	0
320	1	1	0
640	1	1	0
905	6	6	0
1,280	7	3	1 hyperbilirubinemia

Phase I study of REGN421 (R)/SAR153192, a fully-human delta-like ligand 4 (Dll4) monoclonal antibody (mAb), in patients with advanced solid tumors.

Antonio Jimeno, Patricia LoRusso, Robert Matthew Strother, Jennifer Robinson Diamond, Leah Plato, Anne Younger, Wells A. Messersmith, Muaiad Kittaneh, Doug Sawyer, Lieve Adriaens, Liming Liu, Richard J. Kao, A Thomas DiCioccio, Carrie M. Brownstein, Israel Lowy, Pamela Trail, E. Gabriela Chiorean; University of Colorado, Denver, Aurora, CO; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Indiana University School of Medicine, Indianapolis, IN; Division of Medical Oncology, University of Colorado Denver, Aurora, CO; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; University of Colorado Cancer Center, Aurora, CO; Vanderbilt University, Nashville, TN; Regeneron Pharmaceuticals, Inc., Tarrytown, NY; University of Washington, Indianapolis, IN

Background: Dll4, a Notch receptor ligand, may have a role in tumor angiogenesis and is an emerging anticancer target. REGN421 (R) is a fully human IgG_1mAb that binds human Dll4 and disrupts Notch-mediated signaling. **Methods:** Primary objectives of the dose escalation (3+3 design) trial were to determine safety and a recommended phase II dose (RP2D) of R in patients (pts) with advanced cancer. R was given IV at doses of 0.25, 0.5, 1, 2 and 4mg/kg every 3 weeks (Q3W) or 0.75, 1, 1.5, and 3mg/kg every 2 weeks (Q2W). Secondary objectives were PK, immunogenicity, and antitumor activity. **Results:** 53 pts (M/F=22/31, ECOG 0/1=18/35) were enrolled; 31 pts were treated Q3W at doses of 0.25 - 4 mg/kg; 22 pts were treated Q2W at doses of 0.75 - 3 mg/kg. Two DLTs occurred: Grade 3 (Gr3) nausea (0.5mg/kg Q3W) and Gr3 abdominal pain (1 mg/kg Q2W). A maximum tolerated dose was not reached on either schedule. Grade 3/4 AEs occurred in 29 pts; nausea, abdominal pain, dyspnea, hypoxia, and hypertension (HTN) were reported in $\geq$ 5%. Most frequent treatment related AEs were fatigue (30%), headache (26%), HTN (26%), and nausea (15%). Six treatment related SAEs (all reversed off treatment) were reported in 4 patients: BNP increase (0.25mg/kg, Gr1), troponin I increase (4mg/kg, Gr3), right ventricular dysfunction (1.5mg/kg, Gr3), left ventricular dysfunction (3mg/kg, Gr3) and 2 events of pulmonary HTN (1.5mg/kg, Gr 3, and 3mg/kg Gr3). Laboratory abnormalities ($\geq$ Gr3) were neutropenia (3) and anemia (2), and elevated ALP (7), ALT (3), bilirubin (3), AST (2), and decreased albumin (1). Anti-tumor activity included 2 PRs (NSCLC BAL-type with a beta-catenin mutation and ovarian cancer [OvCa]), and 16 pts with SD (3 pts had SD $>$ 6 months). Two of 8 pts with OvCa had CA125 responses. R had non-linear target-mediated PK without accumulation. The half-life of R at 3mg/kg Q2W was 7 days. No immunogenicity was observed. **Conclusions:** REGN421 had an acceptable safety profile, and RP2Ds of 4mg/kg Q3W and 3mg/kg Q2W. Responses and prolonged SD were noted in OvCa pts and other solid tumors. Dose escalation has concluded and disease specific expansion cohorts are ongoing. Clinical trial information: NCT00871559.

2503 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Phase I study of safety and pharmacokinetics (PK) of GDC-0917, an antagonist of inhibitor of apoptosis (IAP) proteins in patients (Pts) with refractory solid tumors or lymphoma.

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Background: GDCE0917 is a small molecule that triggers tumor cell apoptosis by selectively antagonizing IAP proteins. Preclinical studies demonstrated antitumor efficacy of GDC-0917 alone or in combination with chemotherapeutic agents. **Methods:** Oral GDC-0917 was given on Day (d) 1 followed by 2d off and a 2-week (w) on/ 1w off treatment (tx) schedule (21d cycle) starting d4. A modified continual reassessment method was used for dose escalation. Dose-limiting toxicity (DLT, assessed d1-24), PK, adverse events (AEs), pharmacodynamics (PD), and clinical activity were evaluated. **Results:** 42 pts of age 36-86 (median 60.5) were enrolled in 11 cohorts (5-600 mg) and received 1-15 cycles (median 2) of GDC-0917. One DLT, Grade (G) 3 fatigue, was observed at 450 mg. The maximum tolerated dose was not determined although plasma concentrations of preclinically defined IC90 were reached. The most frequent AEs were diarrhea, fatigue and nausea (26.2% each), vomiting (23.8%), and constipation (19%). The most frequent AEs reported as tx-related were mostly G1-2 and included fatigue and nausea (21.4% each), vomiting (14.3%), rash (11.9%) and pruritus (9.5%). AEs reported as tx-related that were $\geq$ G3 in $>$ 1 pt were elevated AST and ALT (2 pts, at 450 and 600 mg). AEs reported as tx-related that resulted in tx discontinuation were G3 fatigue, G2 QTc prolongation, G2 drug hypersensitivity, G2 pneumonitis (1 pt each), and G3 pruritus/G2 rash (same pt). GDC-0917 peak concentrations were observed 2-3h post dosing. Exposure was dose-proportional with a mean plasma elimination $t_{1/2}$of 4-8h and no apparent accumulation at steady state. Rapid down-modulation of cIAP1 was observed in PBMCs at all dose levels. Evaluation of tumor biopsies demonstrated decreases in cIAP1 (2 pts total, at 40 and 200 mg) and increases in activated caspase-3 and cPARP (1 pt at 200 mg). Two pts (4.8%) had a complete response (both unconfirmed, ovarian Ca and MALT lymphoma [PET]); 4 pts (9.5%) had stable disease for $\geq$ 3 months. **Conclusions:** GDC-0917 had a favorable safety, PK and PD profile in pts with advanced malignancies. These encouraging results support further clinical evaluation of this agent. Clinical trial information: NCT01226277.

2504 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

A phase I study of birinapant (TL32711) combined with multiple chemotherapies evaluating tolerability and clinical activity for solid tumor patients.

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Background: Birinapant (B) is a SMAC-mimetic that inhibits IAPs with excellent tolerability, drug exposure, target suppression and apoptotic pathway activation in clinical studies. Preclinical studies demonstrate potent anti-tumor synergy when B is combined with TNFa-inducing chemotherapies (CT). **Methods:** Escalating doses of B were combined with CT in a 5-arm 3+3 phase 1 study for adults (pts) with relapsed/refractory solid tumors to determine maximum tolerated dose (MTD), pharmacokinetics (PK), and efficacy to identify indications for further studies. The arms included carboplatin/paclitaxel (CP), irinotecan (I), docetaxel (D), gemcitabine (G), and liposomal doxorubicin (LD). **Results:** 124 pts were treated with B at doses of 2.8 to 47 mg/m^2. The MTD of B for each arm was CP (47 mg/m^2); I (22 mg/m^2); D (47 mg/m^2). The proposed G regimen could not be administered in heavily pretreated pts and B could not be evaluated for dose escalation; this arm was discontinued and no dose-limiting toxicities (DLT) occurred. LD drug shortage prevented dose escalation for B $>$ 35mg/m^2 (MTD not reached). B did not limit CT administration for CP, I, D, LD, supporting tolerable combination of B with CT. B-associated toxicity of Bell's palsy (Grade 2) was considered a DLT and noted at higher dose levels for I, D, and LD, but not CP. This unusual reversible toxicity occurred during cycle 1 in 7 pts. Six of these pts continued therapy without recurrence. PK studies demonstrated no effect of B on CT. Except for CP, CT did not change the PK of B. CP increased plasma PK for B, possibly due to OATP1B3 transporter effects, but without increased B toxicities. 11 pts had a partial response, 61 pts had stable disease ($>$2 cycles, median 4.6 mo) and 37 pts had progressive disease as their best response, with clinical benefit (CR+PR+SD) of 58%. **Conclusions:** B can be combined with excellent tolerability with multiple CT at standard dosing. B plus CT demonstrated clinical benefit in many tumor types. Notable clinical activity occurred with I + B in pts who had failed prior I. These results support planning for further clinical studies of the I + B, and support the hypothesis for TNFa-mediated I + B synergy. Clinical trial information: NCT01188499.

2505 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

First-in-class, first-in-human phase I trial of KPT-330, a selective inhibitor of nuclear export (SINE) in patients (pts) with advanced solid tumors.

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Background: In cancers, the majority of tumor suppressor proteins (TSP) are transported out of the nucleus exclusively by Exportin 1 (XPO1/CRM1), rendering these TSPs non-functional. KPT-330 is a potent inhibitor of XPO1, and forces the nuclear retention and activation of $>$ 10 TSPs resulting in tumor cell death in vitro, in murine preclinical models and in dogs with spontaneous lymphomas. **Methods:** KPT-330 was administered orally for 10 doses in a 28-day cycle. Detailed pharmacokinetic (PK) and pharmacodynamic (PDn) analyses and serial tumor biopsies were performed. Response evaluation was done every 2 cycles (RECIST 1.1). All pts entering the study had documented progressive disease. **Results:** 23 pts (10 males; median age 62 yrs; ECOG PS 0/1: 5/18) received KPT-330 across 6 dose levels (3 to 30 mg/m^2). There has been no dose limiting toxicity. Nine drug related grade 3/4 adverse events (AEs) post cycle 1 were reported in 6 pts (neutropenia, thrombocytopenia, hyponatremia, increased ALT, fatigue, vomiting [n=2], nausea [n=2]). The most common grade 1/2 AEs were nausea (78%), fatigue (74%) and anorexia (74%). PK analysis demonstrated a fairly proportional increase in C_{max} and AUC with increasing dose, with no accumulation and without affecting half-life or clearance of KPT-330. At 30 mg/m^2, $AUC_{0\text{-last.}}$ (4375 ng*h/mL) was comparable to the anti tumor exposure observed in mice and dogs. T_{max} (~3 hrs) and $T_{1/2}$ (6-7 hrs) were consistent across doses. Significant increase (2-20x) in XPO1 mRNA levels (PDn marker) in circulating leukocytes was observed at all doses, with higher doses demonstrating higher levels of XPO1 mRNA induction. Analysis of tumor biopsies confirmed nuclear localization of TSPs (e.g. p53, FOXO3A, IκB) and apoptosis of cancer cells following KPT-330 administration. RECIST response was evaluable in 13 pts. Stable disease (SD) was noted in 9 pts, with 3 (colon, endocervical & endometrial stromal tumors) remaining with SD at 6+ months (dose levels 3 & 6 mg/m^2), as well as one minor response (colon). **Conclusions:** KPT-330 treatment is generally well tolerated, with favorable PK and PDn properties. Preliminary signals of clinical antitumor activity were observed. Clinical trial information: NCT01607905.

2506^ **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Phase I study of oral selective c-Met inhibitor EMD 1214063 in pts with advanced solid tumors.

Gerald Steven Falchook, David S. Hong, Hesham M. Amin, Siqing Fu, Sarina Anne Piha-Paul, Filip Janku, Vivek Subbiah, Aung Naing, Jennifer J. Wheler, Manfred B. Klevesath, Karola Köhler, Andreas Johne, Friedhelm Bladt, Razelle Kurzrock; Department of Investigational Cancer Therapeutics (Phase I Program), University of Texas MD Anderson Cancer Center, Houston, TX; Department of Hematopathology, University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Merck KGaA, Darmstadt, Germany; Premier Research Germany Ltd, Darmstadt, Germany

Background: To perform the first-in-human study of EMD 1214063, a highly selective, reversible, ATP-competitive c-Met inhibitor that causes growth inhibition and regression of hepatocyte growth factor-dependent and -independent tumors in preclinical models. **Methods:** Primary objective of this dose-escalation study (3+3 design) was to establish the EMD 1214063 MTD (NCT01014936). Secondary endpoints included safety, PK, antitumor effect, and pharmacodynamics (Pd). Eligible pts had advanced solid tumors not amenable to standard therapy. Pts received once daily (QD) oral EMD 1214063 on 1 of 3 regimens (all 21-d cycles): d 1–14 followed by 7-d rest (R1), continuous 3 times weekly (R2), or d 1–21 (R3). An optimized formulation (OF) was introduced in Aug 2011. **Results:** 100 pts were treated (R1:42; R2:41; R3:17). On the initial formulation, doses were escalated from 30–230 mg/d in R1, and 30–115 mg/d in R2. OF data are available for 30–400 mg/d in R1, 60–175 mg/d in R2, and up to 500 mg/d in R3. C_{max} and AUC increased with dose; OF showed higher bioavailability. 4 pts experienced DLTs: G4 lipase and G3 amylase increase (R1; 115 mg/d), G3 lipase increase (R2; 60 and 115 mg/d), and G3 nausea and vomiting (R2; 130 mg/d OF). Other G3 drug-related AEs included G3 peripheral edema (1 pt in R3, 300 mg/d OF). G2 drug-related AEs (R1-3) included fatigue (n=8), lipase increase (n=3), nausea (n=2), decreased appetite (n=2), vomiting (n=2), and neutropenia (n=2). 80% pts had no drug-related AE >G1. Pre- and on-treatment tumor biopsies showed inhibition of phospho-c-Met levels in 13/15 evaluable pts. 2 unconfirmed partial responses were observed (NPC and NSCLC). SD >4 mo was observed in 15 pts. 1 pt with sarcomatoid bladder cancer and multiple MET copies due to Chr 7 polysomy had SD for >32 mo. PK/Pd analysis suggested that 500 mg QD was sufficient for target inhibition, consistent with preclinical models. In the 500 mg QD cohort, which was expanded to 12 pts, no DLTs were observed. 500 mg QD was confirmed as the recommended phase 2 dose (RP2D). A formal MTD was not identified despite dose escalation beyond 500 mg. Dose escalation above 1000 mg is not anticipated. **Conclusions:** EMD 1214063 was safe and demonstrated antitumor activity. 500 mg QD was determined as the RP2D. Clinical trial information: NCT01014936.

2507 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

A phase I study of the safety and pharmacokinetics of DNIB0600A, an anti-NaPi2b antibody-drug-conjugate (ADC), in patients (pts) with non− small cell lung cancer (NSCLC) and platinum-resistant ovarian cancer (OC).

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Background: NaPi2b (*SLC34A2*) is a multi-transmembrane, sodium-dependent phosphate transporter expressed in non-squamous NSCLC and non-mucinous OC. DNIB0600A is an ADC consisting of a humanized IgG1 anti-NaPi2b monoclonal antibody and anti-mitotic agent, MMAE, that shows anti-proliferative activity in xenograft models. **Methods:** This study evaluated safety, pharmacokinetics, and pharmacodynamics of DNIB0600A (0.2-2.8 mg/kg) given every 3 weeks (q3w) to pts with NSCLC or OC. A traditional 3+3 design was used for dose escalation followed by expansion by disease at the recommended Phase 2 dose (RP2D). Tumor NaPi2b expression was evaluated in archival tissue. Anti-tumor activity was evaluated per RECIST 1.1. **Results:** As of 10 Dec 2012, 30 dose escalation pts have enrolled (16 NSCLC; 14 OC), median age 61 (range 45-78), PS 0-1, median number of prior regimens 5 (1-12), received a median of 3 (1-17) doses of DNIB0600A. No DLTs occurred at the maximum assessed dose of 2.8 mg/kg; enrollment in the expansion cohort at 2.4 mg/kg is ongoing. The most common related AEs regardless of Grade were fatigue (43%), decreased appetite (37%), nausea (30%), constipation, dysgeusia, vomiting, and peripheral neuropathy (each 17%), and diarrhea (13%). One pt at 1.8 mg/kg experienced a DLT (Grade 3 dyspnea), however, no additional DLTs occurred through the maximally administered dose of 2.8 mg/kg. Expansion at 2.4 mg/kg was selected based on totality of safety data. No accumulation of total antibody, free MMAE, or conjugated MMAE was observed. Exposure of each analyte was dose proportional. Approximately 70% of NSCLCs and 85% of OC expressed high levels (IHC 2+/3+) of NaPi2b. Of the 18 pts treated at dose levels 1.8-2.8 mg/kg (10 NSCLC; 8 OC) 3 pts had a confirmed partial response (PR) with response durations of 8.8+ (OC), 4.4+ (NSCLC), and 1.4+ (OC) months, censored at data cutoff, and 1 additional pt had an unconfirmed PR (OC). Dose expansion data will be presented. **Conclusions:** DNIB0600A administered q3w has an encouraging safety profile and evidence of anti-tumor activity in both NSCLC and OC. Further studies are planned. Clinical trial information: NCT01375842.

First-in-human phase I study of the liposomal RNAi therapeutic Atu027 in patients with advanced cancer.

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Background: Atu027 is a novel vascular stabilising, anti-metastatic, RNAi therapeutic, targeting systemic endothelial cell function and the tumor vasculature. Atu027 comprises a liposomal particle, containing an siRNA, which silences expression of the PKC pathway signalling molecule PKN3. Atu027 was previously shown to restrict tumor growth, local invasion and both, lymph node as well as pulmonary metastasis in mouse xenograft models. **Methods:** 34 patients with advanced cancer received 10 escalating doses of Atu027 without pre-medication as single and repeated i.v. infusions (qw2x4 per 28-d cycle) with a 3-wks dose intermission. Primary end points were safety, pharmacokinetics and -dynamics (biomarker identification). Response was monitored by CT/MR imaging at baseline, after treatment and at final follow-up (EoS) and was assessed according to RECIST. **Results:** Atu027 was well tolerated up to 0.336 mg/kg (around twice the predicted effective siRNA plasma levels). An MTD was not achieved. Around 50% of patients experienced disease stabilization according to RECIST. 8 patients had stable disease at EoS and 2 with neuroendocrine cancer had disease stabilization for 9 or 22 months. Partial regression of pulmonary metastasis and a regression of liver metastases were observed in subjects with neuroendocrine and breast cancer, respectively. An improved ECOG performance status was observed in patients of higher dose levels. Most AEs were low grade toxicities (1 or 2), including fatigue and increased lipase. Transient complement system activation was observed for certain factors. Area exposure levels of siRNA strands were dose-proportional and peaks were reached during 4 h-infusion. Of 102 plasma proteins assessed, sFLT1 (sVEGF-R1) was the most promising as a potential biomarker, with decreases from baseline in most pts from dose level 4-10 after treatment. **Conclusions:** Atu027 was well tolerated and there was suggestion of a clinically meaningful antitumor activity. In view of this further clinical trials can be initiated at a dose of up to 0.336 mg/kg and sFLT1 will be investigated as a potential biomarker. Clinical trial information: NCT00938574.

2509 **Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

Predictive value of phase I trials for safety and final approved dose in later trials: Analysis of 33,845 patients.

Denis Leonardo Fontes Jardim, Kenneth R. Hess, Patricia LoRusso, Razelle Kurzrock, David S. Hong; The University of Texas MD Anderson Cancer Center, Houston, TX; Karmanos Cancer Institute, Wayne State University, Detroit, MI; University of California, San Diego, San Diego, CA

Background: Phase I trials (Ph1) use data efficiently from a small number of patients (pts) to define a maximum tolerated dose (MTD) and the safety profile of new agents. It is unclear how well these trials perform in predicting the future approved dose of agents and in assuring the safety of pts in later trials. Here we compared data obtained from Ph1 and registration trials of the respective agents. **Methods:** We searched the US Food and Drug Administration (FDA) website for drugs approved in non-pediatric cancers between Jan. 1990 and Oct. 2012. Recommended phase II dose (R2PD), dose-limiting toxicities (DLTs) and grade (G) 3 and 4 adverse events from Ph1 were compared with doses and safety in later trials listed on updated package inserts. Proportions from independent groups were compared using the chi-squared test. Multiple logistic regression analysis adjusted these comparisons for potentially confounding factors. **Results:** A total of 78 Ph1 (3,499 pts) and 88 later trials (33,845 pts) were included. In 60% (n=50) of 84 matched trials in the dose comparison analysis, the dose from the later trial was the RP2D (often derived from the MTD) from a Ph1. In a multivariable analysis, Ph1 of oral drugs were more predictive of the final approved dose (78% adopting the RP2D oral vs. 43% IV drugs, p=0.011). Other Ph1 characteristics (number of pts, dose levels and tumor type) had no influence on the odds of adopting the RP2D. 55% of phase I DLTs were among the 4 most frequent high-grade events in later trials, with a higher frequency for DLTs of cytotoxic agents (p=0.061). Of the 525 clinically significant toxicities in later trials, 70% (n=369) were described in Ph1. There was a clear relationship (p=0.0032) between increasing the number of pts in the Ph1 (up to 60) and the ability to describe future clinically relevant side effects. Among 28,597 pts in later trials with available data the death rate that was possibly related to drug was 1.48%. **Conclusions:** Dosing based on Ph1 was associated with a low toxicity-related death rate on later trials. The ability to predict clinically significant toxicities correlates with the number of pts on the initial Ph1. However, the final dose in later trials was the exact RP2D of the Ph1 in only 60% of cases.

Characterization of the exposure-response relationship leading to recommendations for dosing optimization in a new drug application review.

Jun Yang, Nitin Mehrotra, Hong Zhao, Ruthann Marie Giusti, Suzanne Demko, Patricia Keegan, Brian Booth, Nam Atiqur Rahman; U.S. Food and Drug Administration, Silver Spring, MD

Background: On November 29 2012, the U. S. FDA approved cabozantinib (COMETRIQ) for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). Drug-related toxicity was common at a dose of 140 mg once daily across Phase 1 to Phase 3 trials submitted in this NDA. During the review of this application, these safety findings raised the question whether the optimal cabozantinib dose was selected for the treatment of MTC. Exposure-response (E-R) analyses were performed to assess the appropriateness of the cabozantinib dose. **Methods:** The data were obtained from an international, multi-center, randomized (2:1), placebo-controlled trial enrolling 330 patients with metastatic MTC. To account for variable exposure levels due to dose modification and inter-individual pharmacokinetic variability, average exposure (Starting Dose*Dose intensity/individual CL/F) was used as the exposure metric in the E-R analyses. The relationships between cabozantinib exposure and progression free survival (PFS), and selected safety endpoints including diarrhea, palmar-plantar erythrodysesthesia (PPE) syndrome and time to dose modification (TTDM) were evaluated. **Results:** Kaplan-Meier analyses of PFS for each quartile of average cabozantinib exposure suggest that patients with lower exposure and those with higher exposure may have equivalent PFS, comparatively**.** The multivariate Cox proportional analysis identified individual patient's clearance as a significant covariate for prediction of TTDM with a hazard ratio of 1.95 (95% CI [1.47-2.59]), suggesting that patients with higher exposures required dose modification earlier than patients with lower exposures. The results of the E-R analyses may be difficult to interpret due to the high rate of dose modification. Nevertheless, these results indicate that a lower dose may be as effective with improved tolerability. **Conclusions:** The E-R analyses along with the observed safety and efficacy data in the clinical trials led to an FDA requirement to conduct a post marketing clinical trial to evaluate the safety and efficacy of a lower cabozantinib dose.

2511 **Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

Integrated genomics and avatar mouse models for personalized cancer treatment.

Elena Garralda, Keren Paz, Pedro P. López-Casas, Siân Jones, Amanda Katz, Lisa M. Kann, Fernando López-Ríos, Francesca Sarno, Fatima Al-Shahrour, David Vasquez, Elizabeth Bruckheimer, Samuel V. Angiuoli, Luis A. Diaz, Alfonso Valencia, Victor E. Velculescu, David Sidransky, Manuel Hidalgo; Clinical Research Programme. Spanish National Cancer Research Center (CNIO), Madrid, Spain; Champions Oncology, Baltimore, MD; Personal Genome Diagnostics, Inc., Science and Technology Park at Johns Hopkins, Baltimore, MD; Laboratorio de Dianas Terapeúticas, CIOCC, Madrid, Spain; Centro Integral Oncológico Clara Campal (CIOCC), Madrid, Spain; Ludwig Center for Cancer Genetics and Therapeutics, Johns Hopkins Kimmel Cancer Center, Baltimore, MD; Structural Biology and Biocomputing Programme, Spanish National Cancer Research Center (CNIO), Madrid, Spain

Background: Every cancer has its unique set of molecular changes and the knowledge of such alterations is enabling an individualized approach to cancer treatment. The great intellectual challenge lies in linking confirmed mutations to protein function. **Methods:** Using massive parallel sequencing we performed whole exome sequencing analysis of 30 patients (pts) with advanced solid tumors to identify putatively actionable tumor-specific genomic alterations. We used 2 *in silico* methods (Polyphen and SIFT) to estimate the functional significance of a given confirmed mutation. Avatar models generated by direct engraftment of tumor samples from the patients into immunocompromised mice were used as an *in vivo* platform to test proposed treatment strategies. **Results:** Successful exome sequencing analyses has been obtained for 28 pts. Tumor specific mutations (Muts) and copy number variations were identified ranging from 5 to 952 and 0 to 956 respectively. All samples profiled contained relevant genomic alterations. Some of the most relevant actionable alterations were: CHEK1, FGFR2, IGF1R, MET, BRCA1, XPC, NOTCH, CREB3LB, GNA11, SMAD4, NF1, PTPRC, PI3KA, DDR2 and EGFR. An Avatar model was generated for 15 patients. In occasions actionable alterations such as muts in NF1, PTPRC, PI3KA and DDR2 failed to provide any benefit when a targeted drug was tested in the Avatar and accordingly treatment of the pts with these drugs was not effective. So far 13 pts have received a personalized treatment: two, as expected based on the avatar model, did not response; 5 resulted in durable partial remissions. Eight pts are currently on treatment with at least disease stabilization. Bench testing of candidate treatments in Avatar models correlated with clinical response and helped to select empirical treatments in patients with no actionable mutations. **Conclusions:** The use of full genomic analysis for cancer care is promising but presents important challenges that will need to be solved for broad clinical application. Avatar models are a powerful investigational platform for therapeutic decision making and help to guide cancer treatment in the clinic. While limitations still exist, this strategy should be tested in prospective randomized clinical trials.

2512 **Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

Molecular screening for cancer treatment optimization (MOSCATO 01): A prospective molecular triage trial—Interim results.

Antoine Hollebecque, Christophe Massard, Thierry De Baere, Nathalie Auger, Ludovic Lacroix, Valerie Koubi-Pick, Philippe Vielh, Vladimir Lazar, Rastislav Bahleda, Maud Ngo-camus, Eric Angevin, Andrea Varga, Frederic Deschamps, Anas Gazzah, Clement Mazoyer, Catherine Richon, Gilles Vassal, Alexander M. Eggermont, Fabrice Andre, Jean-Charles Soria; Institut Gustave Roussy, Villejuif, France; Institut de Cancerologie Gustave Roussy, Villejuif, France

Background: Characterization of the genomic alterations (GA) that could drive tumor growth of an individual patient (pt) is now critical to better select targeted therapies in phase I trials. **Methods:** Pts with advanced solid tumors, who failed at least one line of standard therapy, were offered an on-purpose tumor biopsy for molecular characterization. Biopsies were mainly obtained using 18G needles under CT or ultra-sound control, from metastatic or primary tumor sites. DNA extracted from fresh tumor biopsies was analyzed by CGH (Agilent platform) (if $\geq$ 50% tumor cells in the sample) and by sequencing for 30 target genes (if $\geq$ 30% tumor cells in the sample). An expert panel of scientists and clinicians reviewed results to determine the biological signification of the GA and match such pts to the most relevant targeted therapy available (mainly in early clinical trials). PFS using therapy based on GA was compared to the PFS for the most recent therapy on which the pt had just experienced progression (PFS ratio). **Results:** From December 2011 to august 2012, 129 heavily pretreated pts (median of 3 previous lines) were consented. Among them, 111 (86%) had a dedicated tumor biopsy. An actionable target was identified in 52 patients (40%). Among them, 25 pts (23% of biopsied pts) have been treated with a targeted therapy. The median time between biopsy and molecular results was 21 days [17 – 28]. GA of interest encompassed FGF ligand or receptor amplification (n=9), cyclin amplification or deletion (n=4), KRAS/BRAF/NRAS mutation (n=3), PI3K amplification or PTEN deletion (n=3), EGFR amplification or mutation (n=3) (outside lung cancer), HER2 amplification (n=2) (outside breast cancer), EML4/ALK translocation (n=1). Among the 25 pts treated according to their GA, we observed 5 PR (20%), 14 SD (56%) and 3 PD (12%). Three pts (12%) were not evaluable because of early discontinuation of the therapy. PFS ratio was $>$1.3 among 9 out of 19 evaluable pt (47%). **Conclusions:** High throughput molecular analysis is feasible in daily practice. It allows enrichment of phase I trials with specific GA, and leads to promising anti-tumor activity (20% PR as compared to the classical 7-10% PR obtained in all comers phase I trials). Clinical trial information: NCT01566019.

2513 Poster Discussion Session (Board #1), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Final results of the phase I trial of niraparib (MK4827), a poly(ADP)ribose polymerase (PARP) inhibitor incorporating proof of concept biomarker studies and expansion cohorts involving *BRCA1/2* mutation carriers, sporadic ovarian, and castration resistant prostate cancer (CRPC).

Caroline Ogilvie Michie, Shahneen Kaur Sandhu, William R. Schelman, L Rhoda Molife, George Wilding, Aurelius Gabriel Omlin, Vikram Kansra, David G. Brooks, Robert E. Martell, Stanley B. Kaye, Johann Sebastian De Bono, Robert Michael Wenham; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; University of Wisconsin Carbone Cancer Center, Madison, WI; TESARO, Inc., Waltham, MA; Division of Hematology Oncology, Tufts Medical Center, Boston, MA; Department of Women's Oncology, Program of Gynecologic Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: Niraparib(N) is an oral, potent PARP1/2 inhibitor that induces synthetic lethality in BRCA1/2 deficient tumors. PARP is also implicated in transcription regulated by the androgen receptor (AR) and rearranged ETS genes; key targets in CRPC. **Methods:** Dose-escalation was enriched for *BRCA1/2*mutation carriers (BRCA-MCs). Two MTD expansion cohorts were undertaken in patients (pts) with sporadic high grade serous ovarian cancer (HGSOC) and CRPC. In CRPC pts, archival tissue and circulating tumor cells (CTC) were analyzed for PTEN deletion and ETS gene rearrangements. **Results:** 100 pts [ovary (49), CRPC (23), breast (12) others (16)], received N at 10 dose levels: 30mg to 400mg daily (od), continuously. Grade (G) 4 thrombocytopenia was dose limiting at 400mg od; MTD was established at 300mg od. Drug-related toxicities were G1-2 reversible anemia (48%), fatigue (42%), nausea (42%), thrombocytopenia (35%), anorexia (27%), neutropenia (24%), constipation (23%), and vomiting (20%). PKs were dose proportional with a mean elimination $t_{1/2}$of 40 hours. Peripheral blood mononuclear cells had >50% PARP inhibition from 80 mg od. gH2AX foci formation, a marker of DNA damage, was seen in CTCs. Antitumor activity occurred from 60mg od with RECIST and/or CA125 partial responses (PR) in 9/20 (45%) BRCA-MC ovarian cancer pts and 2/4 (50%) BRCA-MC breast cancer pts. Platinum-sensitive vs resistant BRCA-MC HGSOC response rate was 60% vs 33% with median time for responding pts of 429 and 340 days, respectively. In sporadic HGSOC, there were 2/3 PRs in platinum-sensitive pts, and 3/20 PRs plus 4/20 stable disease (SD) >16 weeks in platinum resistant pts. In CRPC, symptomatic benefit and SD >6 months (median 9 months) was seen in 9/21 (43%) pts treated at MTD. CTC declines of >30% (median 80%; range 36%-92%) were observed in 7/10 (70%) pts with evaluable CTC counts (≥5 cells/ 7.5mL blood). **Conclusions:** Niraparib was well tolerated and has promising antitumor activity in BRCA-MCs, sporadic HGSOC and CRPC. Clinical trial information: NCT0074902.

2514 Poster Discussion Session (Board #2), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Phase I/Ib study of the PARP inhibitor olaparib (O) with carboplatin (C) in BRCA1/2 mutation carriers with breast or ovarian cancer (Br/OvCa) (NCT00647062).

Jung-min Lee, Christina M. Annunziata, John L. Hays, Anne M. Noonan, Lori M. Minasian, JoAnne Zujewski, Minshu Yu, Jiuping Jay Ji, Tristan Sissung, Nicole D. Houston, Elise C. Kohn; Molecular Signaling Section, Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD; National Cancer Institute, Bethesda, MD; SAIC-Frederick, Inc.; Frederick National Laboratories, Bethesda, MD

Background: O capsules have single agent activity against Br/OvCa in BRCA1/2^{mut+}carriers. Our goals were to define safety and explore predictive biomarkers for an OC regimen in these pts. **Methods:** 3x3 dose escalation optimized daily oral O (100 or 200mg q12h; DL1&2) with IV C/AUC3 on d8 and q21d, and on DL3-6, O d1-7 at 200 then 400mg q12h with C/AUC3-5 on d2. ≤ 8 OC cycles were given, followed by daily O until progression. Safety was assessed q cycle and response q2 cycles. PBMCs were collected for polymorphism analysis (PARP1; XRCC1), and serially for PAR incorporation by ELISA. Paired tumor biopsies (pre/postC1) were collected in phase Ib pts for protein microarray (RPPA) and TUNEL endpoints. **Results**: 45 women (37Ov/8Br) with BRCA1 (32), BRCA2 (11), 1 each BRCA1&2 and BRCApro 68% received OC. All OvCa pts previously received C (6-55mo prior, median 14). DLT was thrombocytopenia (O 200mg q12h, C/AUC3 2/5 pts). MTD was not reached on the intermittent schedule. RP2D is O 400mg q12hx14, C/AUC5 (1/6: g4 thrombocytopenia). Gr 3/4 AEs included neutropenia (42%), thrombocytopenia (20%), anemia (13%), C hypersensitivity (9%), and fatigue (7%). 7 pts discontinued C early for hypersensitivity reaction (4) or myelosuppression (3). Responses included 1 CR (BrCa, 17mo), PR in 15/34 OvCa (44%; 3-28+mo) and 6/8 BrCa (5-24+ mo), and stabilization in 14/34 OvCa (41%; 3-25+ mo) and a BrCa pt (11mo) for a clinical benefit rate of 85% OvCa, 100% BrCa. RPPA (N=10) showed high FOXO3 and NFκB1 preC1 correlated with time on study (r=0.822, p=0.0035; r=-0.832, p=0.0028, respectively). The change post-preC1 correlated with time on study for the combination of eIF4E/G, caspase 7, pPI3K, FOXO3a, p62, E-cadherin, PCNA, Bim, and Bcl2 (r=-0.855, p=0.0068). Post-preC1 TUNEL results trended to correlate with response (p=0.07). PBMC PAR concentrations and PARP1/XRCC1 polymorphisms did not correlate with response. **Conclusions**: O 400mg q12h x14 with C/AUC5 q21d is active and tolerable in Br/OvCa BRCA^{mut+} pts despite interactive marrow suppression. Exploratory translational studies indicate FOXO3 and NFkB1 may be predictive for response to therapy, requiring a prospective validation. Clinical trial information: NCT00647062.

2515 Poster Discussion Session (Board #3), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Phase I and pharmacokinetic trial of the antitemolerase agent KML001 (KML) and cisplatin (CDDP) in advanced solid tumors.

Martin J. Edelman, Josephine Louella Feliciano, Miroslav Styblo, Tao Liu, Rena G. Lapidus, Jesse Saunders, Joga Gobburu; University of Maryland, Marlene and Stewart Greenebaum Cancer Center, Baltimore, MD; The University of North Carolina at Chapel Hill, Chapel Hill, NC; University of Maryland School of Pharmacy, Baltimore, MD; University of North Carolina, Durham, NC

Background: Telomerase is overexpressed in most solid tumors and rarely expressed in adult tissues and is therefore a promising target. We have previously demonstrated that KML001 (sodium metaarsenite) displaces hTERT from the nucleus and is cytotoxic (Clin Cancer Res 14:4593-602, 2008). We have also demonstrated that it is synergistic with cisplatin. **Methods:** Pts with advanced solid tumors, PS 0-1, normal renal and hepatic function were eligible. Treatment was with CDDP 75 mg/m2 day 1 and KML p.o. daily days 1-14 on a 21 day cycle. It was planned that KML doses would be escalated by 2.5 mg beginning at 15 mg/day. A 3+3 design was employed. Blood specimens for arsenic and platinum pk were obtained at hours 0,1,2,3,4,5,6, 24 and day 15 and 22. Tumor blocks were required to assess for telomerase expression. **Results:** 18 patients (7M,11F) are evaluable for toxicity. Pts were heavily pretreated (median number of prior regimens =3). 16 had prior platinum therapy. The dose limiting toxicity was QTc interval prolongation seen in three patients in cohort 3 (20 mg) (two during cycle 1, one during cycle 2). A PR was seen in a patient with heavily pretreated SCLC in cohort 1. 1 other pt with SCLC and 2 with NSCLC also experienced reduction in disease burden. 10/18 pts received >3 cycles of therapy. Other common toxicities observed were nausea, vomiting and cytopenias. Significant, but not dose limiting, neutropenia or thrombocytopenia (> grade 3) was observed in cohorts 1 and 2. Myelosuppression was primarily seen in pts with prior radiotherapy. Non-compartmental analysis for inorganic arsenic (iAs) and the mono (MAs) and dimethylarsenic (DMAs) metabolites was performed (Table). **Conclusions:** 1. The combination of KML-001 and CDDP is feasible and active. 2. We are currently evaluating CDDP 75 mg/m2 and KML 17.5 mg in an expansion cohorts of advanced SCLC and NSCLC. 3. Studies of telomerase expression are in progress. (R21CA130349-01) Clinical trial information: NCT01110226.

As species	Dose (mg)	AUClast (hour*umol/L)	Cmax (umol/L)	$>t_{1/2}$ (hour)
iAs	15	1.711±1.069	0.243±0.172	7.821±1.281
	17.5	1.738±0.889	0.236±0.132	6.080±2.478
MAs	15	0.682±0.376	0.056±0.032	ND
	17.5	0.682±0.432	0.059±0.033	ND
DMAs	15	0.773±0.438	0.074±0.045	ND
	17.5	1.633±2.559	0.131±0.166	ND

2516^ Poster Discussion Session (Board #4), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

A phase I study of the first-in-class mitochondrial metabolism inhibitor CPI-613 in patients with advanced hematologic malignancies.

Timothy S. Pardee, Denise A. Levitan, David Duane Hurd, Leslie R. Ellis, Scott Isom, Robin Harrelson, Megan Manuel, Sarah Dralle, Susan Lyerly, Bayard L. Powell; Wake Forest University Health Sciences, Winston-Salem, NC; Wake Forest University Health Science, Winston-Salem, NC; Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC

Background: Altered metabolism is a hallmark of cancer, including hematologic malignancies. This altered metabolism is a possible therapeutic target. The lipoate derivative CPI-613 is a first in class agent that targets pyruvate dehydrogenase complex.This trial was designed to determine the maximally tolerated dose (MTD), safety, and efficacy of CPI-613 given as a single agent by IV infusion. **Methods:** CPI-613 was given over a 2 hour infusion on days 1 and 4 for 3 weeks every 28 days with a starting dose of 420 mg/m^2. The dose was escalated in 6 cohorts to a final dose of 3780 mg/m^2. Treatment could be continued if the patient experienced clinical benefit. **Results:** A total of 26 patients with advanced relapsed or refractory hematologic malignancies were enrolled. Patients were heavily pretreated with a median of 3 previous therapies (range 1-11). CPI-613 was well tolerated when infused over 2 hours, with no worsening of cytopenias at any dose level. After the dose was escalated to 2940 mg/m^2 the protocol was amended to a 1 hour infusion. When infused over 1 hour, 2 patients developed grade 3 renal failure. Infusion time was then returned to 2 hours and dose escalation resumed. At a dose of 3780 mg/m^2, one patient experienced prolonged grade 3 nausea and one patient grade 3 renal failure, defining this dose as above the MTD. Renal failure resolved in all but one patient who opted for hospice care. A total of 6 patients were treated at a dose of 2940 mg/m^{2}over 2 hours with no DLTs observed, establishing this as the MTD. Of the 21 patients evaluable for a response, eight achieved a response of stable disease or better for a response rate of 38%. Responses included a complete remission maintained over 27 cycles in one AML patient and clearance of marrow blasts in another, sustained partial response in both a Burkitt's and a cutaneous T cell lymphoma patient maintained over 17 and 8 cycles respectively, and stable disease in 2 multiple myeloma and 2 myelodysplasia patients. **Conclusions:** To our knowledge this is the first report of an agent with activity in aggressive hematological malignancies that is not myelosuppressive. The therapeutic index appears high suggesting CPI-613 should be further studied in phase II trials. Clinical trial information: NCT01034475.

2517 Poster Discussion Session (Board #5), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

A phase I first-in-human study of REGN910 (SAR307746), a fully human and selective angiopoietin-2 (Ang2) monoclonal antibody (MAb), in patients with advanced solid tumor malignancies.

Kyriakos P. Papadopoulos, Solmaz Sahebjam, Robin Katie Kelley, Anthony W. Tolcher, Albiruni R.A. Razak, Amita Patnaik, Philippe L. Bedard, Rebecca Arcos, Lieve Adriaens, Carrie M. Brownstein, Israel Lowy, Bo Gao, A Thomas DiCioccio, Pamela Trail, Lillian L. Siu; START Center for Cancer Care, San Antonio, TX; Princess Margaret Hospital, Toronto, ON, Canada; Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; South Texas Accelerated Research Therapeutics, LLC., San Antonio, TX; Princess Margaret Cancer Center, University Health Network, Division of Medical Oncology & Hematology, Department of Medicine, University of Toronto, Toronto, ON, Canada; Regeneron Pharmaceuticals, Inc., Tarrytown, NY; Princess Margaret Cancer Center, Toronto, ON, Canada

Background: REGN910 is a selective, fully human Ang2 MAb that potently blocks signaling through the Tie2 receptor regulating tumor angiogenesis and growth. In multiple mouse xenograft models of human solid tumors, REGN910 inhibits tumor growth. **Methods:** This first-in-human phase I study (3+3 design) explored the safety, recommended phase II dose (RP2D), pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activity of REGN910 as a single agent. REGN910 was given IV at escalating doses. At RP2D, expansion cohorts were initiated to confirm safety and assess anti-tumor activity in about 20 patients (pts). **Results:** 37 pts [17M/20F; median age 57 (range 22-82); ECOG PS 0(9)/1(28)] were enrolled. Twenty-three (23) pts were enrolled in the dose escalation cohorts. No DLTs were reported, and a MTD was not reached. Most common G1/2 treatment-related adverse events (TRAEs) were fatigue 7(19%), peripheral edema 6(17%), diarrhea 5(14%), abdominal distension 4(11%), and decreased appetite 4(11%). There were no $\geq$ Grade 3 TRAEs. A confirmed sustained PR (16 wks) was observed in 1 pt with adrenocortical cancer treated at 1 mg/kg. SD (range 6.9-46.8 wks) was reported for 17 of 32 (53%) pts evaluable for efficacy. Fourteen pts received treatment $>$16 wks. One pt with thyroid cancer had SD for 46 wks, and 1 pt with hepatocellular cancer had SD for 16 wks with $\geq$50% decline in alpha-fetoprotein. Across all dose levels, REGN910 pharmacokinetics appeared linear and dose-proportional. The PK profile was characterized by an initial distribution and a single mono-exponential elimination phase. Total circulating serum Ang2 levels appeared saturated following treatment in all cohorts, indicating systemic target engagement at all doses tested. **Conclusions:** Administration of REGN910 in patients with advanced cancer is well tolerated, with generally mild and moderate TRAEs. Dose escalation is completed, and enrollment to the expansion cohorts continues. The safety profile supports combination with chemotherapy and/or other anti-angiogenic agents. Clinical trial information: NCT01271972.

2518 Poster Discussion Session (Board #6), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

A phase I study of carboxyamidotriazole orotate (CTO) in of advanced solid tumors.

Alan Sandler, Matthew Hiram Taylor, Walter John Urba, Antonio Marcilio Padula Omuro, Barry Douglas Anderson, Daniel Hansen, Brenda Fisher, Alisa J Claeys, Amy Greathouse, Sean McLean, Rashida A. Karmali; Knight Cancer Institute, Oregon Health and Science University, Portland, OR; Oregon Health & Science University, Portland, OR; Earle A. Chiles Research Institute-Providence Cancer Center, Portland, OR; Memorial Sloan-Kettering Cancer Center, New York, NY; Theradex, Princeton, NJ; Providence Cancer Center, Portland, OR; Tactical Therapeutics, New York, NY

Background: CTO is an orotate salt of carboxyamidotriazole (CAI), which is an inhibitor of calcium-dependent intracellular and extracellular signal transduction pathways (presumably affecting VEGF and PI3K) and has tumor anti-proliferative and anti-invasive properties. The activity of CTO alone and in combination with temozolomide or 5Efluorouracil was demonstrated in human glioblastoma, melanoma, and colon tumor xenografts. **Methods:** This study assessed the maximum tolerated dose (MTD), safety, pharmacokinetics and activity of CTO monotherapy in 34 patients (pts) with advanced solid tumors meeting eligibility criteria with adequate organ function. The CTO study NCT01107522 enrolled pts in 8 cohorts receiving continuous daily oral CTO capsules at doses ranging from 50mg- 555mg/m^2/day. The MTD has not been determined. Pharmacokinetic (PK) sampling was performed during cycle 1 at each dose level. CT scans were performed at baseline and after 8 weeks to assess anti-tumor effect. Patients remained on study if they achieved stable disease (SD) or tumor response and did not experience dose limiting toxicities (DLT). **Results:** The most frequently recorded adverse events (Grade 1 and 2) were fatigue, nausea, vomiting, and dizziness. DLTs of grade 3 fatigue (219 mg/m2) and grade 3 creatine kinase elevation (555 mg/m^2) occurred in one pt each. No cardiac QTc prolongations have been recorded. PK data demonstrated therapeutically relevant CAI levels beginning at the 219mg/m^2 dose. Nine pts continued CTO dosing beyond 2 cycles. Tumor assessments demonstrated SD at different doses of CTO: i) 75mg/m^2 renal carcinoma (1, 12 cycles); ii) 219 mg/m^2-small cell lung cancer (1, 4 cycles), squamous cell lung cancer with PIK3CA mutation (1, 10 cycles and continuing), and lung adenocarcinoma with EGFR mutation (1, 10 cycles and, continuing); iii) 285 mg/m^{2-}1 colon cancer with BRAFV600E mutation (1, 6 cycles), and squamous cell carcinoma (tonsil) with PI3KCA and NRAS mutations (1, 9 cycles, and continuing). **Conclusions:** CTO given as monotherapy up to 555mg/m^2/day is safe and tolerable and without MTD. Six patients with different malignancies and genomic markers achieved SD; combinatorial investigations in malignant gliomas have started. Clinical trial information: NCT01107522.

2519 Poster Discussion Session (Board #7), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Phase I, first-in-human, open-label, dose-escalation study of U3-1565, a fully human anti-HB-EGF monoclonal antibody, in patients with advanced solid tumors.

Kathleen N. Moore, Johanna C. Bendell, Anthony J. Olszanski, Madhuri Desai, Mendel Jansen, Richard David Scheyer, Giorgio Senaldi, Patricia LoRusso; University of Oklahoma Health Sciences Center, Oklahoma City, OK; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; Fox Chase Cancer Center, Philadelphia, PA; Daiichi Sankyo Co., Ltd., Edison, NJ; Daiichi Sankyo Co., Ltd., Gerrards Cross, United Kingdom; Karmanos Cancer Institute, Wayne State University, Detroit, MI

Background: Heparin-binding epidermal growth factor-like growth factor (HB-EGF) is an EGF family member and a ligand for EGFR and Her4. U3-1565 is a fully human anti-HB-EGF monoclonal antibody with preclinical anti-tumor and anti-angiogenesis activity. In this study, we evaluated safety, tolerability, immunogenicity, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity of U3-1565 in patients with advanced solid tumors refractory to standard treatment. **Methods:** The 3+3 method of enrollment and dose-escalation was used to test U3-1565 at 2, 8, 16, and 24 mg/kg once every two weeks (with the second dose given three weeks after the first), and at 24 mg/kg weekly. **Results:** 15 patients (11 females, 4 males; median age 62 (range 47-77) years; 5 CRC, 5 NSCLC, 3 ovarian and 2 other cancer) were enrolled, 3 in each dose level cohort. No dose-limiting toxicity was observed and a maximum tolerated dose was not reached. The highest administered dose of 24 mg/kg weekly generated Cmin above the predetermined target concentration corresponding to Cave resulting in 90% preclinical tumor growth inhibition. U3-1565 was safe and well tolerated with related AE consisting of infrequent and non-dose-related G2 (fatigue, anemia, and appetite loss, seen in 20, 13, and 7% of cases, respectively) and G1 toxicities. No anti-U3-1565 antibody was detected. U3-1565 showed bi-exponential disposition with Cmax and AUC increasing proportional to the dose across all dosing regimens. 13 patients discontinued the study, 12 due to progressive disease and 1 due to non-drug-related AE. After 6 months on study, 2 patients entered study extension phase: A 77 year-old female with NSCLC given 24 mg/kg every two weeks, showed SD (best SLD change -3%) for 26 weeks before progression; and a 76 year-old female with CRC given 24 mg/kg weekly, showed PR (best SLD change -35%) and remains on treatment after 71 weeks. **Conclusions:** U3-1565 is safe and well tolerated up to 24 mg/kg weekly. Anti-tumor activity was observed and is being further explored in an open-label, dose-expansion study. Clinical trial information: NCT0129041.

2520 Poster Discussion Session (Board #8), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

A phase I and biodistribution study of ABT-806i, an ^{111}indium-labeled conjugate of the tumor-specific anti-EGFR antibody ABT-806.

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Background: ABT-806 is a humanized antibody targeting a conformationally exposed epitope only available when tumor Epidermal Growth Factor Receptor (EGFR) is overexpressed or (EGFRvIII) mutated. A prior trial treated 8 patients (pts) with a chimeric homologue (single-dose 5-40 mg/kg), with a minor response in one squamous cell carcinoma of skin pt. A prior phase 1A study of ABT-806 treated 26 pts (2-24 mg/kg IV q2w), with prolonged SD in one head and neck (H&N) cancer pt. No pt had a typical EGFR-inhibitor rash. The current study gathers further ABT-806 clinical data, assesses ABT-806i dosimetry in normal and malignant tissues and examines its relationship to clinical and PK/PD data. **Methods:** Pts with advanced tumors likely to express EGFR, ECOG 0-2, measurable disease and adequate organ function were enrolled. ABT-806i scans comprised ABT-806i 5-7mCi injection followed by whole body and regional SPECT scans over one week. Cohort (C) 1 pts (n=6) had ABT-806i scans alone. C2 pts (n=12) had ABT-806i scans at baseline and at week 6 (after 3 fortnightly doses of ABT-806; 6 pts at 18 mg/kg and 6 at 24 mg/kg). Subjects with PR/SD could receive ABT-806 on an extension study until progression. **Results:** 18 pts (M:F 11:7; median age 57 yrs) with tumors of H&N (6), colon (3), lung (2), brain (2), bladder (1), cervical (1) and other (3) were treated. An H&N pt had a confirmed PR whilst 5 pts had SD (lasting 37 and 24 wks in an adrenal carcinoma and H&N pt respectively). Two potential toxicities were seen at 24mg/kg on the extension study: equivocal rash (G1; three transient lesions on nose) and allergic reaction (Sweet's syndrome, G2). Dosimetry in C1 pts confirmed safe radiation exposure levels to normal tissues. Many pts showed high, specific tumor uptake of ABT-806i, including 1 pt with an intracranial tumor. ABT-806i uptake was not significantly affected by concurrent ABT-806 treatment. Ongoing analyses of how ABT-806i uptake correlates with tumor EGFR and clinical response may inform the recommended phase 2 dose of ABT-806. **Conclusions:** The high therapeutic index and specificity of ABT-806 merits further investigation as monotherapy or an antibody-drug conjugate. ABT-806i may have utility as a bioimaging agent. Clinical trial information: NCT01472003.

2521 Poster Discussion Session (Board #9), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Phase I study of volasertib (BI 6727) combined with afatinib (BIBW 2992) in advanced solid tumors.

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Background: Volasertib is a potent and selective cell cycle kinase inhibitor that induces mitotic arrest and apoptosis by targeting Polo-like kinases (Plk). Volasertib and afatinib, an irreversible ErbB family blocker, have shown single agent anti-tumor activity and manageable safety profiles in patients (pts) with advanced solid tumors. This dose escalation study was designed to determine the maximum tolerated dose (MTD) of two combination schedules of volasertib and afatinib in pts with advanced solid tumors refractory to or not amenable to standard therapy. **Methods:** In a 3 + 3 design, cohorts of 3–6 pts received volasertib 150–300 mg IV d1 Q3W + afatinib 30–50 mg PO QD d2–21 Q3W (Schedule A) or afatinib 50–90 mg d2–6 Q3W (Schedule B). Up to 12 additional pts were enrolled at the MTD. Primary endpoint was the MTD per schedule. Secondary endpoints included pharmacokinetics (PK), safety and efficacy (RECIST). **Results:** 57 pts (median 58 yr; ECOG PS 0/1/2: 35%/60%/5%) were treated (n=29, Schedule A; n=28, Schedule B). MTD was volasertib 300 mg/afatinib 30 mg (Schedule A) and volasertib 300 mg/afatinib 70 mg (Schedule B). Cycle 1 dose limiting toxicities (DLTs) were experienced by 5 (Schedule A) and 7 (Schedule B) pts. Most common DLTs were diarrhea (n=5), neutropenia (n=3), fatigue (n=2) and decreased ejection fraction (n=2) in Schedule A, and thrombocytopenia (n=6), neutropenia (n=5), diarrhea (n=4) and febrile neutropenia (n=3) in Schedule B. Most common grade 3/4 adverse events were neutropenia (n=8), thrombocytopenia (n=6), diarrhea (n=3) and febrile neutropenia (n=3). Volasertib exhibited multi-exponential PK behavior with a long half-life (130 hr), moderate clearance (900 mL/min) and large volume of distribution (Vss >6000 L). Co-administration of volasertib and afatinib had no effect on the PK profile of either drug. Two pts in Schedule A (volasertib 300 mg/afatinib 30 mg) achieved partial responses (tumor types: NSCLC, head and neck). **Conclusions:** MTD of volasertib was 300 mg Q3W combined with afatinib 30 mg d2-21 (Schedule A) or afatinib 70 mg d2-6 (Schedule B). Both agents could be combined at previously shown active single agent doses. At the MTD, treatment was manageable and showed preliminary anti-tumor activity. Clinical trial information: NCT01206816.

2522 Poster Discussion Session (Board #10), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

A first-in-human trial of RG7116, a glycoengineered monoclonal antibody targeting HER3, in patients with advanced/metastatic tumors of epithelial cell origin expressing HER3 protein.

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Background: The Human Epidermal Growth Factor Receptor 3 (HER3) is a key heterodimerization partner for other HER family members thereby acting as a downstream signal amplifier. This is a first in human study evaluating the safety of RG7116, a humanized anti-HER3 monoclonal antibody with potent HER3 signal inhibition. Due to a glycoengineered Fc-part this antibody displays enhanced antibody-dependent cellular cytotoxicity as compared to conventional antibodies. **Methods:** Patients (pts) with advanced or metastatic carcinomas with centrally confirmed HER3 protein expression were included. A "3+3" dose escalation design was performed starting at 100 mg flat dosing in a q2w regimen. In addition to single agent RG7116 (Part A), RG7116 plus cetuximab (Part B) and RG7116 plus erlotinib (Part C) combinations are evaluated. The results of Part A are presented. **Results:** Twenty-five pts have been enrolled in 6 cohorts (100 to 2000 mg). No DLTs were observed. Pts had a median (range) of 3 (2 to 6) prior chemotherapy lines. Nine infusion-related reactions (IRRs) Gr 1 to 3 occurred in 7 pts. Three drug-related AEs Gr 3 were reported, 1 IRR, 1 GGT increase, and 1 neutropenia. Only 1 patient was tested positive for human anti human antibodies (HAHA). The PK of RG7116 was non-linear from 100 mg up to 400 mg, possibly as a result of target-mediated drug disposition. Both C_{max} and AUC showed a greater than doseEproportional increase over the same dose range, accompanied by a decline in total clearance. Dose proportionality was observed from 800 mg onwards. PD effects were observed from the first dose level onwards with HER3 membranous protein down-regulation in skin and from 200 mg onwards in ontreatment tumor samples. Five pts (1 NSCLC, 2 CRC, 1 SCCHN, 1 BC) had a best response of SD. Confirmed SD (>16 weeks) was observed in 2 pts. One BC patient achieved a PR in ^{18} FDG-PET and significant shrinkage of non-target tumor lesions on CT scan. **Conclusions:** RG7116 is the first glycoengineered monoclonal anti-HER3 antibody in clinical development. RG7116 monotherapy was well tolerated, and demonstrated preliminary signs of clinical activity. Clinical trial information: NCT01482377.

2523 Poster Discussion Session (Board #11), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

A phase I, dose-escalation trial of continuous and pulsed-dose afatinib (A) combined with pemetrexed (P) in patients (pts) with advanced solid tumors: Final analysis.

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Background: A is an irreversible ErbB Family Blocker that has shown additive effects when combined with P in EGFR-mutant NSCLC cell lines. This Ph I trial assessed the MTD, safety and PK of continuous and pulsed-dose A + P in pts with advanced solid tumors. **Methods:** In a3+3 dose-escalation design, IV P (500 mg/m^2) was administered on day (d) 1 of each 21-d cycle combined with either continuous oral A qd (Schedule A; SA) on d1–21 (d2–21 in Cycle 1) or pulsed-dose oral A qd (Schedule B; SB) on d1–6 of each 21-d cycle. In SA, A starting dose was 30 mg, escalated to maximum of 50 mg. Once the MTD was reached in SA, A was administered at a starting dose of 50 mg in SB. Pts received up to 6 cycles of P with the option for A monotherapy thereafter. P and steady state A PK were analyzed by intra-individual comparison in SA only for possible drug–drug interaction. **Results:** 53 pts were treated (SA: n=23, median age 58 yrs; ECOG 0/1/2 [30%/65%/4%]; SB: n=30, median age 62 yrs, ECOG 0/1/2 [27%/70%/3%]). MTD of A in SA was 30 mg; 8 pts had dose-limiting toxicities (DLTs) in Cycle 1 (40 mg: 2/3 pts; 30 mg; 6/19 pts). 30-mg cohort included 19 evaluable pts; 1 pt was replaced during expansion (incomplete PK collection) and had a DLT. MTD of A in SB was 50 mg; 11 pts had DLTs in Cycle 1 (70 mg: 4/5 pts; 60 mg: 6/17 pts; 50 mg: 1/6 pts). Most frequent drug-related AEs in SA were diarrhea (91%), stomatitis (65%) and rash (61%) and in SB were diarrhea (83%), rash (83%) and fatigue (80%); most were Grade 1/2. 6 pts in SA and 8 pts in SB completed 6 treatment cycles; 1 pt in each schedule remain on treatment. Best response in SA was 1 confirmed partial response (CPR; NSCLC, prior sequential chemotherapies and erlotinib) and 6 pts with stable disease (SD). In SB, best response was 1 CPR (bladder cancer, prior sequential chemotherapies) and 10 pts with SD. No clinically relevant PK interactions between A and P were observed. **Conclusions:** Continuous or pulsed-dose A combined with P exhibited a manageable safety profile. No clinically relevant PK interactions were seen in SA. Continuous dose A 30 mg/d with P 500 mg/m^2 (d1 of each 21d cycle) is the recommended dose for further Ph II studies. No apparent safety or dose advantage was observed in SB. Clinical trial information: NCT01169675.

2524 Poster Discussion Session (Board #12), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

First-in-human evaluation of CO-1686, an irreversible, selective, and potent tyrosine kinase inhibitor of EGFR T790M.

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Background: Efficacy of existing EGFR tyrosine kinase inhibitors (TKIs) in NSCLC is limited by emergence of the T790M mutation in approximately 50% of patients, and significant skin rash and diarrhea, caused by wild-type (WT)-EGFR inhibition, compromises tolerability. CO-1686 is an orally active TKI that targets common activating EGFR mutations and T790M, while sparing WT-EGFR. Animal models suggest maximal efficacy when trough plasma concentrations exceed 200ng/ml. **Methods:** This is a first in human phase 1 (3+3) dose-finding study of oral CO-1686, administered continuously in 21-day cycles. To be eligible, patients must have EGFR-mutant NSCLC and prior therapy with an EGFR TKI. Endpoints include safety, pharmacokinetics (PK), and efficacy. All patients undergo a biopsy for genotyping before starting study drug. **Results:** As of 18 Jan 2013, 35 patients (18/28 (64%) T790M+; 7 pending) have been treated with CO-1686. Dosing started at 150mg QD and escalated in steps to 900mg QD, 600mg BID and 400mg TID, with a maximum tolerated dose not yet reached. A recommended phase 2 dose is expected to be reached soon. Related AEs of grade 3 or higher were hypoglycaemia (n=1) and hyperglycaemia (n=1). AEs typical of WT-EGFR inhibition (rash, diarrhea) have not been observed. Dose-proportional PK was observed; plasma half-life was 4-5 hrs and at 900mg QD Cmax=3000ng/ml but trough concentrations were $<$ 200ng/ml. At $\geq$300mg BID and TID dosing, trough concentrations can exceed 200ng/ml. At 900mg QD, 2 of 3 patients showed clinical benefit after 2 cycles of CO-1686 including one with clinically-relevant tumor shrinkage (18%) and a second with stabilization of a pleural effusion that had previously required repeat thoracenteses at ~10 day intervals. At 300mg BID, one patient (Del(19)/T790M+) with PK trough concentration $>$200ng/ml exhibited significant tumor shrinkage (29%) after 2 cycles. Further efficacy data from BID/TID cohorts and centrally-confirmed genotypes will be presented at the meeting. **Conclusions:** CO-1686 offers potential for improved activity and better tolerability over current EGFR TKIs, particularly in the treatment of T790M+ disease, an area of high unmet clinical need. Clinical trial information: NCT01526928.

2525 Poster Discussion Session (Board #13), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

A phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of the selective aurora kinase inhibitor GSK1070916A.

Iain McNeish, Alan Anthoney, Paul Loadman, Dan Berney, Simon Joel, Sarah E. R. Halford, Emily Buxton, Amanda Race, Mohammed Ikram, Andrew Scarsbrook, Angela Patikis, Andrea Rockall, Nicola A Dobbs, Christopher Twelves; Barts Cancer Research UK Centre, London, United Kingdom; Leeds Cancer Research UK Clinical Centre, Leeds, United Kingdom; Institute of Cancer Therapeutics, Bradford, United Kingdom; Department of Histopathology, St. Bartholomew's Hospital, London, United Kingdom; St Bartholomew's Hospital, London, United Kingdom; Cancer Research UK Drug Development Office, London, United Kingdom; Department of Cellular Histopathology, London, United Kingdom; Department of Radiology, Leeds, United Kingdom; Department of Nuclear Medicine, London, United Kingdom

Background: GSK1070916A is a potent and selective inhibitor of Aurora B and C. This phase I study in collaboration with GlaxoSmithKline was part of the Cancer Research UK Clinical Development Programme. **Methods:** Patients (pts) with advanced/metastatic solid cancers for whom there was no standard therapy, with adequate performance status and organ function were eligible for GSK1070916A (1 hour i.v. infusion days 1 – 5, every 21 days). The primary objectives were to determine the safety profile, dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of GSK1070916A. The starting dose was 5mg/m^2/day, with initial single pt cohorts, followed by "3 + 3" cohorts and expansion at the MTD. DLTs included prolonged ($>$ 5 days) or complicated grade 4 neutropenia; the MTD was the highest dose at which $<$ 1 of 3 - 6 pts experienced DLT. Cycle 1 blood and healthy skin biopsies were obtained for PK and PD assays. The expanded cohort included 6 pts having pre- and post-treatment functional imaging studies (FDG PET-CT and MRI), and a further 6 having paired tumour biopsies for PD studies. **Results:** Nine single pt cohorts received up to 73mg/m^2/day of GSK1070916A with no grade 3 or 4 related adverse events. At 102.2mg/m^2/day, 1 pt had a DLT (febrile neutropenia) and 2 pts non-DLT grade 4 neutropenia; this dose was considered unacceptably toxic and 23 pts received a lower dose of 85mg/m^2/day; 7/23 pts had prolonged/complicated grade 4 neutropenia, 5 of whom continued GSK1070916A with dose reduction +/- delay. There were no treatment related deaths. A pt with ovarian cancer (102.2mg/m^2/day) had a RECIST PR; 19 pts had stable disease for $<$ 223 days. GSK1070916A PK were linear with a strong correlation between exposure (AUC) and reduction in neutrophils (r^2 0.91). At the 85 mg/m^2 dose, mean day 1 $t_{1/2}$ was 8.98 hours and Cl 9.2 l/h; AUC_{inf} was 10% higher on day 5 than day 1. PD results in healthy skin (phosphoHistone-H3, Ki 67 and cleaved caspase-3) were inconsistent. **Conclusions:** The MTD of GSK1070916A as a 1 hour i.v. infusion on days 1 – 5, every 21 days is 85mg/m^2/day, with predictable and manageable neutropenia as the DLT and evidence of clinical activity. Serum levels of cytokeratin-18, tumour PD and functional imaging data will be presented. Clinical trial information: NCT01118611.

2526 Poster Discussion Session (Board #14), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Phi-53: (NCI#7251): Phase I trial of belinostat (PXD101) in combination with 13-cis-retinoic acid (13c-RA) in advanced solid tumor malignancies—A California Cancer Consortium NCI/CTEP sponsored trial.

Thehang H. Luu, Paul Henry Frankel, Dean Lim, Mihaela C. Cristea, Jan Hendrik Beumer, Leonard Joseph Appleman, Heinz-Josef Lenz, David R. Gandara, Richard Piekarz, Edward M. Newman; City of Hope, Duarte, CA; City of Hope Beckman Research Institute, Duarte, CA; University of Pittsburgh Cancer Institute, Pittsburgh, PA; University of Pittsburgh, Pittsburgh, PA; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; University of California, Davis Comprehensive Cancer Center, Sacramento, CA; National Cancer Institute, Rockville, MD

Background: Belinostat has a reported maximum tolerated dose (MTD) of 1,000 mg/m^2 given days 1 to 5 every 21 days as a single agent, although in one study in hepatocellular carcinoma belinostat was given at 1,400 mg/m^{2}on the same schedule. Pre-clinical evidence suggests HDAC inhibitors enhance retinoic acid signaling with a synergistic impact in a variety of solid tumors. We conducted a phase I study of belinostat and 13c-RA in advanced solid tumors. **Methods:** Dose limiting toxicity (DLT) was defined as cycle 1 hematologic toxicity: ≥grade 3 that not resolved to <grade 1 within 1 week or non-hematologic toxicity: ≥grade 3. We sought the MTD of belinostat days 1-5 with 13-cRA days 1-14, every 21 days, in patients (pt) with advanced solid tumors. Eligibility criteria included normal organ function and QT/QTc interval; 4 weeks from previous therapy. **Results:** 51 pt were treated: median age 61 (range 40-80); 29 men; 57% ECOG 0, 41% ECOG 1, 2% ECOG 2; 13 lung, 11 breast, 8 colorectal, 3 pancreatic. 11 dose levels (DL) were tested starting from belinostat 600 mg/m^2/day and 13c-RA 50 mg/m^2/day to belinostat 2000 mg/m^2/day and 13c-RA 100 mg/m^2/day. Only two DLTs were observed: a grade 3 hypersensitivity reaction with dizziness and hypoxia at DL 8 (belinostat 1700 mg/m^2/day, 13c-RA 100 mg/m^2/day); and a grade 3 allergic reaction in a patient with an ECOG PS 2 at DL 11 (belinostat 2000 mg/m^2/day, 13c-RA 100 mg/m^2/day). The MTD was not reached. Pharmacokinetics of belinostat suggests dose proportionality. Median number of cycles: 2 (range 1–56). 10 patients had SD including: 1 neuroendocrine pancreatic stable for 56 cycles; 1 breast pt for 12 cycles; 1 lung pt 8 cycles. 2 pt had PRs: a keratinizing squamous cell carcinoma (tonsil) and a lung cancer pt. **Conclusions:** Belinostat 2000 mg/m^2 days 1-5and 13-cis-Retinoic acid 100 mg/m^{2}days 1-14, every 21 days, was well-tolerated and an MTD was not reached despite doubling the established single agent MTD. Future studies building on this combination to belinostat are warranted. Support: U01CA062505 and P30CA033572 (City of Hope); U01CA099168 and P30CA047904 (University of Pittsburgh).

2527 Poster Discussion Session (Board #15), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Phase I trial of belinostat in combination with cisplatin (Cis) and etoposide (Etop).

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Background: Histone deacetylase inhibitors (HDIs) are epigenetic therapies in development. To exploit the unique activity in impairing DNA repair, HDIs have been combined with chemotherapy. Belinostat is a potent HDI combined with Cis and Etop based on enhanced DNA damage and apoptosis in small cell lung cancer (SCLC) cells. **Methods:** Patients with relapsed/refractory cancer or previously untreated advanced stage SCLC were eligible. Belinostat was administered by continuous infusion (CIV) over 48h, from 400 mg/m^2/24h, in cohorts of 3. Cis was administered on day 1 and Etop daily X3. Belinostat pharmacokinetics (PK) and several pharmacodynamic (PD) measures were assessed, including lysine acetylation in peripheral blood mononuclear cells (PBMCs) and γH2Ax staining in PBMCs and in hair follicles. **Results:** Five dose levels were explored in 20 patients with solid tumors, including 5 patients with SCLC, two who had no prior therapy. At the first dose level, dose-limiting toxicities (DLT) of gr 4 ANC in 1, and gr 3 HTN in 1 were observed. Cis and Etop were reduced to 60 mg/m^2 and 80 mg/m^2, respectively, and the dose level repeated without DLT. At the next dose level, 800 mg/m^2/24h belinostat, grade 3 HTN and grade 4 pneumonitis were observed. At the MTD of 600 mg/m^2/24h belinostat, DLT was seen in 1 of 6 pts; however, all 6 pts required later dose reductions. We thus considered 500 mg/m^2/24h in combination with Cis and Etop to be the recommended Phase II dose; confirmation ongoing. PKs show belinostat levels at 1 uM over the 48h infusion, decreasing rapidly to the 60h timepoint. In total 11 pts, 3 with SCLC, completed 6 cycles. PR was seen in 6 pts (3 with SCLC). PD studies confirmed γH2AX staining in PBMCs and hair follicles, peaking at 36h and 60h, respectively. Tubulin and lysine acetylation (Ac-K) in PBMCs peaked at 36h; Ac-K recovered more rapidly than tubulin, mirroring γH2AX. **Conclusions:** The MTD of belinostat over 48h by CIV was 600 mg/m^2/24h, in combination with Cis 60 mg/m^2 on day 1 and Etop 80 mg/m^2 on days 1 - 3. PD endpoints indicate that belinostat is active in promoting both acetylation and DNA damage. The HDI combined with chemotherapy requires dose reduction and likely represents an on-target increase in DNA damage. Clinical trial information: NCT00926640.

2528 Poster Discussion Session (Board #16), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Phase I, dose-escalation study of the investigational drug TAK-733, an oral MEK inhibitor, in patients (pts) with advanced solid tumors.

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Background: This first-in-human study evaluated the safety, pharmacokinetics (PK), pharmacodynamics (PD), MTD, and efficacy of TAK-733 – an oral, selective, allosteric inhibitor of MEK1/2 – in pts with advanced solid tumors (NCT00948467; completed study). **Methods:** Eligibility: age ≥18 y; ECOG PS 0–2; evaluable tumors. Pts received escalating doses of TAK-733 QD in a modified 3+3 design for 21 d in a 28-d cycle to determine the MTD based on DLTs in cycle 1. Plasma (PK) and peripheral blood samples (PD: pERK reduction in PBMCs) were obtained pre-dose (d 1, 8, 15, 21) and post-dose (d 1, 21) in cycle1. **Results:** 51 pts (median age 58 y; 51% M) received escalating doses of TAK-733 (0.2–22 mg; median 2 cycles, range 1–11 [5 pts ≥6 cycles]). 4 pts had DLTs: grade 3 acneiform dermatitis, 1 each at 11.8 and 16mg; grade 3 pustular rash and grade 2 rash/stomatitis (qualifying as a DLT) at 22mg, leading to the 16 mg dose being selected as MTD. 45 pts (88%) had a drug-related AE; most frequent was acneiform dermatitis (47%). 10 pts (20%) had a grade ≥3 drug-related AE; most frequent were creatine phosphokinase increase and acneiform dermatitis (each n=3, 6%). 7 pts discontinued due to AEs. TAK-733 exhibited a moderately fast absorption with a median T_{max} of 3 hr. Steady-state exposure of TAK-733 (0.2–22mg) did not increase in a dose proportional manner based on the power model analysis. The mean terminal $t_{1/2}$ (11.8, 16, and 22 mg) was 43 hr. Overall mean accumulation ratio was 3.5 following QD dosing for 21 d. On d 21, E_{max} of blood pERK modulation was 56–99%, and time-averaged modulation over the dosing interval at steady-state was 76–98% at MTD. This range correlates well to the 76–89% for pERK modulation associated with maximal efficacy in xenograft models. 1 pt (16 mg) with melanoma (BRAF L597R) had a confirmed partial response after 4 cycles (treated for 9 cycles). 15 pts had a best response of stable disease (4–11.7 months in 6 pts). **Conclusions:** From preliminary data, TAK-733 appears generally well tolerated, pharmacodynamically active and shows signs of anti-tumor activity in pts with advanced solid tumors. MTD was associated with significant pERK inhibition in peripheral blood. Clinical trial information: NCT00948467.

2529 Poster Discussion Session (Board #17), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Phase I study of everolimus (E, RAD001) and ganitumab (G, AMG 479) in patients (pts) with advanced solid tumors.

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Background: Synergism between IGF and mTOR inhibitors has been documented preclinically. We conducted a phase I study to determine the safety, recommended phase II dose (RP2D), pharmacokinetics (PK), pharmacodynamics (PD), and antitumor efficacy of E with G. **Methods:** Eligible pts had good organ function, ECOG PS 0-1. The study had a standard "3+3" design, using E 5 or 10 mg orally daily (QD), and G 12 mg/kg IV every 2 wks (Q2W) in 28 day cycles (C); an expansion cohort was added at MTD for further efficacy analysis. E was given as single agent during C1D1-7 with PKs on C1D1 and D7, and continuously after C1D16. G was started on C1D15 with single agent PK. PKs for both drugs at steady state were performed on C3D1. PDs (blood and serial tumor biopsies) for IGF and PI3K/Akt/mTOR pathways were performed at baseline, C1D7, C3D1 and time of progression. **Results:** 20 ptswere enrolled to date, M/F: 8/12, median age 55 yrs (24-70); PS: 0/1= 13/7. The table summarizes dose levels and DLTs. The most common toxicities were fatigue (5), diarrhea, mucositis, dysgeusia, anemia and thrombocytopenia (4 each), and rigors (3). Grade (Gr) 3 toxicities were: mucositis (3), anemia (2), thrombocytopenia (2), and diarrhea (1). Pts received a median of 3 cycles (0-9). One pt discontinued study on C1D9 due to intracerebral bleed and 1 pt withdrew consent on C1D15. Among 18 evaluable pts, none responded and 9 pts (50%) had SD with a median duration of 20 wks (range 11-35). Prolonged clinical benefit (SD $\geq$ 20 wks) was noted in refractory fibrolamellar HCC, neuroendocrine, GIST and urachal cancers. PKs showed no significant interaction between E and G. Baseline IGF-1R and PTEN expression, and IGF1 levels did not affect clinical benefit. pS6 downregulation and pAkt upregulation in paired tumor biopsies occurred in all (7/7) or most (6/7) samples evaluated, and did not correlate with efficacy. IGF1 and IGFBP3 levels increased on-treatment in 80-90% of pts. **Conclusions:** E+G is safe and the RP2D is E 10 mg QD + G 12 mg/kg Q2W. While on target pS6 reduction occured, the IGF1-R inhibition did not affect pAkt upregulation from mTOR blockade. Clinical trial information: NCT01122199.

Cohort (# pts)	E (mg)	G (mg/kg)	# DLT	DLT
1* (8)	5	12	1	Gr 3 mucositis
2 (3)	10	12	0	
2 expansion (9)	10	12	1	Gr 3 mucositis

* Two pts not evaluable for DLT.

2530 Poster Discussion Session (Board #18), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Combination of a MEK inhibitor, pimasertib (MSC1936369B), and a PI3K/mTOR inhibitor, SAR245409, in patients with advanced solid tumors: Results of a phase Ib dose-escalation trial.

Rebecca Suk Heist, Leena Gandhi, Geoffrey Shapiro, Naiyer A. Rizvi, Howard A. Burris, Johanna C. Bendell, Jose Baselga, Scott B Yerganian, Karl Hsu, Janet Ogden, Loïc Vincent, Oliver von Richter, Giuseppe Locatelli, Ekatherine Asatiani, Jeffrey R. Infante; Massachusetts General Hospital, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Memorial Sloan-Kettering Cancer Center, New York, NY; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; Sanofi-Aventis, Cambridge, MA; EMD Serono, Inc., Billerica, MA; Sanofi Oncology, Vitry-sur-Seine, France; Merck KGaA, Darmstadt, Germany; Merck Serono S.A., Geneva, Switzerland

Background: PI3K/mTOR and MAPK signaling pathways are often deregulated in tumors. Simultaneous inhibition of these pathways with the MEK1/2 inhibitor, pimasertib, plus the dual PI3K/mTOR inhibitor, SAR245409, (ClinicalTrials.gov NCT01390818) was investigated. **Methods:** This was a phase Ib, modified 3+3, dose-escalation trial in patients (pts) with advanced solid tumors. Pts received pimasertib and SAR245409 at the following dose levels (DLs): DL1, 15/30; DL2a, 30/30; DL2b, 15/50; DL3, 30/50; DL4a, 60/50; DL4b, 30/70; DL5, 60/70; DL6a, 90/70; DL6b 60/90 and DL7, 90/90 mg (once-daily, qd). After the qd maximum tolerated dose (MTD) was established, twice-daily (bid) dosing was tested: DL1a, 60/30; DL1b, 45/50 and DL2 60/50 mg bid. A recommended phase II dose (RP2D) was determined. Enrollment continued at the RP2D in four expansion cohorts (18 pts each): dual *KRAS/PIK3CA* mutated (mt) colorectal cancer (CRC), triple-negative breast cancer, *KRAS* mt non-small cell lung cancer (NSCLC) and *BRAF*mt melanoma. **Results:** 53 pts were treated qd and 7 pts bid. The most common tumors were CRC (n=16), NSCLC (n=8), ovarian and pancreatic (n=7, each). At DL6b 2/3 pts had dose-limiting toxicities (DLTs; both grade [Gr] 3 nausea/vomiting). DL6a was confirmed as the MTD for the qd schedule. At bid DL1a 2/4 pts (both Gr 3 skin rash) and at DL1b 2/3 pts (Gr 3 skin rash and Gr 3 asthenia) had DLTs. DL5 was the RP2D based on tolerability after prolonged exposure. The most common adverse events in qd schedule were: rash (62%, 13% Gr 3), diarrhea (56%, 4% Gr 3), fatigue (51%, 2% Gr 3), nausea (49%, 2% Gr 3), vomiting (45%, 2% Gr 3), peripheral edema and pyrexia (34%, each) and visual impairment with underlying serous retinal detachment (21%). Preliminary pharmacokinetic results suggest no drug-drug interaction. There were 4 partial responses: *KRAS* mt CRC (n=1) and low-grade ovarian cancer (n=3, 1 *KRAS* mt/*PIK3CA* mt and 2 wild-type). Enrollment in expansion cohorts at DL5 is ongoing. **Conclusions:** Continuousqd dosing of pimasertib and SAR245409 is tolerated and has shown signs of activity. Phase II trials are being planned. Clinical trial information: NCT01390818.

2531 Poster Discussion Session (Board #19), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Safety, pharmacokinetics, and preliminary activity of the α-specific PI3K inhibitor BYL719: Results from the first-in-human study.

Ana M. Gonzalez-Angulo, Dejan Juric, Guillem Argilés, Jan HM Schellens, Howard A. Burris, Jordan Berlin, Mark R. Middleton, Martin H. Schuler, Robin Van Geel, Thorunn Helgason, Douglas Bootle, Markus Boehm, Timothy K. Goggin, David Demanse, Cornelia Quadt, Jose Baselga; The University of Texas MD Anderson Cancer Center, Houston, TX; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; Department of Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; The Netherlands Cancer Institute-Antoni Van Leeuwenhoek Hospital, Amsterdam, Netherlands; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; Vanderbilt-Ingram Cancer Center, Nashville, TN; Churchill Hospital Cancer Center, Oxford, United Kingdom; West German Cancer Center, University Hospital Essen, Essen, Germany; Novartis Pharma AG, Basel, Switzerland; Novartis Pharmaceuticals Corp, East Hanover, NJ; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: BYL719 is an oral small-molecule inhibitor of the p110α catalytic subunit of phosphatidylinositol 3-kinase (PI3K), which is encoded by the *PIK3CA* gene, one of the most commonly mutated genes in human cancers. BYL719 inhibits proliferation of PI3Kα-driven cancer cell lines in vitro and causes regression of *PIK3CA*-mutant tumor models in vivo. **Methods:** This Ph I study was performed in patients (pts) with advanced solid tumors carrying a somatic mutation of *PIK3CA*. Dose escalation used an adaptive Bayesian logistic regression model with overdose control. Following determination of the maximum tolerated dose (MTD), an expansion cohort was opened at the MTD to evaluate safety, pharmacokinetics (PK), and clinical activity in pts with *PIK3CA*-mutant advanced solid tumors, including estrogen receptor-positive (ER+) metastatic breast cancer (mBC). **Results:** During dose escalation 36 pts received doses up to 450 mg/d, where 4/9 pts had dose-limiting toxicities (DLTs). The MTD for once-daily dosing was declared as 400 mg/d. As of Nov 20 2012, DLTs were hyperglycemia, nausea, vomiting, and diarrhea. The most common BYL719-related adverse events (all grades, all cohorts, >25%) were hyperglycemia (49%), nausea (45%), diarrhea (40%), decreased appetite (38%), vomiting (30%), and fatigue (27%). 39 pts are enrolled in the MTD dose-expansion cohort. Investigation of a twice-daily regimen is also ongoing. BYL719 has a favorable, approximately dose-proportional PK profile with a T_{max} of 2h and a $T_{½}$ of 11h at the MTD. Partial responses were seen in 7 pts (in ER+ breast [2], cervical, trichilemmal, endometrial, ovarian, and head &neck cancer [1 each]); 17 pts stayed on study for >24 weeks. For 67 pts (76%) treated at doses of ≥270 mg/d, the median progression-free survival (mPFS) was 3.6 months (mo; 95% CI: 3.5–5.5 mo). mPFS in 15 ER+ HER2– mBC pts treated at ≥270 mg/d was 5.5 mo (95% CI: 3–7 mo). **Conclusions:** BYL719 displays dose-proportional and predictable PK. The safety profile is favorable, with mostly manageable on-target toxicities. At doses of ≥270 mg/d, tumor regression and prolonged disease control were observed in heavily pretreated pts with various tumor types carrying a *PIK3CA* mutation. Clinical trial information: NCT01219699.

2532 Poster Discussion Session (Board #20), Tue, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

A pilot study of sirolimus (S) in subjects with Cowden syndrome (CS) with germ-line mutations in PTEN.

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Background: CS is characterized by germline PTEN mutations. Because tumors from CS patients show increased activation of the PI3K/Akt/mTOR pathway, mTOR inhibitor such as S might have activity in such patients. **Methods:** Eligibility: subjects with germline PTEN mutation who meet international diagnostic criteria for CS, age 18, ECOG PS 0-2, and adequate organ function. Subjects were treated with a 56-day course of daily oral S (2 mg). Objective: Inhibition of the mTOR pathway in benign skin/GI lesion, as assessed by IHC (P-AKT, Total S6, P-S6, P-4E-BP1, score 0-4), changes in benign or malignant tumor by CT/MRI/PET, digital dermoscopy/endoscopy, and changes in cerebellar testing by modified SARA (Neurology 2006). Protocol was amended to allow up to 20 subjects. **Results:** A total of 18 pts/16 families were enrolled. Median age 42 (range 19-69). Male/Female: 9/9. Involvement in skin, thyroid, GI polyps, breast, CNS, and all of the five organs was observed in 18, 15, 13, 8, 18, 5 subjects, respectively. 7 had h/o malignancies: 3 renal cell, 4 breast, 3 thyroid, 4 others. 3 cerebellar gangliocytomas and 2 others were measurable by CT or MRI. PTEN mutations: 6 families in Exon 1-2, 1 in Exon 4, 9 in Exon 5-8. All but one (D24H) were truncating mutations. 11 of 16 pts who completed a 56-day course reported subjective improvement in energy, mood, focus or skin lesion. Pts with Ex6-8 mutation ($n=4$) had a median SUV decrease of 29.4%. Regression of skin and GI lesions was observed by dermoscopy or endoscopy. Cerebellar evaluation showed a significant improvement in a total SARA score at 1 month ($n=9$, $p=0.034$). 3 pts were treated for only 28 days due to voluntary withdrawal. IHC analysis in skin and GI benign lesions showed a decrease in average P-S6K, P-S6, Total S6, P-S6/Total S6 in response to S. P-S6K/Total S6 ratios at d14 and d56 were significantly lower than at baseline ($p=0.0026$, 0.0391, respectively). The most common AEs (all grades $>25\%$) were LFTs/Hb (39%), fatigue/hypercholesterolemia (28%). Grade 3 AEs: 1 pt hypophosphatemia/lymphopenia. **Conclusions:** A 56-day course of S was well tolerated in subjects with CS and was associated with improvement in symptoms, skin/GI lesions, cerebellar function and decreased mTOR signaling. Clinical trial information: NCT00971789.

2533 General Poster Session (Board #1A), Mon, 8:00 AM-11:45 AM

Phase Ib safety trial of CVX-060, an intravenous humanized monoclonal CovX body inhibiting angiopoietin 2 (Ang-2), with axitinib in patients with previously treated metastatic renal cell cancer (RCC).

Ashwin Gollerkeri, Michael S. Gordon, John M. Burke, Ralph Hauke, Jiri Tomasek, Donald A. Richards, Christopher DiSimone, Scott S. Tykodi, Amit R. Mehta, Charles Chen, Rachelle Perea, Nicholas J. Vogelzang; Pfizer BioTherapeutics, Cambridge, MA; Pinnacle Oncology Hematology, Scottsdale, AZ; Rocky Mountain Cancer Centers, Aurora, CO; Nebraska Methodist Hospital, Omaha, NE; Masaryk Memorial Cancer Institute, Brno, Czech Republic; Tyler Cancer Center, US Oncology Research, Houston, TX; Arizona Oncology Associates, Tucson, AZ; University of Washington/Seattle Cancer Care Alliance, Seattle, WA; Robert Wood Johnson Medical School; Cancer Institute of New Jersey, Durham, NC; Pfizer Inc., La Jolla, CA; Pfizer, San Diego, CA; US Oncology Research/Comprehensive Cancer Centers of Nevada, Las Vegas, NV

Background: PF-04856884 is a recombinant humanized monoclonal antibody fused to two Ang-2 binding peptides. Axitinib is a potent and selective second-generation inhibitor of vascular endothelial growth factors (VEGFs) that is approved for patients (pts) with advanced renal cell cancer who failed 1 prior therapy. Metastatic RCC (mRCC) is an angiogenic tumor sensitive to VEGF tyrosine kinase inhibitors. Resistance to VEGF targeted therapy may be mediated by Ang-2. **Methods:** In Part I (safety lead in) of the study, the primary endpoint was treatment related dose limiting toxicities (DLT) in pts with mRCC who had received 1-3 prior treatments. Pts received PF-04856884 (15 mg/kg/week) plus axitinib (5 mg BID) for 4 week cycles (the recommended Phase II dose of each) and were assessed for DLT, PK, and potential predictive biomarkers (Ang-2 and VEGF-A). For Part II (Phase II portion), pts with mRCC who had received 1 prior anti-VEGF agent were to be randomized to PF-04856884 + axitinib or axitinib alone to assess median progression free survival. **Results:** Part I enrolled 18 pts with median age of 62.5 years (39-82), and ECOG performance status of 0-1. One pt had a DLT of Grade 4 pulmonary embolism (PE). Most common related AEs: anorexia in 10 pts (56%), diarrhea 8 (44%), fatigue 8 (44%), nausea 7 (39%), hypertension 6 (33%) and vomiting 6 (33%). Treatment-related thromboembolic events (TEEs) were observed: PE in 2 pts (11%), and cerebrovascular accident (CVA), presumed bowel ischemia, and possible cardiac chest pain in 1 pt (6%) each. One pt had Grade 2 venous thrombosis unrelated to either treatment. Due to the reported TEE, PF-04856884 was reduced to 10 mg/kg in pts remaining on study and enrollment to Part II was not initiated. No significant PK interaction was observed. Two pts had partial response (PR) and 1 pt had unconfirmed PR. Twelve pts (66%) remained on study ≥91 days with a median duration of 120 days (8-279). Anti-PF-04856884 antibody results are not available. **Conclusions:** Due to the higher than expected TEEs, alternate doses of PF-04856884 and/or disease settings are being considered. Clinical trial information: NCT01441414.

2534 General Poster Session (Board #1B), Mon, 8:00 AM-11:45 AM

Phase I trial of trebananib (AMG 386) plus temsirolimus (Tr + T) in patients (pts) with advanced solid tumors (PJC-008/NCI#9041).

David Shao Peng Tan, Christian K. Kollmannsberger, Sebastien J. Hotte, David W. Cescon, Ivan Diaz-Padilla, David W. Hedley, Daniel John Renouf, Albiruni R.A. Razak, Karen A. Gelmon, Hal W. Hirte, Lisa Wang, Monika Wizemann, Jeffrey Moscow, Helen X. Chen, Lillian L. Siu, Philippe L. Bedard, Princess Margaret Hospital Phase I Consortium; Princess Margaret Cancer Center, Toronto, ON, Canada; BC Cancer Agency, Vancouver, BC, Canada; Juravinski Cancer Centre, Hamilton, ON, Canada; Princess Margaret Hospital, University Health Network, University of Toronto, Toronto, ON, Canada; Princess Margaret Hospital, Toronto, ON, Canada; Ontario Cancer Institute, Toronto, ON, Canada; Princess Margaret Hospital, Toronto, ON, Canada; British Columbia Cancer Agency, Vancouver, BC, Canada; Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, ON, Canada; J457 KY Clinic, Lexington, KY; CTEP National Cancer Institute, Bethesda, MD; Princess Margaret Cancer Center, University Health Network, Division of Medical Oncology & Hematology, Department of Medicine, University of Toronto, Toronto, ON, Canada

Background: Preclinical data suggest that combined Ang1/2 and mTOR blockade has synergistic anti-cancer activity. The combination of Tr (inhibits angiogenesis by preventing interaction of Ang1/2 with Tie2) with the mTOR inhibitor T was evaluated in pts with advanced solid tumors to determine safety, tolerability, maximum tolerated dose (MTD), pharmacodynamics and preliminary antitumor activity. **Methods:** Pts were enrolled using 3+3 design. Tr and T were dosed on Day 1 (D1), 8, 15 and 22 of a 28-day cycle. Peripheral blood was collected for evaluation of Tie2-expressing monocytes (TEMs) and thymidine phosphorylase (TP) (an angiogenic enzyme increased in TEMs upon Tie2 stimulation) by flow cytometry. Tumor response was assessed every 2 cycles. **Results:** 13 pts have been enrolled, 6 at dose level (DL) 1 (15mg/kg Tr + 25mg T) and 7 (1 died from disease before DLT assessment) at DL -1 (15mg/kg Tr + 20mg T). Median age was 57yrs, ECOG 0-1, median previous chemotherapy lines 3 (range 1-8). In DL 1, 1/6 pts experienced DLT (Grade (Gr) 2 pneumonitis). In view of frequent Gr2 adverse events (AEs) in DL 1, DL -1 was evaluated with DLTs in 2/6 evaluable pts (Gr3 mucositis and intolerable Gr2 limb edema preventing start of cycle 2 within 14 days). The most common related AEs (all Gr across both DL) were: fatigue (77%), edema (69%), anorexia (62%), and nausea (54%). Common Gr≥3 AEs included lymphopenia (23%) and fatigue (23%). Of 10 evaluable pts, best RECIST responses were: 1 breast cancer pt (ER+/ HER2-/ *PIK3CA* mutant) with PR (now in cycle 9), 7 pts with SD, and 2 pts with PD. Four pts with ovarian cancer (1 *PIK3CA*mutant) had SD ≥11weeks with 2/3 pts (1 not evaluable) demonstrating GCIG response (>50% decrease in CA125). In preliminary analyses, TP expression in TEMs was decreased (mean -18%) in 4pts with tumor shrinkage, but increased (+6%) in 1pt with tumor growth, suggesting a trend between reduced TP and tumor response. **Conclusions:** The MTD was exceeded at 15mg/kg Tr and 20mg T weekly. The safety of 10mg/kg Tr and 20mg T weekly is currently being evaluated. The combination of Tr and T shows early signs of antitumor activity. TP expression in TEMs by flow cytometry as an early marker of treatment benefit warrants further evaluation. Clinical trial information: NCT01548482.

2535 General Poster Session (Board #1C), Mon, 8:00 AM-11:45 AM

A phase I study of ombrabulin (O) combined with bevacizumab (B) in patients with advanced solid tumors.

Michael Ong, Gianluca Del Conte, Rastislav Bahleda, Joaquin Mateo, Silvia Damian, Antonella Perotti, Nathalie Lassau, Françoise Farace, Jimena Lovosgaldeano, Nina Tunariu, Marie Hospitel, Paola Mariani, Patrick Cohen, Giuseppe Capri, Jean-Charles Soria, Luca Gianni, L Rhoda Molife, Cristiana Sessa; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Ospedale San Raffaele, Milan, Italy; Institut Gustave Roussy, Villejuif, France; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Istituto Nazionale Tumori, Milan, Italy; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, London, United Kingdom; Sanofi, Vitry-sur-Seine, France; San Raffaele Scientific Institute, Milan, Italy; Ospedale Regionale Bellinzona e Valli, Bellinzona, Switzerland

Background: O, a vascular-disrupting agent derived from combretastatin A4-phosphate, induces rapid tumor vascular shutdown via endothelial cell damage. Resistance to O may occur by surges in circulating endothelial progenitors (CEP) that repopulate the tumor vasculature. Experimental models suggest prolonged and synergistic antitumor activity when O is combined with VEGF-blockade, with reduction in CEP surge. This phase I study was performed to determine the maximum tolerated dose, safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary antitumor activity of O combined with B. **Methods:** Patients (pts) with advanced treatment-refractory solid tumors, ECOG PS $\leq$1, and adequate organ function were eligible. O (mg/m^2) was administered intravenously (IV) on day (d)1 with B (mg/kg) IV on d2 in 21d cycles (C). A Bayesian model informed dose escalation steps. PK sampling, dynamic contrast-enhanced ultrasound (DCE-US) for tumor perfusion, and CEP samples were collected. **Results:** 39 pts (M:F 10:29; median age 51 years [range 25-75]) were treated at 12 dose levels combining O [8 to 50mg/m^2] with B [5, 10, or 15mg/kg]. Ovary (16/39, 41%) and colon (4/39, 10%) were the most common primary sites. No C1 dose-limiting toxicities occurred in 37 evaluable pts. Drug-related grade 3-4 treatment emergent adverse events (AE) were hypertension (6/39, 15%), intestinal perforation (2/39, 5%), headache (1/39, 3%), myocardial infarction (1/39, 3%), and pulmonary embolism (1/39, 3%). 36 pts (14 ovarian) were evaluable for response by RECIST 1.1. Antitumor activity was observed at O 20mg/m^2+ B 10mg/kg and above, with confirmed partial responses in 2/14 pts with ovarian primary (14%), CA125 responses in 2 further ovary/endometrial cancers lasting $\geq$ 6 months, and stable disease in 15/36 pts (42%) lasting $\geq$ 6 months in 3 pts. PK indicated no interactions of O+B. Analyses of CEP levels post O and paired DCE-US data are ongoing. **Conclusions:** The maximum administered dose (MAD) was O 50mg/m^2 with B 15mg/kg, with no dose-limiting toxicities and vascular toxicity that was manageable. Promising antitumor activity was observed at doses below the MAD and warrants further evaluation. Clinical trial information: NCT01193595.

2536 General Poster Session (Board #1D), Mon, 8:00 AM-11:45 AM

Phase I study of safety, tolerability, and pharmacokinetics of pazopanib in combination with oral topotecan in patients with advanced solid tumors.

Bojana Milojkovic Kerklaan, Martijn P. J. K. Lolkema, Lot A. Devriese, Emile E. Voest, A. Nol-Boekel, M. Mergui-Roelvink, Kristine Mykulowycz, Joseph E Stoebenau, Lei Fang, Philippe Legenne, Paul Stephen Wissel, Deborah A. Smith, Bruce J. Giantonio, Jan HM Schellens, Petronella Witteveen; The Netherlands Cancer Institute-Antoni Van Leeuwenhoek Hospital, Amsterdam, Netherlands; University Medical Center Utrecht, Utrecht, Netherlands; Netherlands Cancer Institute, Amsterdam, Netherlands; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; GlaxoSmithKline, Research Triangle Park, NC; GlaxoSmithKline, Uxbridge, United Kingdom; GlaxoSmithKline, Collegeville, PA; The Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; DGOG and University Medical Center Utrecht, Utrecht, Netherlands

Background: To determine the maximum-tolerated dose (MTD), safety, tolerability and pharmacokinetics of the oral anti-angiogenic drug pazopanib in combination with oral topotecan, an inhibitor of topoisomerase-I. **Methods:** Two-stage, two-arm, dose escalation and pharmacokinetic phase I study of pazopanib and oral topotecan in patients with advanced solid tumors, (NCT00732420, www.clinicaltrials-.gov). This interim report describes the bioavailability and safety results for daily pazopanib combined with oral topotecan (days 1, 8, 15) in a 28-day cycle. **Results:** Twenty-eight of 32 patients completed at least one cycle and were evaluable for analysis. Three dose-limiting toxicities (DLTs) occurred: grade 3 hand-foot-syndrome, diarrhea and neutropenia. Pazopanib 800 mg/topotecan 10 mg exceeded the MTD with two DLTs in six patients. The most frequent treatment-related toxicities were grade 3 anemia (3/28), leukocytopenia, neutropenia and fatigue (2/28 each). One death due to hepatic failure occurred at pazopanib 800mg/toptecan 2mg in a heavily pre-treated patient with sarcoma that may have been related to paracetamol ingestion but attribution to the pazopanib can not be excluded. Topotecan $AUC_{0-\infty}$ increased 1.58-fold (90%CI: 1.09–1.29) and C_{max} increased 1.78-fold (90%CI: 1.08-2.92) when given with pazopanib compared to single administration (n=7). Pazopanib AUC_{0-24} and C_{max} ratios were not increased when co-administered with topotecan: 0.98 (90%CI: 0.95-1.02) and 0.96 (90%CI: 0.92-1.01). Twenty-three patients were evaluable for response (RECIST): PR (2/23; 9%, both ovarian cancer); SD (13/23; 57%) and PD (8/23; 35%). Pazopanib 800 mg/topotecan 8 mg is currently being explored in an expansion cohort. A second treatment arm of pazopanib 800 mg with topotecan daily x5 is ongoing and will be reported separately. **Conclusions:** Daily pazopanib and weekly oral topotecan is tolerable with handfoot syndrome, neutropenia and fatigue as dose limited side effects. Pazopanib increased topotecan exposure 1.58-fold ($AUC_{0-\infty}$) and 1.78-fold (C_{max}). Clinical trial information: NCT00732420.

2537 General Poster Session (Board #1E), Mon, 8:00 AM-11:45 AM

Pharmacodynamic study using FLT PET/CT in patients treated with axitinib.

Glenn Liu, Peter Scully, Jill Kolesar, Justine Yang Bruce, Jens C. Eickhoff, Scott Perlman, Lakeesha Carmichael, Jennifer Heideman, Robert Jeraj; University of Wisconsin Carbone Cancer Center, Madison, WI; University of Wisconsin Department of Medical Physics, Madison, WI; Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI; Department of Radiology, University of Wisconsin, Madison, WI; Department of Biostatistics, University of Wisconsin, Madison, WI; Department of Medical Physics, University of Wisconsin, Madison, WI

Background: Axitinib (AX) is a potent VEGFR2 TKI. The objective of this study was to characterize tumor vascular and proliferative changes in patients treated with AX. **Methods:** Thirty pts with solid malignancies with at least one target lesion appropriate for FLT PET/CT imaging were enrolled. Pts were treated in Cycle #1 (C1) with AX at 5 mg BID x 2 wks, followed by a 1 wk drug holiday. Subsequent cycles continued the AX BID on a continuous basis until progression or unacceptable toxicity. In cohort A, FLT PET/CT was obtained at baseline, C1D14 (during AX) and C1D21 (AX withdrawal). Cohort B used the same treatment schedule, but FLT PET/CT was obtained on C1D14, C1D16 and C1D21. At each imaging time, peak FLT Standardized Uptake Values (SUV_{peak}), AX pharmacokinetics and plasma VEGF levels were obtained. **Results:** Of the 30 total pts, 28 had at least 1 PET/CT scan with 24 completing all planned PET/CT scans (13 in Cohort A; 11 in Cohort B). Strong proliferative flare (36% increase in SUV_{peak} from C1D14 to C1D21) was observed in majority of pts with most of the flare occurred within two days after AX withdrawal (25% increase in SUV_{peak} from C1D14 by C1D16). A robust vascular flare paralleled proliferative flare ($R=0.57$). A trend linking short progression free survival with high withdrawal flare was seen (44% increase in SUV_{peak} for PFS $\leq$ 6mo vs 11% increase in SUV_{peak} for PFS $>$ 6 mo; $p=0.14$). VEGF levels and AX PK levels increased during treatment, followed by decrease during withdrawal. **Conclusions:** The observed AX pharmacodynamics is consistent with our prior observation with another VEGFR TKI and suggests that acute AX withdrawal results in a robust withdrawal flare. This information suggests that the timing of cytotoxic chemotherapy during the flare may increase the therapeutic index, as opposed to concurrent administration which may be antagonistic. This study also shows the power of quantitative molecular imaging, which can simultaneous evaluate treatment response heterogeneity, as well as compensatory effects that may lead to early treatment failure. Clinical trial information: NCT00859118.

2538 General Poster Session (Board #1F), Mon, 8:00 AM-11:45 AM

A phase I trial and pharmacokinetic study of trebananib (AMG386) in children with recurrent or refractory solid tumors: A Children's Oncology Group Phase 1 Consortium report.

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Background: Trebananib is a first-in-class peptibody (peptide-Fc fusion protein) that selectively inhibits Angiopoietin 1 and Angiopoietin 2 to inhibit interaction with the Tie2 receptor tyrosine kinase and prevent angiogenesis by a VEGF independent mechanism. A pediatric phase 1 trial was performed to define the dose limiting toxicities (DLT), maximum tolerated dose (MTD) and pharmacokinetics (PK) of trebananib. **Methods:** Trebananib was administered as a weekly 30 - 60 minute IV infusion. Three dose levels (10, 15 or 30 mg/kg/dose) were evaluated using a rolling-six design. PK sampling and analysis of peripheral blood biomarkers was performed during the first 4 weeks of therapy. **Results:** Fifteen eligible patients (14 evaluable for toxicity) with a median age of 14 yrs (range, 3 to 20) and diagnoses of neuroblastoma (n=4), rhabdomyosarcoma (n=3), Ewing sarcoma (n=3), osteosarcoma (n=2), other soft tissue sarcoma (n=2), or nasopharyngeal carcinoma (n=1) have been enrolled. There were no DLTs observed at either the 10 mg/kg (n=6 pts) or 15 mg/kg (n=3 pts) dose. 1/6 pts receiving 30 mg/kg/dose developed DLT (venous thrombosis at a central line site). Non-dose limiting grade 3 or 4 toxicities included lymphopenia (n=2) hypertension (n=1), and neutropenia (n=1). Response in evaluable patients after eight weeks of therapy included stable disease (n=6 pts) and progressive disease (n=7 pts). PK were linear over the 3 dose levels, with $t_{1/2}$ and Cl_pvalues of 69±18 h and 1.6±0.5 ml/h/kg, respectively. **Conclusions:** Trebananib is well tolerated in pediatric patients with recurrent or refractory solid tumors with recommended Phase 2 dose of 30 mg/kg. Correlative biology studies will be presented. Further study is planned to evaluate tolerability and changes in vascular permeability in patients with primary CNS tumors. Clinical trial information: NCT01538095.

2539 General Poster Session (Board #1G), Mon, 8:00 AM-11:45 AM

Treatment of cancer and cancer stem cells by blocking the Notch pathway.

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Background: Current treatments often fail to cure cancer. It has been shown (JCO, 26, June 10, 2008) that Cancer Stem Cells, (CSCs), are responsible for the initiation, metastasis and recurrence of many cancers and may be a key reason for the failure of current therapies.The NOTCH pathway is an important pathway in the development of many tumors ,and cancer stem cells in particular. **Methods:** We have generated genetically and synthetically a hybrid protein (Antp-DNMAML) .consisting of the truncated version of MastermindElike (MAML) that behaves in a dominant negative (DN) fashion inhibiting Notch activation, and the cell penetrating peptide Antennapedia (Antp). **Results:** It is demonstrated that Antp-DNMAML translocates into the nucleus and suppresses Notch activation. Attenuation of Notch signaling with AntpEDNMAML reverts the transformed phenotype, inhibits the anchorageEdependent growth, induces self contact inhibition and apoptosis in highly tumorigenic epithelial human breast cancer cells. More significantly, we provide direct evidence that inhibiting Notch signaling at the transcriptional level with the Antp-MAML protein ,suppresses the expression of downstream Notch targets, induces tumor cell apoptosis, and inhibits or eliminates human tumor growth in nude mice, without organ or systemic toxicity. **Conclusions:** Intracellular delivery of dominant-negative transcription complex proteins using the Antp platform is a new and specific approach for cancer therapy.

2540 General Poster Session (Board #1H), Mon, 8:00 AM-11:45 AM

First-in-human evaluation of the human monoclonal antibody vantictumab (OMP-18R5; anti-Frizzled) targeting the WNT pathway in a phase I study for patients with advanced solid tumors.

David C. Smith, Lee S. Rosen, Rashmi Chugh, Jonathan Wade Goldman, Lu Xu, Ann Kapoun, Ranier K Brachmann, Jakob Dupont, Robert J. Stagg, Anthony W. Tolcher, Kyriakos P. Papadopoulos; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; University of California, Los Angeles, Division of Hematology-Oncology, Santa Monica, CA; University of Michigan, Ann Arbor, MI; Hematology and Oncology, University of California, Los Angeles, Santa Monica, CA; OncoMed Pharmaceuticals, Inc, Redwood City, CA; South Texas Accelerated Research Therapeutics, LLC., San Antonio, TX; START Center for Cancer Care, San Antonio, TX

Background: The WNT pathway is a key oncologic pathway in numerous tumor types. Vantictumab is a first-in-class anti-Cancer Stem Cell (CSC) antibody that interacts with the extracellular domain of 5 Frizzled receptors (1, 2, 5, 7, 8) and blocks canonical Wnt signaling (*PNAS 109, 11717*). In patient-derived xenograft models, vantictumab inhibits growth of many tumor types, reduces CSC frequency, promotes differentiation of tumor cells, and synergizes with many chemotherapeutic agents. **Methods:** Using a 3+3 design, vantictumab was given intravenously, first every 1 week (q1w) or q2w, and, ultimately, q3w. Objectives were determination of maximum tolerated dose, safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy. **Results:** 18 patients have been treated in 5 dose-escalation cohorts (0.5 & 1 mg/kg q1w; 0.5 mg/kg q2w; 1 & 2.5 mg/kg q3w). Most common related adverse events (AEs) included Grade 1 and 2 fatigue, vomiting, abdominal pain, constipation, diarrhea and nausea. Only related Grade ≥3 AEs were dose-limiting toxicities of Grade 3 diarrhea and vomiting in 1 patient at 1 mg/kg q1w. Vantictumab clearance was dose-dependent, consistent with target-mediated drug disposition, with the half-life ranging from 1.5 (0.5 mg/kg) to 3 days (2.5 mg/kg). Exposure at highest dosed cohorts correlates with efficacy in preclinical tumor models. PD biomarkers indicate manipulation of WNT pathway in patient tumors and surrogate tissue. 1 patient at 0.5 mg/kg q1w had a bone fracture on Day 110 with an ~4-fold increase by Day 28 of β-C-terminal telopeptide (β-CTX), a marker for bone degradation. A revised safety plan and less frequent dosing enabled further dose escalation. Upon β-CTX doubling, 2 patients received zoledronic acid, and β-CTX returned to baseline. 3 patients with neuroendocrine tumors (NETs) had stable disease (SD) for 7+, 3.5, and 9+ months; ~2-, 4- and 7-fold longer, respectively, than on prior therapy. **Conclusions:** Vantictumab is well tolerated up to 2.5 mg/kg q3w. Bone toxicity appears manageable and reversible. Prolonged SD in 3 patients with NETs may represent single-agent activity. Dose escalation continues. Clinical trial information: NCT01345201.

2541 General Poster Session (Board #2A), Mon, 8:00 AM-11:45 AM

Effects of a soluble activin type 2B receptor Fc fusion protein (STM 217) in TOV-21G, a mouse xenograft model of clear cell ovarian cancer.

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Background: Response rate and survival with the clear cell subtype of ovarian cancer is has not been improved by the introduction of platinum and taxane chemotherapy. Elevated serum activin is associated with inferior ovarian cancer survival, suggesting that activin inhibition may provide a new treatment strategy. STM 217 (recombinant hu-sActR2B-Fc) is a potent (IC_{50} < 1nM) inhibitor of activin and myostatin signaling that was tested for anti-ovarian tumor activity. **Methods:** Athymic nude mice received TOV-21g (clear cell ovarian cancer model) xenografts in the abdominal flank region and after 14 days, weekly subcutaneous STM 217 was administered alone or in combination with 5-fluorouracil (5-FU). Mice were monitored for body weight and tumor volume. **Results:** After 52 days from tumor cell injection, STM 217 treatment resulted in a statistically significant 43% ($p<0.0001$) tumor growth reduction, versus the vehicle-treated tumor bearing group tested using ANOVA. In the combination efficacy experiment, 5-FU monotherapy resulted in a 47% ($p<0.0001$) tumor growth reduction, and the combination of STM217 and 5-FU together resulted in a 73% ($p<0.0001$) tumor growth reduction. During the course of the study, body weight of the mice receiving STM 217 increased by 26%, mice receiving STM 217 and 5-FU increased by 22%, while control tumor bearing mice receiving vehicle exhibited a 10% body weight loss. **Conclusions:** Our study demonstrates that inhibition of activin signaling by use of a ligand trap results in antitumor activity, both as a monotherapy, and that additive activity was observed in combination with chemotherapy. Increases in body weight were not impaired by concomitant administration of 5-FU chemotherapy. This study suggests that a phase 1 clinical trial of activin inhibition in metastatic ovarian cancer is warranted.

2542 General Poster Session (Board #2B), Mon, 8:00 AM-11:45 AM

A dose-escalation phase I study of a first-in-class cancer stemness inhibitor in patients with advanced malignancies.

Adrian Langleben, Jeffrey G. Supko, Sebastien J. Hotte, Gerald Batist, Hal W. Hirte, Harry Rogoff, Youzhi Li, Wei Li, David Kerstein, David Leggett, Matthew J. Hitron, Chiang Li; Oncology Department, McGill University, Montreal, QC, Canada; Massachusetts General Hospital, Boston, MA; Juravinski Cancer Centre, Hamilton, ON, Canada; McGill University and Segal Cancer Centre, Jewish General Hospital, Montreal, QC, Canada; Boston Biomedical, Inc., Cambridge, MA; Boston Biomedical, Inc., Cambrige, MA

Background: Cancer Stem Cells (CSC) are considered to be fundamentally responsible for malignant growth, relapse, metastasis, and resistance to conventional therapies. BBI608 is an orally-administered first-in-class cancer stemness inhibitor which blocks CSC self-renewal and induces cell death in CSC as well as non-stem cancer cells by inhibition of the Stat3, Nanog and b-catenin pathways, and has shown potent anti-tumor and anti-metastatic activities pre-clinically. **Methods:** A phase 1 dose escalation studyin adult patients with advanced cancer who had failed standard therapies was conducted to determine the safety, tolerability, recommended phase 2 dose (RP2D), pharmacokinetics and preliminary anti-tumor activity of BBI608. A modified Simon accelerated titration scheme was used for dose escalation, with a cycle consisting of twice-daily oral administration of BBI608 for 4 weeks. Cycles were repeated every 4 weeks (28 days) until progression of disease, unacceptable toxicity, or other discontinuation criteria were met. **Results:** Fourteen cohorts (N=41) were dosed from 20 mg to 2000 mg/day with adverse events being generally mild; the most common being grade 1-2 diarrhea, nausea, anorexia and fatigue. Four grade 3 events included diarrhea (n=3) and fatigue (n=1). MTD was not reached and further dose escalation was limited by pill burden. By the 400 mg/day dose level the plasma concentration of BBI608 was sustained for over 8 hours at a concentration above 1.5 uM (several fold above the IC_{50}). 17/26 patients evaluable for tumor response achieved SD, for a DCR of 65%. Prolonged TTP was observed in 12/26 evaluable patients (46%), including patients with colorectal (CRC), head and neck, gastric, ovarian, melanoma, and breast cancer. In the subset of patients with CRC (N=18), SD was seen in 8/12 evaluable (67%). A median PFS of 14 weeks and median OS of 47 weeks were observed in evaluable CRC patients. **Conclusions:** Dose escalation of BBI608, a first-in-class cancer stem cell pathway inhibitor, has been achieved without dose limiting toxicity. BBI608 has shown an excellent safety profile, favorable pharmacokinetics, and encouraging signs of clinical activity particularly in CRC Clinical trial information: NCT01775423.

2543 General Poster Session (Board #2C), Mon, 8:00 AM-11:45 AM

Therapeutic p53 gene agent in the treatment of refractory cancer cases: A phase I study.

Xia He, Jianhua Xu, Jie Wen; Jiangsu Cancer Hospital, Nanjing, China

Background: To evaluate the benefit of adding therapeutic p53 gene agent into the standard treatment regimens for refractory cancer cases. **Methods:** Recombinant adenoviral human p53 gene (rAd-p53), was given intravenously at a dose of 2×10^{12} viral particles /day on 5 consecutive days one week before routine anti-cancer treatment start, and was repeated after an interval of 16 days. The inclusion criteria include: 1.Pathologically confirmed recurrent cancers; 2. Disseminated cases; 3. Patients with key organ metastasis; 4.Unresectable lesions; 5.Chemo- or radio-therapy resistant cases. The exclusion criteria include: 1.With severe liver, kidney, heart or hemotologic disorders; 2.Pregnancy; 3.Without informed consent. Efficacy was evaluated according to the results of contrasted MRI or CT. **Results:** A total of 16 patients entered the study with a median age of 59 years old (range 30-76 years), 13 were male and 3 were female. 5 were recurrent cases(4 HNSCC and 1 esophageal cancer), 5 were widely infiltrated unresectable HNSCC, esophageal carcinoma(2 cases) and undifferentiated thyroid carcinoma(1 case). 3 were disseminated cases(2 NPC and 1 Lung cancer). Two cases were breast cancer with multiple brain metastasis. One was refractory central nervous lymphoma. One patient did not finish the planned chemoradiation due to radiation-induced pneumotitis. Another one patient experienced chemotherapy delay due to A grade 4 hemotologic toxicity. 93.8% patients had shivering and fever after injection of rAd-p53. Other acute toxicities during the treatment included: leukopenia(Grade 3/4) 43.8%, thrombocytopenia (Grade 3/4) 25.0%, oral mucositis(Grade 3/4) 18.8%, vomiting(Grade 2 and above) 31.3%, ALT elevation (Grade 2 and above) 6.3%. No Cr elevation was observed. The acute toxicities were controllable and reversible. At the 3 months after treatment, PR, SD and PD rate were 56.3%, 25.0% and 18.7%, respectively. **Conclusions:** The therapeutic p53 gene agent can be intravenously safely added to routine anti-cancer regimens with controllable and reversible acute toxicities. A randomized controlled phase II is needed to make clear the role of the therapeutic p53 gene agent.

2544 General Poster Session (Board #2D), Mon, 8:00 AM-11:45 AM

Phase I study of c-Met inhibitor ARQ197 in combination with FOLFOX for the treatment of patients with advanced solid tumors.

Suzanne Fields Jones, Carla Kurkjian, Manish R. Patel, Jeffrey R. Infante, Howard A. Burris, F Anthony Greco, Michael Brian Hemphill, Adil I. Mohyuddin, Dana Shelton Thompson, Patrick Murphy, Eric Raefsky, Johanna C. Bendell; Sarah Cannon Research Institute, Nashville, TN; Stephenson Cancer Center/SCRI, Oklahoma City, OK; Florida Cancer Specialists/SCRI, Fort Myers, FL; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; Tennessee Oncology, PLLC/SCRI, Nashville, TN

Background: C-Met protein is a receptor tyrosine kinase which is overexpressed or mutated in a variety of tumor types, causing cell proliferation, metastasis, and angiogenesis. Tivantinib is an orally bioavailable small molecule which binds to the c-Met protein. This phase I study was designed to determine the maximum tolerated dose (MTD) of tivantinib in combination with standard dose FOLFOX for the treatment of patients with advanced solid tumors. **Methods:** Patients with advanced solid tumors for which FOLFOX (5-FU IV 400 mg/m^2 day 1; 5-FU CIV 2400 mg/m^2 day 1; Leucovorin IV 400 mg/m^2 day 1; Oxaliplatin IV 85 mg/m^2 day 1) would be appropriate chemotherapy received escalating doses of tivantinib BID (days 1-14) in a standard 3 + 3 design. Dose-limiting toxicities (DLTs), non-dose-limiting toxicities (NDLTs), safety, and preliminary efficacy were evaluated. **Results:** Fourteen patients (50% colorectal) were treated across 3 dose levels: 120 mg (n=3); 240 mg (n=5); 360 mg (n=6). No DLTs were observed until the 3rd dose level (treatment delay ≥3 days, secondary to grade 3 neutropenia). Common related adverse events (% grade 1/2; % grade 3/4) included: diarrhea (36%; 0%), neutropenia (0%; 29%), nausea (14%; 14%), vomiting (14%; 14%), dehydration (14%; 7%), and thrombocytopenia (14%; 0%). To date, 7 patients have been evaluated for response including 4 (57%) with stable disease evident at the 8-week evaluation (CRC, 2 patients; unknown primary favoring CRC, 1 patient; esophageal, 1 patient) and 3 (21%) with disease progression. The 4 patients with stable disease are continuing on treatment; three (CRC and unknown primary) had received prior FOLFOX. **Conclusions:** The addition of tivantinib to standard therapy FOLFOX appears tolerated up to its recommended phase II monotherapy dose of 360 mg. Preliminary efficacy is encouraging, and a phase II study is proceeding with this regimen for the first line treatment of advanced gastroesophageal patients. Clinical trial information: NCT01611857.

2545 General Poster Session (Board #2E), Mon, 8:00 AM-11:45 AM

Characteristics and survival of patients with advanced cancer and *TP53* mutations in phase I clinical trials.

Rabih Said, Yang Ye, David S. Hong, Filip Janku, Siqing Fu, Aung Naing, Jennifer J. Wheler, Razelle Kurzrock, Christoforos Thomas, Gary A. Palmer, Kenneth R. Hess, Robert A. Wolff, Apostolia Maria Tsimberidou; The University of Texas Health Science Center at Houston, Houston, TX; Department of Investigational Cancer Therapeutics (Phase I Program), University of Texas M. D. Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Investigational Cancer Therapeutics (Phase I Program), University of Texas MD Anderson Cancer Center, Houston, TX; University of California, San Diego, San Diego, CA; University of Houston, Houston, TX; Foundation Medicine, Inc., Cambridge, MA

Background: The classical hot spot mutations within the central sequence-specific DNA-binding region of *p53* protein (R175H in exon 5 and G245S, R248Q, R249S, R273H and R282W in exon 8) disrupt its ability to bind to DNA. These inactivating point mutations of *p53* may result in loss of its function and/or acquisition of a gain of function, which has been associated with the development of invasive and metastatic tumors in mouse models. We assessed the frequency and survival of *p53* mutations in patients with advanced cancer. **Methods:** *P53* mutation in patients' tumor was identified in a CLIA-certified laboratory using PCR, sequenom analysis or next generation sequencing. **Results:** *P53* mutations were identified in 212 patients. Median survival by tumor type and distribution of *p53* mutations by exon are shown in the Table. The median survival (from time of referral to Phase I clinic) by mutations in "hot spot" amino acids was as follows: R175H, 9.1 months (n=18); R248Q, not reached/5 deaths (n=22); R273H, 12.6 months (n=11); other mutations, 11.9 months (n=160). The median survival of patients with a tumor mutation in exons 5 or 8 appeared to be shorter than that of patients with mutations in other exons (9.4 vs. 14.6 months) although the difference was not statistically significant (p=.12) owing to the small number of patients. **Conclusions:** Our results demonstrate that the distribution and clinical significance of various *p53* mutations differs by tumor type and suggest that mutations in R248Q may be associated with longer survival.

Cancer type	No. of pts.	Median survival, months	Exon 5 (%)	Exon 6 (%)	Exon 7 (%)	Exon 8 (%)	Other exon (%)
Colorectal	46	13.0	15 (33)	5 (11)	10 (21)	9 (19)	7 (14)
Ovarian	23	9.5	9 (39)	3 (13)	4 (18)	6 (26)	1 (4)
Gastrointestinal, other	17	9.4	5 (29)	1 (6)	4 (24)	4 (24)	3 (17)
Lung	16	4.4	5 (30)	5 (30)	2 (13	2 (13)	2 (13)
Genitourinary	12	6.7	2 (17)	2 (17)	3 (25)	3 (25)	2 (16)
Gynecologic other	12	9.9	2 (17)	4 (34)	2 (17)	3 (24)	1 (8)
Head and neck	12	10.2	3 (25)	2 (17)	3 (25)	1 (8)	3 (25)
Breast	11	11.1	2 (18)	2 (18)	2 (18)	1 (9)	4 (37)
Sarcoma	8	11.4	3 (38)	1 (12)	0	2 (25)	2 (25)
Endometrial	7	9.7	2 (29)	1 (14)	4 (57)	0	0
Melanoma	7	33.2	1 (14)	4 (58)	1 (14)	0	1 (14)
Pancreatic	3	19.2	0	0	2 (67)	1 (33)	0
Thyroid	3	9.6	0	0	1 (33)	1 (33)	1 (33)
Other	35	12.6	7 (20)	5 (14)	7 (20)	7 (20)	9 (26)

2546 General Poster Session (Board #2F), Mon, 8:00 AM-11:45 AM

Effects of gefitinib and vandetanib on human equilibrative nucleoside transporter 1 and on gemcitabine cytotoxicity.

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Background: Combination chemotherapy with tyrosine kinase inhibitors (TKIs) and gemcitabine has been attempted with little added benefit to patients. We hypothesized that TKIs that were designed to bind to ATP pockets of growth factor tyrosine kinases also bind to proteins that recognize nucleosides, thereby potentially interfering with gemcitabine pharmacology. **Methods:** Interaction of TKIs with human nucleoside transporters (NTs) was studied using recombinant NTs produced in yeast. Effects of TKIs on uridine transport, gemcitabine transport and accumulation, regulation of NT activity and cytotoxicity with and without gemcitabine were evaluated in human A549 lung cancer cells. **Results:** In yeast, vandetanib inhibited two equilibrative NTs (hENT1, hENT2) and three concentrative NTs (hCNT1, hCNT2, hCNT3) with the greatest inhibition seen with hENT1 whereas gefitinib strongly inhibited hENT1 and hCNT1 only. In A549 cells, which possess major hENT1 and minor hENT2 activities, [^{3}H]uridine uptake was inhibited by vandetanib and gefitinib with IC_{50} values of 16 $\pm$ 4 and 5 $\pm$ 0.3μM, respectively. Both TKIs also inhibited [^{3}H]gemcitabine transport and accumulation in A549 cells. hENT1 protein levels were decreased during exposures to vandetanib or gefitinib for 24 hours, and cytotoxicity was greatest when gemcitabine was given prior to vandetanib or gefitinib. **Conclusions:** Vandetanib and gefitinib inhibited human NTs, especially hENT1, resulting in reduced intracellular gemcitabine accumulation. Gefitinib or vandetanib levels achieved in plasma and tumor tissues are sufficient to inhibit hENT1 activity. Because TKIs can block uptake of nucleoside chemotherapy drugs in cultured cancer cells, attention must be paid to TKIs and nucleoside pharmacokinetic properties when scheduling TKIs and nucleoside chemotherapy.

2547 General Poster Session (Board #2G), Mon, 8:00 AM-11:45 AM

MLN2480, an investigational oral pan-RAF kinase inhibitor, in patients (pts) with relapsed or refractory solid tumors: Phase I study.

Drew Warren Rasco, Anthony J. Olszanski, Amita Patnaik, Guillermo Espino, Rachel Neuwirth, Stephanie Faucette, Michael Bargfrede, Esha A. Gangolli, Russell M Walker, Michelle Kneissl, Viviana Bozon; South Texas Accelerated Research Therapeutics (START), San Antonio, TX; Fox Chase Cancer Center, Philadelphia, PA; Millennium Pharmaceuticals, Inc., Cambridge, MA

Background: MLN2480 is an investigational pan-RAF kinase inhibitor. *In vivo*, MLN2480 showed antitumor activity in melanoma, colon, lung, and pancreatic cancer xenograft models. This first-in-human study aimed to evaluate the safety of MLN2480, determine the MTD/recommended phase 2 dose (RP2D), and evaluate pharmacokinetics (PK) and preliminary efficacy. **Methods:** Pts aged ≥18 yrs with advanced solid tumors who had failed/were not candidates for standard therapy received oral MLN2480 every other day (Q2D) in 22-d cycles, with dose escalation (3+3 design) based on DLTs in cycle 1. AEs were graded per NCI-CTCAE v4.03. Blood samples for plasma PK assessment were taken pre-dose and at multiple times post-dose, d 1 and 21, cycle 1. **Results:** 24 pts (10 male, median age 64.5 yrs [range 37–83]) have been treated at 20, 40, 80, 135, 200, and 280 mg (n=4, 3, 3, 3, 4, and 7), respectively. The most common tumors included colorectal cancer in 11 pts and non-small-cell lung cancer in 2 pts. Pts received a median of 2 (range 1–6) cycles. 2 pts treated at 280 mg had DLTs: grade 3 macular rash and grade 3 periorbital edema. 20 pts had drug-related AEs, including fatigue 46%, arthralgia 25%, maculopapular rash 21%, and myalgia 17%. 4 pts had drug-related grade ≥3 AEs, which included the 2 DLTs listed above, anemia, dyspnea, and fatigue. No keratocanthomas/ squamous cutaneous carcinomas have been seen to date. 4 pts discontinued due to AEs. There were 3 on-study deaths (1 treatment-related per investigator; dyspnea and respiratory failure). At 20–200 mg MLN2480 PK data (13 pts) exhibited rapid absorption (median T_{max} 2 hr), low fluctuation at steady state (mean peak to trough ratio 2.1), and mean accumulation half-life of 67 hr. Overall mean accumulation was 2.6-fold following repeated Q2D dosing for 21 d. Steady-state (d 21) exposures increased in an approximately dose-proportional manner over 20–200 mg range. No pts had an objective response to date; no pts with BRAF mutation enrolled to date. **Conclusions:** In this first-in-human study (n=24), the safety profile of MLN2480 up to 200 mg Q2D was acceptable. Accrual continues at 200 mg to confirm the MTD. Melanoma expansion cohorts are planned at the RP2D using a Q2D 28-d cycle. Clinical trial information: NCT01425008.

2548 General Poster Session (Board #2H), Mon, 8:00 AM-11:45 AM

Efficacy of the Royal Marsden Score (RMS) to improve the selection patients (pts) considered for participation to dose-seeking phase I trial.

Veronique Favre, Fatima-Zhora Meniai, Philippe Alexandre Cassier, Carlos Alberto Gomez-Roca, Nicolas Isambert, Stephanie Clisant, Peggy Philippe, Alice Levart, Isabelle Desmoulins, Juliette Bouchet, Jean-Pierre Delord, Nicolas Penel; Centre Georges François Leclerc, Dijon, France; Centre Oscar Lambret, Lille, France; Centre Léon Bérard, Lyon, France; Institut Claudius Regaud, Toulouse, France

Background: Selection of pts entering in phase trials remains difficult. An international network of expert centers had validated the efficacy of the RMS as selection tool in such context. Nevertheless, RMS have been developed (Arkenau EJC 2008) and validated (Olmos et al. JCO 2012) in cohorts of already enrolled pts, whereas that the question of eligibility is crucial at the time of screening. We have then implemented and measured the efficacy of the RMS in 453 pts entering in the screening process in 4 expert centers. **Methods:** We have analyzed pts having signed the PIS/IC. RMS (0 to 3) is sum of the following prognostic factors: LDH>ULN, met. sites>2 and albumin <35 g/L. We have established the rates of enrolled pts, of pts dying within 90 days, of pts having completed PK/PD analysis, with accurate tumor assessment, having to be replaced according to RMS value. **Results:** Score was as follows: 0 (122/453, 27.0%), 1 (147/453, 32.4%), 2 (79/453, 17.4%), 3 (20/354, 4.4%) & not assessable (84/453, 19.2%). OS according to RMS value were 615, 299, 239 & 136 days (p=0.0001). The rates of 90-day mortality were 5.3%, 12.6%, 26.6% & 41.1% (p=0.0001). The rates of enrolled pts were 79.5%, 77.5%, 60.7% & 50.0% (p=0.001). Among enrolled pts, the rates of pts having completed the PK/PD analysis were 87.6%, 79.8%, 70.8% & 50.0% (p=0.007). Among enrolled pts, the rates of tumor assessment available were 95.8%, 88.6%, 89.5% & 70.0% (p=0.006). The rates of pts having to being replaced 4.1%, 5.2%, 2.0% & 50.0% (p=0.04). The time under study was 118, 81, 56 and 62 days (p=0.005). **Conclusions:** We confirm that the RMS is a reliable, easily obtained tool for selecting pts in such context. The enrollment of pts with RMS=3 is associated with a high risk of attribution rate & risk to be replaced. The time under study was significantly lower in cases of RMS =[2-3].

2549 General Poster Session (Board #3A), Mon, 8:00 AM-11:45 AM

Survival of patients considered for participation to contemporary dose-seeking phase trial: Matter of tumour burden, nature of treatment or of dose-levels?

Juliette Bouchet, Nicolas Isambert, Philippe Alexandre Cassier, Carlos Alberto Gomez-Roca, Stephanie Clisant, Jean-Pierre Delord, Veronique Favre, Peggy Philippe, Isabelle Desmoulins, Alice Levart, Fatima-Zhora Meniai, Nicolas Penel; Institut Claudius Regaud, Toulouse, France; Centre Georges François Leclerc, Dijon, France; Centre Léon Bérard, Lyon, France; Centre Oscar Lambret, Lille, France

Background: We have analyzed the survival of pts considered for participation to contemporary phase 1 trial. **Methods:** All consecutive pts having signed the PIS/IC have been analyzed. OS have been measured using Kalan-Meier method. RMS had been calculated, RMS (0 to 3) is sum of the following prognostic factors: LDH>ULN, met. sites>2 and albumin <35 g/L. Comparisons have been done with Log-rank tests and Cox model. **Results:** OS of the entire cohort was 448 days. 73.4% of pts having been enrolled. Among not enrolled pts, 74.1% of pts received another treatment. The OS was 497, 247 and 110 days, in pts enrolled in phase I trial, in pts not enrolled but receiving another treatment and in non-treated pts (p=0.001). After adjustment to RMS and with pts not enrolled but receiving other treatment as reference, the HR was 0.47 (95-CI:0.34-0.66; p=0.0001) in pts enrolled in phase 1 compared and 3.54 (1.92-6.52; p=0.0001) in non-treated pts. We have then more specifically analyzed the pts enrolled in single-agent dose-escalating phase I. The OS was 894, 272 and 395 days in pts receiving the 2 first dose-levels, in those receiving intermediate dose-levels and those receiving the phase 2-recommended dose, respectively (p=0.001). The OS was 328 in pts receiving molecular targeted agent and 539 in those receiving cytotoxic agents (p=0.004). In a multivariate analysis, the nature of investigational agent and the dose-level were not associated with better outcome. The sole prognostic factor for OS in multivariate analysis was the RMS (0+1 vs 2+3: HR=3.80 [1.76-8.20], p=0.01). **Conclusions:** Inclusion in phase 1 trial was associated with better outcome in both crude analysis and after adjustment to RMS. Among enrolled pts, in multivariate analysis RMS reflecting the tumor burden was the sole prognostic factor, the nature of the drug and the dose-level were not associated with the outcome.

2550 General Poster Session (Board #3B), Mon, 8:00 AM-11:45 AM

Phase Ib trial of combining aldoxorubicin plus doxorubicin.

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Background: Aldoxorubicin is a novel drug that covalently binds to albumin in the circulation with release in low pH environments. Preclinical studies in pancreatic and ovarian tumor xenograft models demonstrated that aldoxorubicin plus doxorubicin administered at 50% of their MTD provided complete and prolonged tumor remission in these models with less toxicity than each drug administered at their MTD. We evaluated the toxicity profile of a fixed dose of doxorubicin and escalating doses of aldoxorubicin in subjects with advanced solid tumors. **Methods:** Phase 1b open label, dose-escalation study of aldoxorubicin administered at either 175, 240 or 320 mg/m^2 (130, 180, or 240 mg/m^2 doxorubicin equivalents) iv + 35 mg/m^{2}doxorubicin iv, both on Day 1 of 21 day cycles, for up to 8 cycles. The MTD is the dose level immediately below where 2/6 subjects experience a dose limiting toxicity (DLT) , or the maximum dose of 320 mg/m^{2}aldoxorubicin. Additional subjects may be enrolled at the MTD to provide more safety data. **Results:** 10 subjects have been treated as of January 21, 2013. No DLT was observed and the MTD was defined as 320 mg/m^2 aldoxorubicin and 35 mg/m^2 doxorubicin iv administered on Day 1 of 21 day cycles. A median of 4.5 cycles have been received. 3/10 subjects were terminated due to either progressive disease (2) or death (1). No subject was terminated due to an adverse event. Grade 3 or 4 neutropenia was seen at all dose levels (8/10 subjects). 4/10 subjects exhibited grade 3 or 4 thrombocytopenia and 3/10 subjects had grade 3 or 4 anemia. Neutropenic fever occurred in 3/10 subjects. Other grade 3/4 adverse events seen in 2 or fewer subjects included fatigue, increased liver enzymes and dehydration. No significant mucositis or cardiotoxicity was observed. At this time the best response has been stable disease in 6/10 subjects and a partial response in 1 subject (malignant fibrous histiocytoma). **Conclusions:** The combination of aldoxorubicin (320 mg/m$^{2)}$) + doxorubicin (35 mg/m^2) can be safely administered to subjects with solid tumors. Hematologic toxicity is common and can be controlled with growth factors. The dose of aldoxorubicin is 90% of the MTD of aldoxorubicin administered as a single agent. Thus, doxorubicin does not appear to add to the toxicity of this combination. Clinical trial information: NCT01673438.

2551 General Poster Session (Board #3C), Mon, 8:00 AM-11:45 AM

Phase I dose escalation study of the protein kinase C iota inhibitor aurothiomalate for advanced non-small cell lung cancer, ovarian cancer, and pancreatic cancer.

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Background: Protein kinase C iota (PKCi) is overexpressed in non-small cell lung (NSCLC), ovarian and pancreatic cancers and promotes tumorigenesis. The gold compound aurothiomalate (ATM) inhibits downstream activation of Rac1 by PKCi. We sought to determine the maximum tolerated dose (MTD) of ATM. **Methods:** We conducted a phase I dose escalation trial of ATM in patients with NSCLC, ovarian or pancreatic cancer. In the dose escalation cohort patients received ATM IM weekly for three cycles (cycle duration 4 weeks) at 25 mg, 50 mg or 75 mg in a 3+3 design. The dose was not escalated for individual patients. Up to 9 subjects were allowed to enroll in the expansion cohort at the MTD. Blood samples were analyzed for elemental gold levels. Patients were evaluated for response every eight weeks with computed tomography using modified response evaluation criteria in solid tumors. **Results:** Fifteen patients, all pretreated, enrolled in this study. There were ten patients with NSCLC, four with ovarian cancer and one with pancreatic cancer. Six patients were treated at the 25 mg dose, 6 patients at 50 mg, and 2 at 75 mg. There was 1 dose limiting toxicity (DLT) at 25 mg (hypokalemia), 1 DLT at 50 mg (urinary tract infection), and none at 75 mg. There were 3 grade 3 hematologic toxicities in the dose escalation cohort. The recommended MTD of ATM is 50 mg, and 1 subject was treated in the expansion cohort at 50 mg. Patients received treatment for a median of 2 cycles (range 1-3). The best response observed was stable disease in 2 subjects. There appeared to be a dose-related accumulation of steady-state plasma concentrations of gold with concentrations exceeding 20 μM after one month of therapy with 75 mg of ATM and after 2 months of therapy with 50 mg of ATM, consistent with linear pharmacokinetics. **Conclusions:** In summary, this phase I study was successful in identifying ATM 50 mg IM weekly as the MTD. In this heavily pre-treated group of patients in who we observed at best stable disease, it remains unclear whether future investigations that target PKCi should focus on single agent ATM, combination therapy with ATM, or other PKCi inhibitors that are currently in development. Clinical trial information: NCT00575393.

2552 General Poster Session (Board #3D), Mon, 8:00 AM-11:45 AM

Heat shock protein 90 (HSP90) inhibition in squamous cell carcinoma of the head and neck (SCCHN): An in vitro analysis with a focus on p16 status.

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Background: Despite advances in therapy, the overall 5 year survival for SCCHN is close to 50%. Cisplatin and radiation therapy remain the current standard for treating locally advanced SCCHN. Novel treatment approaches are urgently needed, especially in HPV negative disease. We examined the expression of HSP90 in HPV positive and negative SCCHN and investigated if the HSP90 inhibitor ganetespib can sensitize mutant p53 SCCHN to cisplatin and radiation therapy in vitro. **Methods**: Phase 1 trials of ganetespib at 150 mg/m^2 have shown the maximum clinically achievable concentration (CAC) in patients to be ~166 nM. We treated p53 deficient or mutant p53 SCCHN cells (SCC25 and Detroit 568, CAL27and FADU, respectively) with ganetespib at 10-50 nM alone and in combination with cisplatin or radiation therapy and assessed survival. We measured HSP90, HSP70 and p53 protein expression levels in SCCHN cell lines by immunoblotting and analyzed HSP90 protein levels in p16 positive and p16 negative SCCHN tumor samples by immunohistochemistry. **Results**: Ganetespib at CAC was significantly more cytotoxic in mutant p53 compared to p53 deficient SCCHN cells ($p < 0.05$). When combined with CAC doses of cisplatin or radiation therapy, ganetespib displayed strong sensitizing activity ($p < 0.05$ and $p < 0.01$ respectively). Ganetespib treatment upregulated HSP70 and HSP90 expression while decreasing p53 expression in the mutant cell lines. HSP90 expression was significantly higher in p16 negative than p16 positive SCCHN tumor samples (79.5% vs. 51%, ANOVA $p = 0.016$). **Conclusions**: Our results demonstrate a potential efficacy of ganetespib as a single agent and in combination with cisplatin and radiation therapy in SCCHN. HSP90 expression is upregulated in p16 negative SCCHN. Further exploration of the role of HSP90 in SCCHN, and utility of HSP90 inhibitors, is warranted.

2553 General Poster Session (Board #3E), Mon, 8:00 AM-11:45 AM

CTEP #8342 autophagy modulation with antiangiogenic therapy: A phase I trial of sunitinib (Su) and hydroxychloroquine (HCQ).

Nataliya Melnyk, Xiaoqi Xie, Danny Ju Yong Koh, Megha Rajpal, Rebecca Anne Moss, Darlene Gibbon, James M. Cleary, Minh-Thu Tran, Pamela Scott, Mark N. Stein, Antoinette R. Tan, Shari Adams, Diana C. Lindquist, Pamela Jo Harris, Naoko Takebe, Hongxia Lin, Joseph Aisner, Eileen White, Robert S. DiPaola, Janice M. Mehnert; University of Medicine and Dentistry of New Jersey, New Brunswick, NJ; University Of Medicine and Dentistry of New Jersey, Piscataway/New Brunswick, NJ; Robert Wood Johnson Medical School, Piscataway/New Brunswick, NJ; The Cancer Institute of New Jersey, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ; The Cancer Institute of New Jersey, New Brunswick, NJ; Dana-Farber Cancer Institute, Boston, MA; Cancer Institute of New Jersey, New Brunswick, NJ; National Cancer Institute, Bethesda, MD; Investigational Drug Branch, Cancer Therapy Evaluation Program, Rockville, MD

Background: Angiogenesis inhibitors promote autophagy, a response to nutrient deprivation in which autophagosomes (AP) and lysosomes fuse to recycle intracellular constituents, leading to sustained tumor viability. We hypothesized that the VEGF-R2, c-kit, PDGFR inhibitor Su induces autophagy. The autophagy inhibitor HCQ may then interfere with autophagy dependent tumor survival, possibly improving patient (pt) outcomes. **Methods:** This trial determined the MTD of Su+HCQ in pts with advanced malignancies using a 3+3 design. Su 50 mg qd was given in 4 week on/2 week off cycles (C) with daily HCQ in escalating dose cohorts. A MTD expansion cohort of 12 pts was also enrolled. Modulation of autophagy was measured by changes in the AP marker light chain-3 (LC3)II/I ratio in paired PBMC samples from C1 and C2. **Results:** 21 pts, median age 59, PS 0 (7), 1 (13) or 2 (1) enrolled, including 5 colon, 2 renal and 5 sarcomatous tumors. 4 DLTs were observed: 3 DLTs (gr 3 confusion, gr 3 colon fistula, gr 3 thrombocytopenia) in DL2 (50 mg Su, 200 mg bid HCQ), and 1 DLT (gr 3 dehydration) in DL1 (50 mg Su, 200 mg HCQ). DL1 was thus declared the MTD. Gr 3/ 4 toxicities included: related to Su, thrombocytopenia (14%), fatigue (19%), neutropenia (14%), hypertension (14%), intestinal perforation (10%); related to HCQ, fatigue (14%). PK data of Su alone, its active metabolite SU012662 and the total were evaluated using noncompartmental analysis. Cmax and AUCs of the active metabolite SU012662 significantly increased ($p<0.005$) during C2 relative to C1, indicating drug-drug interactions between HCQ and Su. 9 of 21 (43%) had stable disease for $>$ 3 cycles (median 73 days). Inconsistent autophagy modulation was seen in PBMCs. LC3 immunohistochemistry on baseline tumor blocks to assess individual tumor autophagy levels is in progress. **Conclusions:** pK interaction between Su and HCQ resulting in accumulation of Su metabolites may be responsible for the predominantly Su-associated toxicities observed which prohibited further HCQ dose escalation. Lack of evidence for autophagy modulation is likely due to the inability to escalate HCQ to doses necessary to induce autophagy inhibition. Further study of this combination seems unwarranted. Clinical trial information: NCT00813423.

2554 General Poster Session (Board #3F), Mon, 8:00 AM-11:45 AM

Phase I trial and pharmacokinetic (PK) study of satraplatin in children and young adults with refractory solid tumors including brain tumors.

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Background: Satraplatin is an orally bioavailable platinum analog. Based on pre-clinical activity (IC_{50}0.02-8 μg/ml) including activity in cisplatin resistant cell lines, and clinical activity without neuro-, nephro-, or ototoxicity in adults with refractory tumors, we developed a phase 1 trial to determine the toxicities, maximum tolerated dose (MTD), and PKs of satraplatin in children with refractory solid tumors. **Methods:** Satraplatin (10 and 50 mg capsules) was administered orally once daily on days 1 - 5 of a 28 day cycle to cohorts of 3-6 patients (pts) at 60 mg/m^2/dose (DL 1) and 80 mg/m^2/dose (DL 2). Plasma ultrafiltrate (PUF) platinum was measured using atomic absorption spectroscopy during cycle 1 for PK analysis. **Results:** 9 pts [5 male, 4 female, median age 17 years (range 8-19)] with malignant glioma (n=4), ependymoma (n=2), medulloblastoma (n=1), osteosarcoma (n=1), or hepatoblastoma (n=1) received 1-10+ cycles (median 2). The MTD was exceeded at DL 2 as 2/4 pts had dose limiting toxicities (DLT) of delayed and prolonged myelosuppression (grade 3 thrombocytopenia, n=1; grade 3-4 neutropenia, n=2). 0/5 pts at DL 1 had DLTs. Grade 1 ototoxicity was seen in 1 pt at cycle 10. Non-DLTs included myelosuppression, gastrointestinal toxicities, fatigue, headache, liver enzyme elevation, and electrolyte abnormalities. No objective responses were observed, but 1 pt with gliomatosis cerebri has had radiographic stable disease through cycle 10+. Satraplatin mean exposure (AUC) and peak concentration (C_{max}) were similar at both dose levels [day 1 PUF $AUC_{0\text{-}24h}$ 1.22 $\pm$ 0.55 μg/ml*h at DL1 (n=3), 1.02 $\pm$ 0.45 μg/ml*h at DL2 (n=3); C_{max}0.17 $\pm$ 0.08 μg/ml at DL 1 (n=3), 0.16 $\pm$ 0.05 μg/ml at DL 2 (n=3)]. Terminal half-life was 14 $\pm$ 6 h and apparent clearance was 76 $\pm$ 29 L/h (n=6). **Conclusions:** The MTD of oral satraplatin in children with solid tumors is 60 mg/m^2/dose daily x 5 q28 days. The toxicity profile was similar to adults, and delayed myelosuppression was DLT. Satraplatin exposure appears higher in pediatric pts compared to adults (PUF $AUC_{0\text{-}24h}$ 0.25-0.47 μg/ml*h at 60-80 mg/m^2/dose). DL 1 will be expanded to gain additional experience regarding toxicities and PKs in a broader age range. Clinical trial information: NCT01259479.

2555 General Poster Session (Board #3G), Mon, 8:00 AM-11:45 AM

A drug-drug interaction study between the strong CYP3A4 inhibitor ketoconazole (keto) and ixazomib citrate (MLN9708), an investigational, orally active proteasome inhibitor, in patients with advanced solid tumors or lymphoma.

Neeraj Gupta, Karthik Venkatakrishnan, Dennis A Noe, Michael J Hanley, Jiang Yu, Alberto Bessudo, Sunil Sharma, Robert Matthew Strother, Yaping Shou, John J. Nemunaitis; Millennium Pharmaceuticals, Inc., Cambridge, MA; California Cancer Associates for Research and Excellence, San Diego, CA; University of Utah, Salt Lake City, UT; Indiana University, Indianapolis, IN; Mary Crowley Cancer Research Center, Dallas, TX

Background: MLN9708 is an oral proteasome inhibitor currently being investigated in multiple myeloma and amyloidosis in phase 3 studies. MLN9708 immediately hydrolyzes to its biologically active form, MLN2238, in aqueous solutions or plasma. Metabolism by multiple cytochrome p450s (CYPs) including 3A4 and 1A2 (>25% contribution by each) was expected to be the primary clearance mechanism for MLN2238 based on human liver microsomal metabolism studies. This open-label, multicenter study (NCT01454076) characterizes the effect of CYP3A4 inhibition with keto on single-dose pharmacokinetics (PK) of MLN9708 in a fixed sequence design. **Methods:** Patients received MLN9708 2.5 mg on d 1 and 15, and keto 400 mg (PO) daily on d 12–25. On d 15, MLN9708 and keto were administered concomitantly. Serial blood samples were collected over 0–264 hr after MLN9708 doses on d 1 and 15 for PK characterization. Plasma PK parameters were estimated by non-compartmental methods. The effect of keto co-administration on MLN9708 $AUC_{0-264hr}$ and $C_{max}$was evaluated by Analysis of Variance of log-transformed values. **Results:** 16 PK-evaluable patients (11 Caucasian, 3 African American, 2 Hispanic; 6M, 10F) with mean (range) age of 61 years (48–79) and body surface area of 1.8 m^2 (1.5–2.3) were enrolled. Co-administration of MLN9708 and keto resulted in a 2-fold increase in MLN9708 $AUC_{0-264hr}$ but no change in C_{max}(Table). No differences in adverse events were observed +/- the addition of keto, to a single dose of 2.5 mg MLN9708. **Conclusions:** The observed 2-fold increase in MLN9708 $AUC_{0-264hr}$with a strong CYP3A4 inhibitor suggests the contribution of CYP3A4 clearance to the total clearance of MLN9708 is significant. These results support the continued exclusion of strong CYP3A4 inhibitors in ongoing and planned clinical trials of MLN9708. Clinical trial information: NCT01454076.

	D 1 MLN9708 alone (Reference)	D 15 MLN9708+keto (Test)	Test vs Reference, least square geometric mean ratio (90% CI)
C_{max}, ng/mL[a]	41.3 (46)	41.6 (63)	1.0 (0.8–1.3)
AUC_{0-264}, ng*hr/mL[a]	608 (30)	1249 (40)	2.1 (1.9–2.3)
T_{max}, hr[b]	1.1 (0.5–2.1)	1.5 (0.5–3.1)	-

[a]Geometric mean (%CV) [b]Median (range).

2556 General Poster Session (Board #3H), Mon, 8:00 AM-11:45 AM

A phase I dose-escalation study of volasertib (BI 6727) combined with nintedanib (BIBF 1120) in advanced solid tumors.

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Background: Volasertib (V) is a potent and selective cell cycle kinase inhibitor that induces mitotic arrest and apoptosis by targeting Polo-like kinases. Nintedanib (N) is a triple angiokinase inhibitor of VEGF, PDGF, and FGF receptors. Both have shown clinical activity with a manageable safety profile in patients (pts) with advanced solid tumors. This study was designed to determine the maximum tolerated dose (MTD) of V combined with N in these pts. **Methods:** Cohorts of 3–6 pts received V (100–450 mg IV Q3W) + oral standard dose N (200 mg BID continuously, except V infusion day). Treatment continued until clinical progression. Up to 12 pts were treated at the MTD for additional safety data. Primary endpoint was the MTD; secondary endpoints were pharmacokinetics (PK), overall safety, and preliminary efficacy. **Results:** 30 pts were treated (median age, 56.5 yr; ECOG PS 0/1/2, 33%/60%/7%; ≥3 prior therapies, 87%). At V doses >200 mg, 7 pts experienced 13 dose-limiting toxicities (DLTs) during cycle 1: increased alanine aminotransferase [ALT] or aspartate aminotransferase [AST], neutropenia and thrombocytopenia. The MTD was V 300 mg (Table). At the MTD, the most common all grade (Gr) adverse events (AEs) were neutropenia (69%), asthenia and thrombocytopenia (62% each), increased ALT, increased AST and diarrhea (54% each). Median (range) duration on treatment was 4 (1–18) cycles. Treatment was discontinued due to progressive disease (80%), DLT (3%) and other non-AE related reasons (17%). 2 objective responses were observed (1 complete [breast cancer] and 1 partial [NSCLC]), both with the 300 mg dose. 6 pts had SD for ≥ 6 mo. PK data will be presented at the meeting. **Conclusions:** MTD of V + standard dose N (200 mg BID) was determined to be 300 mg Q3W (the same as the recommended phase II single agent dose of V in solid tumors). This combination had a manageable safety profile without unexpected or overlapping toxicities and showed preliminary antitumor activity. Clinical trial information: NCT01022853.

Cycle 1 DLTs.

V (mg)	Pts	Pts with DLTs	DLTs (n of pts)
100	3	0	–
200	4	0	–
300	13	3	Gr 4 neutropenia (1); Gr 3 ALT increase (3); Gr 3 AST increase (2)
350	8	2	Gr 4 neutropenia (2); Gr 4 thrombocytopenia (1); Gr 3 ALT increase (1)
400	2	2	Gr 4 thrombocytopenia (2); Gr 4 neutropenia (1)

2557 General Poster Session (Board #4A), Mon, 8:00 AM-11:45 AM

A pharmacokinetic and dose-escalating study of paclitaxel injection concentrate for nano-dispersion (PICN) alone and with carboplatin in patients with advanced solid tumors.

Wen Wee Ma, Elaine Tat Lam, Grace K. Dy, Jennifer Robinson Diamond, Yujie Zhao, Lynne A. Bui, Gerald J. Fetterly, Wattanaporn Abramowitz, Ronald Harning, Pepi Pencheva, Shravanti Bhowmik, Ganesh Harishchandra Divekar, Ann Marie DiRaddo, S. Gail Eckhardt, Alex A. Adjei, Antonio Jimeno; Roswell Park Cancer Institute, Buffalo, NY; University of Colorado Denver, Aurora, CO; Division of Medical Oncology, University of Colorado Denver, Aurora, CO; Sun Pharma Advanced Research Co., Ltd., Cranbury, NJ; DP Clinical, Rockville, MD; Sun Pharma Advanced Research Co., Ltd., Mumbai, India; University of Colorado Cancer Center, Aurora, CO; University of Colorado, Denver, Aurora, CO

Background: PICN is a novel Cremaphor-free composite of paclitaxel nano-particles stabilized with polymer and lipid using Nanotecton Technology. The MTD of PICN alone was previously determined to be 295 mg/m^2 iv every 3 weeks in a South Asian population. This study aimed to determine the pharmacokinetic (PK) profile of PICN alone and with carboplatin (C), and the MTD of PICN plus C. **Methods:** Patients (pt) with advanced solid malignancies and ECOG PS 0-1 were eligible. Part A was a PK study designed to examine cohorts of 3 pts, receiving PICN over 30 min at dose levels of 175, 260, and 295 mg/m^2 every 3 weeks; PK were performed at pre-determined time-points. Part B used a '3+3' dose escalation scheme, designed to determine the MTD of PICN (220, 260, and 295 mg/m^2) when combined with C at AUC 6. Only standard anti-emetic pre-medications were used. Adverse events (AEs) were graded using CTCAE 4.0 and tumor response by RECIST 1.1. **Results:** A total of 18 evaluable pts (9 in Part A, 9 in Part B) were enrolled from 2 US academic centers. No infusion reactions were observed with PICN. No dose limiting toxicity (DLT) was observed in Part A. In Part B, the DLTs were G3 febrile neutropenia and G4 thrombocytopenia requiring platelet transfusion at PICN 260/C AUC 6. A total of 6 pts were treated at PICN 220/C AUC 6 with no DLT. G3 or worse AEs for all cycles were as follow: Part A, bilateral lower extremity weakness, neuropathy, anorexia and neutropenia; Part B, anemia, thrombocytopenia, neutropenia and empyema. Partial responses were observed in biliary(Part A; PICN 260 mg/m^2), breast (Part B 220/6) and anal cancers (Part B 260/6). PK analysis showed dose-proportional increase in total plasma paclitaxel level. **Conclusions:** PICN alone was tolerable in the dose range evaluated. When administered with C AUC 6, the MTD of PICN was 220 mg/m^2 administered every 3 weeks. Anti-cancer activity was observed in biliary, breast, and anal cancers. Final PK, toxicity and efficacy data of PICN alone and with C will be presented at the conference. Clinical trial information: NCT01304303.

2558 General Poster Session (Board #4B), Mon, 8:00 AM-11:45 AM

Phase I clinical trial of the intraperitoneal (IP) administration of a novel nanoparticle formulation of paclitaxel (NTX).

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Background: IP therapy is an attractive option for patients with IP carcinomatosis as many of these malignancies remain confined IP. Agents whose plasma clearance rates substantially exceed their rates of uptake from the peritoneal cavity are especially suited for IP administration. Pre-clinical studies of a novel formulation of nanoparticulate paclitaxel in animal tumor models demonstrated superior activity and substantially reduced systemic toxicity. This allowed for significant IP doses and concentrations, yet yielded very low systemic concentrations of paclitaxel. We report here the results of a Phase I trial of IP administered NTX. **Methods:** Patients (ECOG≤2) had relapsed, treatment refractory solid IP tumors and adequate organ function. NTX was administered IP as a bolus injection after 500 ml saline followed by IP administration of up to 2 L of saline. We utilized an accelerated dose escalation scheme until one DLT occurred during cycle 1, followed by a standard dose escalation (3+3 design) based on CTCAE V3 toxicities. The pharmacokinetics of IP administered NTX were characterized in plasma and ascites fluid. Secondary objectives were to define the recommended phase 2 dose of NTX, and characterize preliminary activity and toxicity. **Results:** 20 patients were treated at dose levels from 50 – 275 mg/M2 q 28 days. Primary malignancy was ovarian cancer (74%). Treatment was well tolerated at all dose levels. Common toxicities potentially related to NTX were: gastrointestinal (68%), constitutional (42%), and pain (42%). Average number of cycles received was 2 (range 1 to 6). Best response was stable disease (4 patients, 21%). Median length of disease stability was 99 days (range 85 to 151 days); median time on study patients with stable disease was 313 days (range 142 to 740 days). All Cmax in plasma were less than 35 ng/mL, with ascites fluid Cmax generally greater than 1000 ng/mL. **Conclusions:** IP NTX is well tolerated. MTD has not yet been reached. Pharmacokinetic data demonstrate significant, persistent IP exposure to paclitaxel with minimal systemic exposure. Accrual at the 275 mg/M2 dose level continues; updated results will be presented. Further clinical development of NTX is indicated. Clinical trial information: NCT00666991.

2559 General Poster Session (Board #4C), Mon, 8:00 AM-11:45 AM

A phase I trial of GBS-01 for advanced pancreatic cancer refractory to gemcitabine.

Masafumi Ikeda, Akihiro Sato, Nobuo Mochizuki, Kayo Toyosaki, Chika Miyoshi, Rumi Fujioka, Shuichi Mitsunaga, Satoshi Shimizu, Izumi Ohno, Hideaki Takahashi, Hiroyuki Okuyama, Hiromi Hasegawa, Shogo Nomura, Toshiki Ohkubo, Satoshi Yomoda, Satoshi Kishino, Hiroyasu Esumi; Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; National Cancer Center Hospital East, Kashiwa, Japan; Department of Medication Use Analysis and Clinical Research, Meiji Pharmaceutical University, Tokyo, Japan; Clinical Trial Section, National Cancer Center Hospital East, Kashiwa, Japan; Cancer Physiology Project, National Cancer Center Hospital East, Kashiwa, Japan; Kampo Research Laboratory, Kracie Pharma, Ltd., Toyama, Japan; Department of Medication Use Analysis and Clinical Research, Meiji Pharmaceutical University,, Tokyo, Japan

Background: Arctigenin, which is abundant in the seeds of *Arctium lappa* Linné, was found by a novel strategy to attenuate cancer cells' tolerance to glucose deprivation (antiausterity) and showed antitumor activity in mouse xenograft models. GBS-01 is an orally administered drug and contains rich arctigenin extracted from *Arctium lappa* Linné, which is one of the traditional herbal medicine. This study investigated the maximum-tolerated dose of GBS-01 based on the frequency of dose-limiting toxicities (DLT) in patients with refractory advanced pancreatic cancer, which is considered as one of the hypoxic cancer. **Methods:** Histologically or cytologically proven advanced pancreatic adenocarcinoma patients refractory to gemcitabine were enrolled. GBS-01 was administered orally at escalating doses from 3g to 12g qd. DLT was defined as grade 4 hematological toxicities and grade 3 or 4 non-hematological toxicities during first 28 days of the treatment. Response evaluation based on RECIST criteria and progression-free survival were set as secondary endpoint for efficacy evaluation. **Results:** Fifteen patients (GBS-01 3g: 3 patients, 7.5g: 3 patients, 12g: 9 patients) were enrolled in this trial. All patients were refractory to S-1 as well as gemcitabine. All patients at the three dose levels did not demonstrate any sign of DLT. The main adverse events of this agent were increased γGTP, hyperglycemia, and increased total bilirubin, but all toxicities were extremely mild. Of all 15 enrolled patients, 1 patient showed a partial response and 4 patients had a stable disease. The median progression-free and overall survival time for all patients were 1.05 months and 5.68 months, respectively. **Conclusions:** The recommended dose of GBS-01 was 12 g qd (4 g as a extract of *Arctium lappa* Linné), and favorable clinical responses were obtained. A multicenter phase II trial is being planned to evaluate the efficacy and safety of this agent. Clinical trial information: 000005787.

2560 General Poster Session (Board #4D), Mon, 8:00 AM-11:45 AM

Phase I study of cabazitaxel (Cbz) plus cisplatin (Cis) in patients (pts) with advanced solid tumors: Substudy to evaluate the impact of a strong CYP3A inhibitor (ketoconazole; K) or inducer (rifampicin; R) on the pharmacokinetics (PK) of Cbz.

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Background: Cbz is approved for treatment of pts with hormone-refractory metastatic prostate cancer after progression on a docetaxel-containing regimen. The dose-escalation part of this Phase I study (NCT00925743) found the maximum tolerated dose (MTD) of Cbz/Cis to be 15/75 mg/m^2. No Cbz–Cis PK interactions were seen. As Cbz is mainly metabolized by CYP3A, the study also evaluated the impact of a strong CYP3A inhibitor (K; study part 3) or strong CYP3A inducer (R; study part 4) on the PK of Cbz in combination with Cis. **Methods:** The study included pts with metastatic or unresectable solid tumors for which Cis-based therapy was considered appropriate. Pts received Cbz/Cis every 3 weeks at MTD, with K 400 mg (part 3) or R 600 mg (part 4) administered orally once daily prior to, on, and after Cycle 2 Day 1 for a total of 10 (K) or 14 (R) days. In part 3, the Cbz/Cis dose was 5/75 mg/m^2 in Cycles 1 and 2 to provide a safety margin to the MTD. Effects on Cbz PK were assessed with a linear mixed-effects model. The primary endpoint was Cbz clearance (CL). Safety assessments included adverse events (AEs) and laboratory abnormalities. **Results:** The PK population included 23 pts (part 3) and 21 pts (part 4). Repeated administration of K resulted in a 20% decrease in Cbz CL (L/h/m^2) (geometric mean ratio [GMR]: 0.80; 90% confidence interval [CI]: 0.55, 1.15; n = 18), corresponding to a 25% increase in AUC (ng*h/mL/mg/m^2) (GMR: 1.25; 90% CI: 0.86, 1.81; n = 18). Repeated administration of R resulted in a 21% increase in Cbz CL (L/h/m^2) (GMR: 1.21; 90% CI: 0.95, 1.53; n = 20), corresponding to a 17% decrease in AUC (ng*h/mL/mg/m^2) (GMR: 0.83; 90% CI: 0.65, 1.05; n = 20). The GMR of $AUC_{0-24}$was 1.09 (90% CI: 0.9, 1.33; n = 21), suggesting a low impact of R during the initial phases of Cbz elimination. The most frequent AEs included nausea (part 3: 68%; part 4: 74%), vomiting (part 3: 68%; part 4: 74%) and fatigue (part 3: 52%; part 4: 70%). **Conclusions:** The CL of Cbz was decreased by 20% by co-administration with K and increased by 21% by co-administration with R. Safety results were consistent with prior findings for this Cbz/Cis combination. Clinical trial information: NCT00925743.

2561^ General Poster Session (Board #4E), Mon, 8:00 AM-11:45 AM

Phase I dose-escalation, open-label study of HSP990 administered orally in adult patients with advanced solid malignancies.

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Background: NVP-HSP990 is a synthetic small molecule that potently and selectively inhibits heat-shock protein 90. HSP990 leads to degradation of client proteins, offering potential simultaneous blockade of multiple oncogenic signaling pathways. The primary objective of this Phase 1 first-in-man study (NCT00879905) was to determine the single-agent MTD of HSP990 administered once (*qw*) or twice (*biw*) weekly to patients (pts) with advanced solid malignancies (preselected CYP2C9 genotypes only). Secondary objectives included safety, efficacy, PK, and biomarkers. **Methods:** HSP990 was administered orally *qw* or *biw* in 28-day cycles. Dose escalation was guided by a Bayesian logistic regression model. The MTD was determined by assessing DLTs in Cycle 1. Eligible pts included those with histologically confirmed advanced solid tumors that had progressed on standard therapy or for whom no standard therapy exists. **Results:** 64 pts (median age 57 yr: 44% male; 37.5% Stage IV; WHO PS 0/1) received HSP990. 53 pts received HSP990 *qw* at 2.5, 5, 10, 20, 30, 50 or 60 mg; and 11 pts received HSP990 *biw* at 25 mg. Median duration of exposure was 8 wks; 12 pts remained on treatment for >16 wks. DLTs occurred in 7 pts: 4/22 at 50 mg *qw* (including G3 diarrhea, G3 QTc prolongation, G4 ALT/AST elevations); 2/5 at 60 mg *qw* (including G3 tremors); and 1/11 at 25 mg *biw* (including G2 ataxia, G2 confusion, G2 visual hallucination). The 50-mg *qw* dose was declared as the MTD. Further dose escalation was not possible due to neurologic toxicity. Most common reported CTCAE G3/4 AEs were diarrhea (12.5%), increased ALT/AST (11% each), anemia, or cholestasis (6% each). HSP990 had Tmax of 3 h and T½ of ~20 h. Large inter-patient variability in PK exposures was observed. For *qw* dosing, approximate dose-dependent HSP70 induction was observed from 5−30 mg *qw*, which plateaued after 20 mg *qw*. There were no objective responses; however, 25 pts (39%) had SD. (RECIST v1.0). No pt showed a complete metabolic response (MR; by FDG-PET) and 11 pts (17%) showed a partial MR. All pts discontinued treatment, primarily due to disease progression (84%). **Conclusions:** The single-agent MTD of HSP990 in pts with advanced solid tumors was 50 mg *qw*. SD was observed in 39% of pts. Clinical trial information: NCT00879905.

2562 General Poster Session (Board #4F), Mon, 8:00 AM-11:45 AM

Use of gene expression profiling to identify responsive patients treated with carboplatin (Carb), paclitaxel (Pac), and everolimus as first-line treatment for cancer of unknown primary (CUP): NCCTG N0871 (Alliance).

Matthew P. Goetz, Nathan R. Foster, Jeffery P. Meyers, Preston D. Steen, Daniel W. Visscher, Harry H. Yoon, Raji Pillai, Debra M. Prow, Christopher M. Reynolds, Benjamin T. Marchello, Rex B. Mowat, Bassam Ibrahim Mattar, Charles Erlichman, Alliance for Clinical Trials in Oncology; Mayo Clinic, Rochester, MN; Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN; Roger Maris Cancer Center, Fargo, ND; Pathwork Diagnostics, Redwood City, CA; Iowa Oncology Research Association CCOP, Des Moines, IA; Michigan Cancer Research Consortium, Ann Arbor, MI; Montana Cancer Consortium, Billings, MT; Toledo Community Hospital Oncology Program CCOP, Toledo, OH; Wichita Community Clinical Oncology Program, Wichita, KS

Background: Empiric chemotherapy (taxane/platinum) is standard for CUP. Because prognosis is poor, novel approaches are needed. The PI3K/mTOR pathway is frequently dysregulated in cancer. Everolimus (E), an mTOR inhibitor, is approved for multiple malignancies. We performed a phase II study of Pac + Carb + E as first-line therapy in metastatic CUP patients (pts). We additionally determined if a gene expression profiling (GEP) test that identifies tissue of origin (Pathwork Tissue of Origin) could identify responsive pts. (NCT00936702) **Methods:** Newly diagnosed, untreated CUP pts were eligible. Central pathology review confirmed CUP prior to registration; GEP was performed on formalin fixed tumor tissue. Pac (200 mg/m^2), Carb (AUC=6) and E (30 mg once weekly) were delivered every 3 wks until progression or intolerable adverse events (AEs). The primary endpoint was confirmed response, with ≥11 of 50 responses (22%) needed for trial success. Secondary endpoints were OS, progression-free survival (PFS) and AEs. **Results:** 46 pts (median age 61) received a median 4 cycles (range: 1-33). 39 (85%), 21 (46%) and 1 (2%) experienced ≥1 grade (gr) 3+, 4+, or 5 (sepsis) AE, with gr 3+ hematologic AE most common (74%). Of 44 evaluable pts, 15 had a confirmed response (RR 34%, 95% CI: 21-50%), with a median PFS and OS of 4.1 and 10.1 mos, respectively. Adequate tissue for GEP was available in 36 pts and predicted 10 different sites of origin. In pts with a predicted tissue of origin in which taxane/platinum is standardly used, higher RR and significantly longer PFS and OS were observed compared with pts whose GEP identified a malignancy where taxane/platinum is not standard (Table). **Conclusions:** In pts with untreated CUP, Carb +Pac +E demonstrated promising antitumor activity. The GEP test identified patients clinically responsive to Carb/Pac/E therapy, and may be useful to select CUP pts for specific antitumor regimens. Clinical trial information: NCT00936702.

	Predicted tissue of origin		
	Lung, breast, ovary, bladder	Pancreas, colon, kidney, sarcoma, hepatocellular, gastric	P
	N=18	N=18	
RR	50% (9/18)	28% (5/18)	0.17
Median PFS (mo)	5.8	3.7	0.039
Median OS (mo)	15.5	10.0	0.026

2563 General Poster Session (Board #4G), Mon, 8:00 AM-11:45 AM

Phase Ib study evaluating safety and pharmacokinetics (PK) of the oral transforming growth factor-beta (TGF-ß) receptor I kinase inhibitor LY2157299 monohydrate (LY) when combined with gemcitabine in patients with advanced cancer.

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Background: Based on animal studies, the combination of a TGF-β inhibitor and gemcitabine is expected to enhance antitumor activity of gemcitabine. Hence, we started a combination study of LY with gemcitabine to assess the safety of this combination therapy. **Methods:** Gemcitabine was administered as approved and LY was given daily as intermittent dosing (14 days on/14 days off=1 cycle). A dose escalation consisting of 3 cohorts (80 mg/day, 160 mg/day, and 300 mg/day) evaluated the safety of LY in combination with gemcitabine. Toxicity was assessed using the CTCAE, version 4. Pharmacokinetic (PK) profile of LY in combination with gemcitabine was determined. **Results:** A total of 14 patients were evaluated (cohort 1 [n=5, 4 adenocarcinoma of colon, 1 non-small cell lung cancer, cohort 2 [n=4, adenocarcinoma, 1 each of esophageal, well differentiated, pancreas, lung], cohort 3 [n=5, 3 pancreatic, 2 rectal cancer]) in this study. The median number of cycles was 2 (range (1-6). Regardless of causality, the following treatment-emergent adverse events (TEAEs) were observed in ≥25% of patients: anemia (n=10), nausea (n=8), thrombocytopenia (n=6), neutropenia (n=6), vomiting (n=6), anorexia (n=5), fatigue (n=5), diarrhea (n=5) asthenia (n=5), pyrexia (n=4), AST increased (n=4), and constipation (n=4). Possibly related to LY, (Grade, Gr, 3/4 as mentioned) TEAEs observed were: nausea (n=5), asthenia (n=4), fatigue (n=3, 1 Gr 3), neutropenia (n=3, 1 Gr 3), anemia (n=3, 2 Gr 3), and in 2 patients each, thrombocytopenia (both Gr 3), headache, edema peripheral, rash, anorexia, diarrhea (1 Gr 3), mucosal inflammation, vomiting and reversible rhabdomyolysis (n=1, Gr 4). No change in the PK profile of LY was shown when LY was combined with gemcitabine. **Conclusions:** There were no dose limiting toxicities observed and no clinically meaningful cardiotoxicities were detected. Because of the observed manageable safety profile, LY at 300 mg/day has been advanced into a randomized Phase 2 trial in pancreatic cancer in 1st line setting to assess the antitumor activity of the combination. Clinical trial information: NCT01373164.

2564 General Poster Session (Board #4H), Mon, 8:00 AM-11:45 AM

PHI-55: (NCI#7427): A phase I study of halichondrin B analog (E7389) in combination with cisplatin (CDDP) in advanced solid tumors: A CCC, NCI/CTEP-sponsored trial (grant U01 CA 062505).

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Background: E7389 is a structurally simplified synthetic macrocyclic ketone analog of the marine sponge natural product Halichondrin B, which inhibits microtubule dynamics via a novel mechanism characterized by suppression of microtubule growth, lack of effect on microtubule depolymerization, and sequestration of tubulin into nonfunctional aggregates. **Methods:** The goals of this trial were to determine the DLT, the MTD, and PK of E7389 (administered on days 1, 8 and 15 every 28 days) in combination with CDDP (administered on day 1 every 28 days) in patients (pts) with advanced solid tumors. The protocol was amended after dose level 4 (E7389 1.4 mg/m^2, CDDP 60 mg/m^2) when it was not feasible to administer E7389 on day 15 due to neutropenia; the treatment schedule was changed to E7389 days 1 and 8 and CDDP day 1 every 21 days. Eligibility criteria included normal organ function and $<$ 2 prior chemotherapy regimens. **Results:** To date, 36 pts have been treated (E7389 0.7-1.4 mg/m^2 and CDDP 60-75 mg/m^2). Median age 61 years; 19 males; the most common tumor types were lung (8), pancreatic (5), head and neck (6). 36% ECOG 0, 56% ECOG 1, 8% ECOG 2; Median number of cycles was 3 (1 – 8). There were 3 pts with DLT's on the 28-day cycle: gr 4 febrile neutropenia (1.0/60); gr 3 anorexia/fatigue/hypokalemia (1.2/60); and gr 3 stomatitis/fatigue (1.4/60). There were 3 pts with DLTs treated on the 21-day schedule: gr 3 hypokalemia/hyponatremia (1.4/60); gr 4 mucositis (1.4/60); and gr 3 hypokalemia (1.2/75). With 2 DLTs out of 6 pts at E7389 1.4 mg/m^2 and CDDP 60 mg/m^2, E7389 was reduced, CDDP was escalated, and the MTD was determined to be E7389 1.2 mg/m^2 and CDDP 75 mg/m^2(1 patient out of 6 with a DLT). At the MTD, protocol defined dose modifications or delays were required in 2 of the 6 patients by cycle 2. Notably, all DLTs were observed in patients exposed to at least 2 prior lines of chemotherapy. Two pts had an unconfirmed PR (pancreatic, breast) and 2 had a PR (esophagus, transitional bladder). **Conclusions:** On a 21 day schedule,E7389 in combination with CDDP appears well tolerated and showed preliminary activity. The MTD was determined to be E7389 1.2 mg/m^2 and CDDP 75 mg/m^2. Clinical trial information: 00400829.

2565 General Poster Session (Board #5A), Mon, 8:00 AM-11:45 AM

Phase I study to evaluate the safety and to assess the food effect of HM781-36B, a novel pan-HER inhibitor continuously given in patients with advanced solid tumors.

YuJung Kim, Jisu Oh, Tae Min Kim, Sae-Won Han, Keun Wook Lee, Jee Hyun Kim, Seock-Ah Im, Kyun-Seop Bae, Yook-Hwan Noh, Hyun-Jin Nam, Kyung-Mi Park, Jeewoong Son, Yung-Jue Bang; Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Soengnam-SI, South Korea; Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, South Korea; Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea; Department of Clinical Pharmacology and Therapeutics, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea; Clinical Reserch Center, Hanmi Pharm. Co., Ltd., Seoul, South Korea; Research and Development Center, Hanmi Pharmaceutical Co., Ltd., Seoul, South Korea; Seoul National University Hospital, Seoul, South Korea

Background: HM781-36B, a novel pan-HER tyrosine kinase inhibitor, showed potent in vitro and in vivo antitumor activities for EGFR mutant models including T790M mutation. In the previous 2-weeks on, 1-week off phase I study, the maximum tolerated dose (MTD) was determined as 24 mg/day. Phase I study with a continuous daily dosing schedule was conducted to determine the recommended dose (RD), and to assess the effect of food on pharmacokinetics (PK) in patients (pts) with advanced solid tumors. **Methods:** Eligible pts had advanced malignancies refractory to standard therapies. Standard 3+3 scheme was used in the dose escalation study, and additional 8 patients were enrolled to test food effects. **Results:** 20 pts (median age: 55 years [range32-77], M:F=13:7, ECOG PS 0/1/2/3 8/12/0/0) were enrolled (5 NSCLC, 4 colon cancer, 3 stomach cancer, 2 breast cancer, 2 rectal cancer, 2 common bile duct cancer, 1 pancreatic cancer and 1 esophageal cancer); 12 in the dose escalation and 8 in the food effect study cohort. Twelve pts were heavily pretreated($\geq$4 regimens). Dose limiting toxicities (DLTs) were G3 anorexia in 1 pt at 18mg/day, G3 diarrhea and anorexia in 1 pt, and drug compliance $<$80% due to G2 adverse events in 1 pt at 24mg/day. The MTD was determined as 18 mg/day, and RD was determined as 16 mg/day. The most common drug-related adverse events were diarrhea, stomatitis, skin rash, paronychia, pruritus and anorexia. Among 16 evaluable pts, 4 achieved partial responses (PR)[1 NSCLC, 2 breast cancer, 1 common bile duct cancer], and the duration of response were 32, 40+, 21, and 8 weeks, respectively. Five pts had stable disease (SD). The median duration of treatment in pts with PR or SD was 33.5 weeks (range, 15-82). Under both fasted and fed condition, there were no significant differences of AUC_{last} values, whereas C_{max} values were lower in fed condition than in fasted condition. **Conclusions:** Continuous daily dosing schedule of HM781-36B is safe and well tolerated in advanced solid tumors. It exerts anticancer activity, without being influenced by food. Updated data will be presented at the meeting. Clinical trial information: NCT01455584.

2566 General Poster Session (Board #5B), Mon, 8:00 AM-11:45 AM

A first-in-human (FIH) dose-escalation study of the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of intravenous BAL101553, a novel microtubule inhibitor, in adult patients with advanced solid tumors.

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Background: BAL101553, a pro-drug of the small molecule BAL27862, is a novel microtubule targeting agent (MTA) with cytotoxic and vascular disrupting properties. Pre-clinical data showed anti-proliferative activity in several *in vitro* and xenograft tumour models, including tumours refractory to conventional MTAs through diverse resistance mechanisms. Primary objectives of this FIH study were determination of the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT). Secondary objectives included the evaluation of PK, PD and anti-tumour activity. **Methods:** An accelerated titration dose-escalation design was used. Eligible patients (pts) with advanced solid tumours, who had failed standard therapy, received BAL101553 as a 2-h intravenous infusion on days 1, 8 and 15 of a 28-day cycle. Adverse events (AEs) were assessed according to CTCAEv4. Disease response was assessed by RECIST 1.1 every 2 cycles. **Results:** 16 pts (7 male; median age 52 years; range 29-80) with solid tumours were treated at 4 dose levels (15, 30, 45 and 60 mg/m^2). DLTs were observed at 60 mg/m^2 and included rapidly reversible grade (G) 3 hypertension (HTN) and G3 reduced mobility/ dizziness. DLT criteria for HTN were subsequently modified. Frequent drug-related AEs were injection site reactions, nausea, vomiting (all G1-2), and G2-3 HTN (transient during the infusion; responding to nifedipine). One pt experienced G2 peripheral neuropathy at 60 mg/m^2. PK analyses indicated conversion of BAL101553 to the active BAL27862, dose proportional exposure for both compounds and a half-life of BAL27862 in a range of 11 to 27 h. Preliminary tumour PD data comparing pre/post biopsies showed loss of CD34+ capillaries and focally decreased proliferation. A confirmed partial response was demonstrated in 1 pt with ampullary (pancreaticobiliary) cancer maintained on treatment for >16 cycles with intra-pt dose escalation. 2 pts (laryngeal and rectal cancer) demonstrated stable disease >16 weeks. **Conclusions:** BAL101553 is well tolerated up to 60 mg/m^2 with evidence of anti-tumour activity. Dose escalation continues to determine the MTD. Clinical trial information: NCT01397929.

2567 General Poster Session (Board #5C), Mon, 8:00 AM-11:45 AM

Clinical pharmacokinetics (PK) and translational PK-pharmacodynamic (PD) modeling and simulation to predict antitumor response of various dosing schedules to guide the selection of a recommended phase II dose (RP2D) and schedule for the investigational agent MLN0128.

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Background: MLN0128 (INK128) is an investigational oral, potent, and highly selective inhibitor of mammalian target of rapamycin complex 1 and 2 (mTORC1/2) currently in clinical investigation. In the phase1 study INK128-001, MLN0128 was administered once daily (QD), once weekly (QW), QDx3D/week, and QDx5D/week, with respective MTDs of 6, 40, 16, and 10 mg. To guide selection of dose/schedule for further investigation, PD modulation in skin (pS6, p4EBP1, pNDRG1, pPRAS40) was put into context of clinical PK in INK128-001. A preclinical translational dynamic-PK efficacy model was used to describe the relationship and determine PK drivers of efficacy in tumor xenograft models. This model was implemented using human PK parameters to predict tumor volume-time curves, which was utilized to help determine the optimal MLN0128 dose/schedule. **Methods:** Phoenix NLME v1.1 was used for compartmental modeling of clinical and preclinical PK data, and modeling the preclinical PK-efficacy relationship of MLN0128. PD activity in skin was measured by immunohistochemistry, reported as H scores. Tumor growth curves were simulated using NONMEM v7.2; predicted tumor growth curves were plotted in S-Plus v8.1. **Results:** Clinical skin PD data suggests exposure dependent inhibition of pS6, and p4EBP1. A two compartment PK model adequately described the PK characteristics of MLN0128 [mean (%CV) ka: ~5.305 h^{-1} (114), k12: ~0.490 h^{-1}(85), k21: ~0.67 h^{-1}(69), V/F: ~180 L (44), Tlag: 0.317 h (73)]. Simulation of human tumor volume-time curves suggest efficacy is dependent on schedule and that MLN0128 administered in more frequent schedules (QD, QDx5D) provides stronger antitumor effect vs less frequent schedules (QW, QDx3D). **Conclusions:** The results indicate that per unit MLN0128 plasma exposure, QD and QDx5D may be optimal in comparison with QDx3D and QW dosing. However, these results will also need to be put into context with the overall safety profile and respective MTDs and RP2Ds for each schedule with their resultant achievable total cycle dose by schedule. Clinical trial information: NCT01058707.

2568 General Poster Session (Board #5D), Mon, 8:00 AM-11:45 AM

Influence of mild and moderate hepatic impairment on the pharmacokinetics (PK) of the pan-HER inhibitor dacomitinib.

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Background: Dacomitinib (D) is a highly selective irreversible small molecule inhibitor of the HER family of tyrosine kinases in clinical development for NSCLC.Prior clinical studies of D, which has minimal renal excretion (~3%), enrolled pts with protocol-defined adequate liver function. Liver metastases, leading to abnormal liver function tests, are common in pts with advanced cancer. This study evaluated the effect of hepatic impairment on PK and safety of D following a single oral dose in subjects with mild or moderate hepatic impairment. **Methods:** In this phase I, open-label, parallel group study, 25 subjects with either normal hepatic function (n=8) or mild (Child-Pugh A; n=8) or moderate (Child-Pugh B; n=9) hepatic impairment were administered a single, oral dose of D (30 mg). PK samples were collected at intervals up to 264 h post-dose and safety was assessed by laboratory abnormalities, physical examination, vital signs, ECGs, and AE monitoring. Analysis of variance was performed on natural log-transformed AUC and $C_{max}$to estimate adjusted mean differences between groups and 90% CIs, which were exponentiated to produce the adjusted GMR and 90% CI of the ratios. **Results:** GMR and 90% CI for AUC_{inf} and C_{max} (preliminary analyses) are listed.Mean D exposure (AUC_{inf} and C_{max}) was similar in subjects with normal hepatic function and those with mild impairment. Moderate hepatic impairment decreased D exposure by 15% and 20% for AUC_{inf} and C_{max}, respectively, vs normal hepatic function, but the 90% CI was relatively wide, and included 1. Plasma protein binding of D was similar in the 3 groups. No clinically significant treatment-related AEs were reported. **Conclusions:** Mean D exposure (AUC_{inf} and C_{max}) was similar in subjects with normal hepatic function and those with mild impairment. Mean D exposure appeared slightly lower in subjects with moderate impairment. Dose reduction of D in subjects with mild or moderate hepatic impairment may not be necessary. A single 30 mg dose of D was well tolerated in subjects with mild or moderate hepatic impairment. Clinical trial information: NCT01571388.

	GMR (90% CI) vs normal hepatic function	
Hepatic impairment	**AUC_{inf}**	**C_{max}**
Mild	1.00 (0.73–1.38)	1.03 (0.69–1.53)
Moderate	0.85 (0.62–1.15)	0.80 (0.55–1.17)

2569 General Poster Session (Board #5E), Mon, 8:00 AM-11:45 AM

Phase I trial of ADI-peg 20 plus docetaxel (DOC) in patients (pts) with advanced solid tumors.

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Background: ADI-PEG20 is an enzyme that degrades arginine (Arg), an amino acid relevant to biosynthetic pathways of normal and malignant cells. It has shown tolerability and activity in several solid tumors. Preclinical studies have shown that Arg deprivation by ADI-PEG 20 in cancer cells induces autophagy, caspase-independent apoptosis, and potentiates DOC-induced cytotoxicity in prostate cancer (PC) models. A phase I trial (standard 3+3 design) of ADI-PEG20 (IM weekly) plus DOC (IV on day 1 q 3 weeks) was conducted to assess feasibility and safety of the combination. **Methods:** Eligible pts were >18 years of age, had advanced malignant solid tumors, adequate end organ function, and performance status (PS) 0-2. ADI-PEG 20 was escalated over 4 dose levels (4.5, 9, 18, 36 mg/m2). DOC dose was 75 mg/m2. Dose limiting toxicity (DLT) was defined as any of the following in cycle 1: thrombocytopenia [grade (Gr) 3 with bleeding/transfusion, or Gr 4]; neutropenia with fever or documented infection attributable to ADI PEG20; or any ≥ Gr 3 non-heme toxicity related to study drug except alopecia. Allergic reaction associated with DOC was not considered a DLT. Serum levels of Arg were serially measured. **Results:** 18 pts were accrued: median age, 64.5 yrs; male, 83%; PS 0, 72%. Most common tumors were NSCLC (8), PC (3), and tongue cancer (TC) (2). Median number of prior systemic therapies was 3. One DLT was seen in dose level 1 (urticarial rash) requiring expansion of that dose level to 6 pts. No additional DLTs attributable to ADI PEG20 were seen. Serious adverse events (all expected and attributed to DOC) were recorded in 11/18 pts, including Gr IV neutropenia (6, 33%) and Gr IV anemia (2, 11%). There were 2 on-study deaths unrelated to protocol therapy. In 11 pts with evaluable disease, 1 with TC had a partial response (PR), 6 had stable disease (SD) (3 NSCLC, 2 PC, 1 TC). Arg levels decreased in the 1st cycle for 6/11 pts with available data, including 2 with SD, and 1 with PR. **Conclusions:** The combination of ADI PEG20 and DOC is feasible with reasonable tolerability in this heavily pre-treated cohort. Full doses of both agents were achievable: ADI-PEG 20 at 36mg/m2 with DOC 75 mg/m2. An expansion cohort of castration resistant PC pts is now accruing at this recommended dose. Clinical trial information: NCT01497925.

2570 General Poster Session (Board #5F), Mon, 8:00 AM-11:45 AM

A genotype-directed study to optimize dosing of irinotecan according to the *UGT1A1* genotype.

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Background: The risk of severe neutropenia from irinotecan (I) is in part related to *UGT1A1*28*, a polymorphism that reduces the elimination of SN-38, the active metabolite of I. We aimed to identify the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of I in advanced solid tumor patients (pts) stratified by**1/*1*, **1/*28*, and **28/*28* genotypes. We hypothesized that **1/*1* pts would tolerate a higher MTD than the standard 350 mg/m^2 dose and that **28/*28* pts would require dose reduction. **Methods:** 68 pts (30 lung, 30 gastrointestinal, 8 other cancers) received q3w, flat-dose I. Genotype frequencies were 46% (**1/*1*), 41% (**1/*28*), and 13% (**28/*28*). Pts (66% males, median age 68 years) had 0-1 PS (only one pt had PS 2). 82% were Caucasians, 13% African Americans, and 4% Hispanics. The I starting dose was 700 mg in **1/*1* and **1/*28* pts, and 500 mg in **28/*28* pts. Pharmacokinetics was obtained at cycle 1. DLT at cycle 1 was defined as grade (G) 4 neutropenia (N) for ≥4 days, G≥3N on a treatment day, G≥3 febrile N, G4 anemia or thrombocytopenia, or G≥3 non-hematological toxicity. **Results:** In **1/*1* pts, the MTD was 850 mg (4 DLTs/16 pts), and 1000 mg was not tolerated (2 DLTs/6). In **1/*28* pts, the MTD was 700 mg (5 DLTs/22) and 850 mg was not tolerated (4 DLTs/6). In **28/*28* pts, the MTD was 400 mg (1 DLT/6) and 500 mg was not tolerated (3 DLTs/3). DLTs were mainly G4N, G≥3 febrile N, and G3 diarrhea. I clearance followed linear kinetics. I and SN-38 AUCs were associated with decreased $\log_{10}$ANC nadir (r^2 0.27 and 0.30, respectively, $p<0.0001$). At the MTD, I AUC in **28/*28* pts was 50% and 62% lower than that of **1/*28* and **1/*1* pts (16.8±4.4, 33.4±11.9, 44.2±11.3 h*ug/ml [mean±SD], respectively). At the MTD, SN-38 AUC in **28/*28* pts was 30% and 26% lower than that of **1/*28* and **1/*1* pts (620±407, 881±715, 841±888 h*ng/ml). 3 PRs were observed (NSCLC-700 mg-**1/*28*, gastric-850 mg-**1/*1*, small bowel-850 mg-**1/*28*). **Conclusions:** In a heavily pretreated population, *UGT1A1*28* information can be used to individualize dosing of I. Additional studies should evaluate the effect of genotype-guided dosing on efficacy in pts receiving I. Clinical trial information: NCT00708773.

2571 General Poster Session (Board #5G), Mon, 8:00 AM-11:45 AM

Dose-ranging randomized pharmacokinetic (PK) and pharmacodynamic (PD) study of vorinostat in patients with advanced solid tumors.

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Background: Continuous 400 mg daily vorinostat (V) is effective treatment for cutaneous T-cell lymphoma, but has displayed erratic activity in combination therapy for solid tumors. Short-course high-dose vorinostat may have a better therapeutic index for solid tumors, but dose/exposure/PD relationships have not been tested in sufficiently powered studies. **Methods:** Patients (pts) were randomized to either V 1600 mg daily, days (d) 1-3 then 400 mg d8-10 or 400 mg d1-3 then 1600 mg d8-10 with complete PK sampling on d3 and d10 to determine the increase in Cmax upon increasing V from 400 to1600 mg. To assess safety and tolerability of high dose V added to carboplatin, pts then received high dose V d15-17 with carboplatin AUC 5 on d17; this combination was repeated every 21d thereafter. Platelet counts were determined weekly. To detect with 80% power a difference in vorinostat Cmax between 400 and 1600 mg required at least 10 pts in each sequence. In vitro studies of gene expression in solid tumors suggested as a secondary endpoint the frequency of pts achieving Cmax $>$ 1000 ng/mL. **Results:** 24 pts (11 men/13 women) enrolled between April 2011 and March 2012 and were evaluable for study endpoints. No sequence dependence of change in Cmax was detected. Cmax for V 1600 mg was nearly double that for 400 mg (1184+/-631 vs. 616+/-442 ng/mL, $p < 0.001$). The PD effect on platelets (d10) was greater for the higher dose (median -76 vs. -14 K/μL, $p = 0.02$). There were no dose limiting toxicities. Of 24 pts, 11 achieved Cmax $>$ 1000 ng/mL. **Conclusions:** The 1600 mg dose of vorinostat results in a higher Cmax than 400 mg and greater PD effect than 400 mg and is tolerable in combination with carboplatin. The carboplatin/vorinostat doublet serves as a DNA-damaging/epigenetic modifier module to be combined in more complex regimens. Clinical trial information: NCT01281176.

2573 General Poster Session (Board #6A), Mon, 8:00 AM-11:45 AM

A phase I, first-in-human study to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of IMGN853 in patients (Pts) with epithelial ovarian cancer (EOC) and other FOLR1-positive solid tumors.

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Background: IMGN853 is an antibody-drug conjugate (ADC) comprising a folate receptor 1 (FOLR1)-binding antibody and the potent maytansinoid, DM4. FOLR1 is over-expressed on many solid tumors, particularly EOC, endometrial cancer, non-small cell lung cancer (NSCLC), and clear-cell renal cell cancer. **Methods:** The primary study objectives are to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). Secondary objectives include evaluation of safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy. In dose escalation, patients with any type of FOLR1-expressing, refractory solid tumor may be enrolled. Once the MTD is defined, 3 expansion cohorts will evaluate patients with (1) primary platinum refractory or resistant EOC; (2) relapsed/refractory EOC, amenable to biopsy, and (3) relapsed/refractory NSCLC. Cohorts 2 and 3 will have IMGN853 PD assessment by pre-and post-dose tumor biopsy and by FLT-PET imaging, respectively. IMGN853 is given intravenously (IV) on Day 1 of each 21-day cycle. During dose escalation, an accelerated titration design was used. Responses are assessed using RECIST and GCIG criteria (as appropriate). **Results:** Eleven patients have been enrolled across 6 dose levels ranging from 0.15 to 5.0 mg/kg: 7 patients with EOC and 4 patients with endometrial cancer. No study drug-related serious adverse events (SAEs) or dose-limiting toxicity (DLT) have been reported. Among these 11 patients, 3 patients reported adverse events (AEs) considered study drug related; these were mild or moderate. At the 3.3 mg/kg dose level, one patient with serous EOC had an 82% reduction in CA125 (confirmation pending). The other 2 patients at this dose level, one with EOC and one with endometrial cancer, have stable disease. Drug exposure has been measured in 8 patients and has been found to generally increase linearly, with a half life at 3.3 mg/kg (3 patients) of approximately 4 days. **Conclusions:** IMGN853 is well tolerated at doses up to 3.3 mg/kg. Safety evaluation continues at 5 mg/kg and dose escalation is ongoing. Clinical trial information: NCT01609556.

2574 General Poster Session (Board #6B), Mon, 8:00 AM-11:45 AM

Phase I study of inotuzumab ozogamicin (INO) combined with R-GDP for relapsed CD22+ B-cell non-Hodgkin lymphoma (B-NHL).

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Background: CD22 is expressed on most B-NHL. INO, an anti-CD22 antibody linked to calicheamicin, has activity in refractory B-NHL. This study hypothesized that INO plus rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP) for relapsed CD22+ B-NHL was safe and tolerable. **Methods:** Patients (pts) with relapsed CD22+ B-NHL treated with ≥1 prior R-chemo regimen were enrolled using an up-and-down independent dose-escalation schema for G and P. INO (0.8 mg/m^2 day 2) was combined with R-GDP (R 375 mg/m^2, G, and P day 1; oral D 40 mg days 1-4) on a 21-d cycle for up to 6 cycles. Dose-limiting toxicity (DLT) included febrile neutropenia, grade (Gr) 4 ANC lasting ≥7 d, Gr 4 platelets ≥7 d, Gr ≥3 platelets with bleeding and transfusion support, Gr ≥3 QTc prolongation, Gr 4 AST/ALT, Gr 2 bilirubin ≥7 d, G-CSF during cycle 1, Gr ≥3 clinically significant or drug-related nonhematologic toxicity ≥7 d, and Gr ≥2 drug-related nonhematologic toxicity causing dose delay of ≥7 d. **Results:** Thirty-seven pts were treated: 15 DLBCL, 11 FL, 7 MCL, 1 MZL, 1 SLL, and 2 indolent B-NHL. Characteristics: aged 33 to 81 y (median 65 y); 34 with ECOG PS £1; median of 2 prior chemo regimens (range 1-6); 5 refractory to prior therapy. No DLTs were observed at the starting dose of G 500 mg/m^2, P 37.5 mg/m^2 (n = 6); 2 DLTs (febrile neutropenia, Gr 2 platelets) at G 1000 mg/m^2, P 37.5 mg/m^2 (n = 3); no DLTs at G 1000 mg/m^2, P 0 mg/m^2 (n = 6); 2 DLTs (febrile neutropenia; Gr 4 ANC ≥7 d) at G 500 mg/m^2, P 50 mg/m^2 (n = 8); and 2 DLTs (Gr 3 hypokalemia, Gr 4 neutropenic sepsis) at G 500 mg/m^2, P 75 mg/m^2 (n = 4). In a maximum tolerated dose (MTD) confirmation cohort of 10 additional pts, 3 pts had DLTs (2 with Gr 4 platelets, 1 with febrile neutropenia); thus MTD was determined to be INO 0.8 mg/m^2, R 375mg/m^2, G 500 mg/m^2, D 40 mg, P 50 mg/m^2. Gr ≥3 adverse events included thrombocytopenia (68%), neutropenia (54%), lymphopenia (32%), anemia (27%), leukopenia (24%), hypokalemia (22%), fatigue (11%), and febrile neutropenia (11%). Median treatment cycle was 4 (range 1-6). There were 8 complete and 9 partial responses. **Conclusions:** INO 0.8 mg/m^2 with R-GDP is tolerable at reduced doses of G (500 mg/m^2) and P (50 mg/m^2). Preliminary efficacy is being explored in the ongoing MTD expansion cohort. Clinical trial information: NCT01055496.

2575 General Poster Session (Board #6C), Mon, 8:00 AM-11:45 AM

Phase I dose-escalation clinical trial with 5-imino-13-deoxydoxorubicin in cancer patients.

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Background: 5-imino-13-deoxydoxorubicin (DIDOX; GPX-150) is a doxorubicin (dox) analog modified in two locations to prevent formation of a) cardiotoxic metabolites and b) reactive oxygen species. In a rabbit model comparing the cardiotoxicity of dox vs. DIDOX, chronic doses of each caused similar myelosuppression, but only dox caused cardiotoxicity as assessed by echocardiography and histopathology scoring. In view of the non-cardiotoxic nature of DIDOX along with its anticancer efficacy in preclinical studies, DIDOX was entered into a Phase I, open-label, non-randomized dose-finding study in up to 30 patients with solid tumors. **Methods:** Inclusion criteria included progressing solid tumors and cardiac ejection fraction (CEF) 110% of lower limit of institutional normal (assessed by MUGA). There are 8 dose cohorts and up to 8 cycles/cohort, dosing (iv) once every 3 weeks with an accelerated titration dosing design at the three lowest cohorts. Cohort A =14, B=28, C=56, D=84, E=112, F=150, G=200, and H=265 mg/m^2/cycle. Dose was escalated to next dose level if $<$ 1 dose limiting toxicity (DLT) is reported. Maximum tolerated dose (MTD) will be exceeded when 2 or more patients in a cohort elicit DLT; the next lower dose is defined as the MTD. DLT occurs when a decrease in CEF is grade 2 or higher, or grade 4 neutropenia lasts $>$ 5 days. **Results:** Cohorts A-G have been completed. Number of patients for the cohorts are: A=1, B=1, C=1, D=4 E=3 F=3 G=4, and H = 2 (with 4 more to be enrolled in H). No decrease in CEF occurred in any cohorts. There were no DLTs in cohorts A-G. One patient in H had neutropenia grade 4 for 11 days (a DLT). Another patient in H had neutropenia grade 4 for 4 days. There was no disease progression at the completion of dosing for 6 of the 12 patients in cohorts E-H. In contrast, all 7 patients had disease progression in cohorts A-D. **Conclusions:** No cardiotoxicity was observed in any patient. No DLT was observed in cohorts A-G. With one DLT in cohort H, one more DLT will define MTD for DIDOX at 200 mg/m^2. At higher DIDOX doses (E-H), 6 of 12 patients showed no disease progression. (IND No. 77,051). Clinical trial information: NCT00710125.

2576 General Poster Session (Board #6D), Mon, 8:00 AM-11:45 AM

ProGem1: Phase I first-in-human study of the novel nucleotide NUC-1031 in adult patients with advanced solid tumors.

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Background: NUC-1031 is a novel nucleotide (ProTide) that evades all three key cellular resistance mechanisms associated with gemcitabine (dFdC). NUC-1031 bypasses nucleoside transporters, is activated independent of deoxycytidine kinase and is resistant to cytidine deaminase-mediated degradation. NUC-1031 has demonstrated broad antiproliferative activity in vitro and in vivo. **Methods:** Patients with relapsed/refractory advanced solid tumors entered in sequential cohorts of up to 6 patients, with escalating doses of NUC-1031 administered as a 5-10 minute IV injection weekly or twice-weekly. Ongoing objectives are to determine recommended phase II dose, safety profile, pharmacokinetics (PK) and preliminary anti-tumor activity. **Results:** 8 patients (5 female, 3 male) with pancreatic (2), colorectal (2), breast (1), and ovarian (1) cancers; cholangiocarcinoma (1) and unknown primary (1) have been enrolled. Two dose levels - 500mg/m^2 (4) and 1000mg/m^2 (1) weekly and one dose level - 375 mg/m^2(3) twice-weekly. No DLTs have been observed. Mean AUC (0 - 24 h) for NUC-1031 was 150.3 $\pm$ 84.8 μM/h (n=5). dFdC and dFdU were detected in plasma up to 24 h (range of 0 - 5.8 μM for dFdC and 0 - 14.9 μM for dFdU). NUC-1031 excreted in urine mainly as dFdU. The Table shows rapid elimination of NUC-1031 from plasma and high intracellular levels of the active gemcitabine triphosphate at 2 and 24 h. Stable disease achieved in 1 patient with rapidly progressing breast cancer. Two further patients had symptomatic relief and improved QOL, including a dramatic reduction in ascites and pain. **Conclusions:** PK data show NUC-1031 has $\geq$ 10x higher intracellular levels of the active compound, dFdCTP, and significantly lower plasma Cmax levels of the toxic metabolite, dFdU, compared to equivalent levels of gemcitabine. NUC-1031 has shown better intracellular delivery and toxicity profile than gemcitabine with some promising early indicators of clinical efficacy. Clinical trial information: NCT01621854.

	Time (h)	
	2	24
Plasma NUC-1031	1.8 $\pm$ 2.1 μM	0.18 $\pm$ 0.20 μM
Intracellular NUC-1031	0.67 $\pm$ 0.71 μM/mg	0.20 $\pm$ 0.47 μM/mg
Intracellular dFdC	$<$ 0.01 μM/mg	$<$ 0.01 μM/mg
Intracellular dFdCMP	0.04 $\pm$ 0.04 μM/mg	0.70 $\pm$ 1.53 μM/mg
Intracellular dFdCTP	3.36 $\pm$ 1.64 μM/mg	0.43 $\pm$ 0.23 μM/mg

2577 General Poster Session (Board #6E), Mon, 8:00 AM-11:45 AM

Novel toxicity endpoint for dose-finding designs evaluating molecularly targeted agents (MTA).

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Background: The emergence of MTA in oncology has revolutionized the phase I design paradigm. The usual dose-limiting toxicity (DLT) endpoint is an oversimplification of the complex toxicity profile resulting in loss of information. Moreover, MTAs can induce less DLTs but more multiple moderate toxicities that may lead to dose reduction in long lasting treatment. We thus sought to develop a new toxicity endpoint, the Total Toxicity Profile (TTP), to incorporate multiple toxicities. **Methods:** We reanalysed the phase I trial that evaluated erlotinib (75, 100, 125, 150 mg/m^2) in children with brain stem glioma (NCT00418327). Only 2/21 patients experienced protocol defined DLTs, but multiple moderate toxicities were observed. The TTP endpoint is a weighted combination of all toxicities experienced by the patient (Euclidean norm of the weights), where the weights (ranging from 0 to 10) reflect the clinical importance of each grade and type of toxicity. The weights and the acceptable toxicity target (target TTP) were elicited from 3 clinicians using hypothetical patient cohorts with various toxicity outcomes. They were asked to make a decision of where the next cohort of patients would be treated: higher, lower or same dose level. The target TTP was defined as the mean of TTPs of the cohorts associated with a decision to repeat the dose. We used the TTP-driven Quasi-Likelihood Continual Reassessment Method (QL-CRM) to re-estimate the recommended dose. **Results:** Clinicians identified 5 main dermatological toxicity types possibly attributable to erlotinib. The consensus weights (table below) as well as the target TTP (set at 4.66) were easily obtained, confirming the feasibility of the process. The weights differed from the CTCAE grades, confirming the interest of the approach. The recommended dose based on the retrospective analysis of all grades toxicity was lower than that identified by the DLT-driven CRM (100 instead of 125mg/m^2). **Conclusions:** By neglecting multiple moderate toxicities, DLT-driven designs may over-estimate the recommended dose when investigating MTA. Our proposal is an appealing alternative design for MTA.

	CTCAE grade		
Toxicity	**1**	**2**	**3**
Folliculitis	2	4.5	8
Erythema	1	3	6
Pruritis	2	4	7
Xerosis	1	3	6
Long eyelashes	1	3	6

2578 General Poster Session (Board #6F), Mon, 8:00 AM-11:45 AM

A first-in-human phase I study of CZ48, a lactone ring protected oral camptothecin, in patients with advanced solid tumors.

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Background: CZ48, the 20-O-propionate ester of camptothecin (CPT), is a prodrug of CPT first described by Cao et al. in 1998. The side-chain is enzymatically cleaved in tissues. This gives rise to CPT, a potent inhibitor of topoisomerase I. **Methods:** An open-label, single-arm, dose-escalation Phase I study was performed to determine the maximum tolerated dose (MTD) of CZ48 in patients with advanced solid tumors. Initial dosing started *qd po* 80mg/m^2, advancing to 2560mg/m^2 for 21 consecutive days, followed by 7 days rest. Dosing was restarted in cohorts of 3 patients *tid po* at 18mg/m^2 and escalated to 1g/m^2on a 5 days on, 2 days off schedule for 28 days. Patients were prescreened by measuring CPT levels in plasma following a single pilot dose of CZ48. Dose was doubled until occurrence of at least Grade 2 adverse event, at which time 3+3 patient cohorts with a dose escalation of 33%-100% were implemented. DLT in 2/6 patients defined the MTD as the preceding DLT dose. PK parameters were measured prior to dosing, days 1-5, and day 28 of Cycle 1. **Results:** Poor absorption led to initial *qd* dosing reaching 2560mg/m^2 with no signs of DLT. Subsequent *tid* dosing showed improved plasma levels and arrival at DLT. 34 patients were treated across 8 dose levels from 18 to 1000 mg/m2. The most frequent study-related adverse effects were cystitis, vomiting, diarrhea and fatigue. Grade IV toxicities observed were febrile neutropenia, anemia, and thrombocytopenia. Preliminary PK data in the *qd* dosing showed poor correlation between dose and C_{max} or AUC, while PK in *tid* patients showed slightly improved correlation between dose and both CZ48 AUC (Pearson's correlation coefficient ϱ=0.476, $p<0.01$) and CZ48 C_{max}(ϱ =0.51, $p<0.01$). Evidence of clinical activity with stable disease $\geq$ 6 months was observed in 2 heavily pre-treated colon and one breast cancer patient. **Conclusions:** The MTD of *tid po* CZ48 administered 5 days on, 2 days off of 28-day cycle is between 750 mg/m^2 and 576 mg/m^2. Overall toxicity is relatively mild, with DLT being cystitis and myelosuppression. Even with *tid* dosing, PK values correlate poorly to dose. A new formulation with 3-5 fold higher preclinical absorption values is being considered for introduction into the trial. Clinical trial information: NCT00947739.

2579 General Poster Session (Board #6G), Mon, 8:00 AM-11:45 AM

Phase I study of olaparib in combination with carboplatin and/or paclitaxel in patients with advanced solid tumors.

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Background: This three-center phase I study evaluated the PARP1/2 inhibitor olaparib (O) in combination with carboplatin (C), paclitaxel (Pa) or both (CPa) in patients (pts) with advanced solid tumors refractory to standard therapies (NCT00516724). **Methods:** This ongoing study consists of multiple parts (P) in which escalating doses of O capsule and tablet formulations were studied. Capsule formulation data are presented; continuous O with C (P1; 21 day cycle), CPa (P2a; 21 day cycle) and weekly Pa (P2b; 28 day cycle) or intermittent O with CPa (P3; 21 day cycle). Primary and secondary objectives were safety/tolerability and antitumor activity (RECIST), respectively. **Results:** This analysis (non validated data) included 87 enrolled pts (P1 [n=25] P2a [n=20] P2b [n=12] and P3 [n=30]). Most common tumor types were breast (26%), melanoma (10%) and ovarian (7%). 12 pts had known g*BRCA1/2* mutations. A tolerable continuous dosing schedule of O with CPa was not determined. Most common AEs (all grades) were myelosuppression (71%) notably neutropenia (54%) and thrombocytopenia (26%), and fatigue (77%). Excessive treatment cycle delays due to hematologic toxicity occurred with continuous O combined with standard doses of C or CPa. Two doses were identified as tolerable: continuous O 100 mg bd with weekly Pa 80 mg/m^2 and intermittent O 200 mg bd (d1–10) with CPa AUC4/175 mg/m^2 q 3 weeks. 14/87 pts (16%) had an objective response (complete response [CR] 5%; partial response [PR] 11%); 28% had stable disease for ≥4 months. Activity appeared greater in pts with *BRCA1/2* mutations (CR 17%; PR 33%). **Conclusions:** Continuous O in combination with CPa exacerbated hematologic toxicities leading to schedule delays. Tolerability improved with intermittent O. Antitumor activity was highest in pts with a *BRCA1/2* mutation. This study identified two tolerable O capsule treatment schedules for further development. Clinical trial information: NCT00516724.

	Treatment schedule		
Part	Olaparib (mg, bd)	Carboplatin (AUC; q 3 wks)	Paclitaxel (mg/m^2; q 3 wks)
Continuous			
P1	50	4	
P1	100	4	
P1	50	5	
P1	200	4	
P2a	50	4	90
P2a	50	4	135
P2a	50	4	175
P2a	100	4	175
P2b	100		80*
P2b	200		80*
	Intermittent		
P3	200 (d1–10)	4	175
P3	200 (d1–10)	5	175
P3	400 (d1–10)	4	175
P3	200 (d1–5)	5	175
P3	400 (d1–5)	5	175

* Weekly; wks, weeks; d, days.

2580 General Poster Session (Board #6H), Mon, 8:00 AM-11:45 AM

First-in-human trial of novel oral PARP inhibitor BMN 673 in patients with solid tumors.

Johann Sebastian De Bono, Lida A. Mina, Michael Gonzalez, Nicola J. Curtin, Evelyn Wang, Joshua W. Henshaw, Manpreet Chadha, Jasgit C. Sachdev, Daniela Matei, Gayle S. Jameson, Michael Ong, Bristi Basu, Zev A. Wainberg, Lauren Averett Byers, Rashmi Chugh, Andrew Dorr, Stanley B. Kaye, Ramesh K. Ramanathan; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Indiana University, Indianapolis, IN; Northern Institute for Cancer Research, Newcastle University, Newcastle Upon Tyne, United Kingdom; BioMarin Pharmaceutical, Novato, CA; Virginia G. Piper Cancer Center at Scottsdale Healthcare/TGen, Scottsdale, AZ; Virginia G. Piper Cancer Center at Scottsdale Healthcare, Scottsdale, AZ; Indiana University School of Medicine, Indianapolis, IN; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Michigan, Ann Arbor, MI; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, London, United Kingdom; Virginia G. Piper Cancer Center Clinical Trials at Scottsdale Healthcare/TGen, Scottsdale, AZ

Background: BMN 673 is the most potent and specific inhibitor of PARP1/2 in clinical development ($IC_{50}<1nM$). In tumors genetically dependent on DNA repair by homologous recombination PARP inhibition induces synthetic lethality. **Methods:** Pharmacokinetics (PK), pharmacodynamics (PD), safety and anti-tumor activity of BMN 673 were evaluated in a 2-stage dose-escalation study with 3-6 patients (pts)/dose level. In dose escalation (Stage 1) cycle 1 was 6 wks, with drug taken on days 1 and 8-35, for PK and PD assays, followed by daily continuous dosing in 4-wk cycles. Stage 2 (expansion at MTD) recruits pts with tumors defective in DNA repair: Ewing sarcoma, small cell lung cancer or tumors associated with BRCA mutation (mut). **Results:** 39 pts (33F/6M) were enrolled in 9 cohorts from 25 to 1100 μg/d that defined a MTD of 1000 μg/d. Median (range) age was 58 (19-81), PS 0 (0-1) and # of prior therapies 4 (1-13). Tumors (# with deleterious BRCA 1/2 mut) included 23 ovarian/primary peritoneal (17); 8 breast (6); 3 pancreas; 2 colon; 1 prostate (1), and 1 mullerian carcinosarcoma. 17 and 8 pts had BRCA 1 and 2 mut, respectively. Dose-limiting thrombocytopenia occurred in 1/6 and 2/5 pts at 900 and 1100 μg/d, respectively. Potentially-related adverse events in $>10\%$ of pts (# grade 1 and 2/grade 3 and 4) included fatigue (10/0); nausea (10/0); flatulence (4/0); anemia (5/2); neutropenia (4/3); thrombocytopenia (1/3); and grade 1 alopecia (10). Inhibition of PARP activity in PBMCs was observed at doses $\geq$ 100 μg/d. BMN 673 plasma concentrations peaked 1-2 hrs post-dose; exposure increased dose proportionally. Steady state plasma concentrations were reached by the end of the 2nd week of daily dosing; mean C_{max}: 0.30 - 25.4 ng/mL and AUC_{0-24}: 3.96 - 203 ng-hr/mL across the 25 to 1100 μg/d dose range after 28d of daily dosing. RECIST and/or CA-125 responses occurred at doses $\geq$ 100 μg/d in 11/17 BRCA carrier ovarian/peritoneal cancer pts. Objective responses occurred in 2/6 BRCA-carrier breast cancer pts. **Conclusions:** BMN 673 is well tolerated with impressive anti-tumor activity in pts with BRCA mut with a single agent recommended Phase II trial dose of 1000 μg/d due to dose-limiting thrombocytopenia. Clinical trial information: NCT01286987.

2581 General Poster Session (Board #7A), Mon, 8:00 AM-11:45 AM

Phase IB study of olaparib (AZD2281) plus gefitinib in EGFR-mutant patients (p) with advanced non-small-cell lung cancer (NSCLC) (NCT01513174/GECP-GOAL).

Rosario García Campelo, Enriqueta Felip, Bartomeu Massuti, Margarita Majem, Enric Carcereny, Felipe Cardenal, Miguel Angel Molina-Vila, Alex Martinez Marti, Juan Luis Marti-Ciriquian, Guillermo Alonso-Jaudenes Curbera, Cinta Pallares, Ramon Palmero, Maria Carmen Gonzalez-Arenas, Clara Mayo-de las Casas, Maria Sanchez-Ronco, Rafael Rosell; Complejo Hospitalario Universitario A Coruña, A Coruña, Spain; Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain; Alicante University Hospital, Alicante, Spain; Hospital De Sant Pau, Barcelona, Spain; Medical Oncology, Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Spain; Catalan Institute of Oncology, Section of Medical Oncology, Barcelona, Spain; Pangaea Biotech, Laboratory of Translational Oncology, Barcelona, Spain; Complexo Hospitalario Universitario A Coruña, A Coruña, Spain; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Catalan Institute of Oncology, Section of Medical Oncology, L'Hospitalet de Llobregat, Spain; AstraZeneca, Madrid, Spain; Alcala de Henares University, Madrid, Spain; Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Pangaea Biotech, Cancer Therapeutics Innovation Group, USP Institut Universitari Dexeus, Barcelona, Spain

Background: Progression-free survival (PFS) and response to EGFR tyrosine kinase inhibitors (TKIs) vary in p with NSCLC driven by EGFR mutations. In our experience, high BRCA1 mRNA expression was associated with shorter PFS in EGFR-mutant p treated with erlotinib. We hypothesized that since olaparib downregulates BRCA1 expression, the addition of olaparib to gefitinib could improve PFS in these p. **Methods:** This is a Phase IB dose escalation study to identify the maximum tolerated dose (MTD), dose limiting toxicity (DLT), pharmacokinetics, and clinical activity of orally administered olaparib in combination with gefitinib in EGFR-mutant advanced NSCLC p. In a standard 3+3 design, p were treated with gefitinib 250mg once daily plus olaparib tablets at escalating doses ranging from 100mg BID to 250mg TDS during a 28-day cycle. **Results:** 18 p have been included across four dose levels of olaparib: 100mg BID (3), 200mg BID (6), 200mg TDS (3) and 250mg TDS (6). Median age, 69; male, 4; PS 0, 17; EGFR TKI treatment-naïve, 10. Toxicities: anemia (66.6%), leucopenia (33.3%), nausea (33.3%), diarrhea (33.3%), asthenia (27.7%), rash (22.2%) vomiting (11%), decreased appetite (16%), and hyperlipasemia (5.5%). Most toxicities were G1-2; G3 drug-related events included leucopenia (1) and anemia (3). No DLT at dose levels 1, 2, and 3; 1 DLT at dose level 4 (G3 anemia and repeated blood transfusion within 4-6 weeks). Few dose reductions or interruptions were needed. 1 p died due to pulmonary embolism unrelated to treatment. Partial responses (PR) were observed in 7 p (41.1%), all EGFR TKI-naïve; stable disease (SD) in 7 (41.1%), most previously treated; progressive disease (PD) in 3 (17.6%), all previously treated. Durable PR and SD were observed in EGFR TKI-naïve and previously treated p. 8 patients are still on treatment. Enrollment to dose level 4 will be completed in February 2013. **Conclusions:** This phase IB trial of gefitinib plus olaparib, has confirmed the activity and tolerability of the combination. The final recommended dose of olaparib is expected to be between 200 and 250 mg TDS. A phase II randomized trial in treatment-naïve EGFR-mutant advanced NSCLC will be opened in 2013. Clinical trial information: NCT0151317.

2582 General Poster Session (Board #7B), Mon, 8:00 AM-11:45 AM

Assessment of γH2AX levels in circulating tumor cells in patients treated with veliparib in combination with doxorubicin and cyclophosphamide in metastatic breast cancer.

Antoinette R. Tan, Deborah Toppmeyer, Serena Tsan-Lai Wong, Hongxia Lin, Murugesan Gounder, Rebecca Anne Moss, Mark N. Stein, Janice M. Mehnert, Sinae Kim, Alice P. Chen, Robert S. DiPaola; The Cancer Institute of New Jersey, New Brunswick, NJ; National Cancer Institute, Bethesda, MD

Background: Veliparib (V) is a potent PARP inhibitor that delays repair of DNA damage induced by chemotherapeutic agents. In metastatic breast cancer pts, we evaluated V with doxorubicin (A) and cyclophosphamide (C) given both on day 1 with V at 100 mg po BID for 7 days post-chemotherapy every 21 days, to increase DNA damage. We report use of γH2AX, (phosphorylated histone protein), a marker of DNA double-strand breaks, in circulating tumor cells (CTCs) to assess DNA damage. We evaluated number of CTCs and percentage of γH2AX-positive CTCs pre- and post-treatment. **Methods:** Eligibility included prior A $\leq$ 300 mg/m^2 and EF $\geq$ 50%. Further A was omitted after a cumulative dose of 420 mg/m^2. Primary objective was to assess DNA damage response to treatment by measuring γH2AX-positive CTCs during cycle 1 on days 1 (pre-treatment), 2, 7, and 14. Cell Search System was used to enumerate CTCs. γH2AX was quantitated using a validated assay. **Results:** Eleven pts enrolled. Median age was 53 (34 – 73); median ECOG PS 1 (0 – 2); there were 1 ER-negative/HER2+, 4 triple-negative (*BRCA2*+, n =1), and 6 ER+/PR+/HER2-negative (*BRCA2*+, n =2) tumors. Most common drug-related toxicities were grade (gr) 4 neutropenia, gr 2 anemia and thrombocytopenia, and gr 1 nausea and vomiting. In *BRCA2*+ pts, there were 2 PRs and 1 SD. In *BRCA* wt or unknown status, 5 pts had SD $\geq$ 3 mo and there were 3 PDs. CTCs ($\geq$ 8) were detected in 10/11 pts on days 1 and 2. Day 7 samples were not obtainable in 2 pts. On day 7, 1/8 pts had 0 CTCs and rest had $\geq$ 3 CTCs. A decrease in CTCs ($p < 0.0001$) occurred from day 1 (median: 22, range, 8-1216) to day 7 (median: 5, range 3-37). At baseline, 7 pts had $\geq$ 10% γH2AX-positive CTCs. Fraction of CTCs positive for γH2AX increased to $\geq$ 50% by day 7 in 6/7 pts and persisted to day 14 in 5 pts. **Conclusions:** The toxicity profile of V 100 mg BID days 1-7 with AC (60/600 mg/m^2) on day 1 on a 21-day cycle was expected. Objective antitumor activity was seen in *BRCA* mutation carriers. CTCs decreased and percentage of γH2AX-positive CTCs increased after combination treatment with a PARP inhibitor and chemotherapy. This observation is notable and we plan to extend dosing of V to 14 days. This work is supported by NCI U01-CA132194. Clinical trial information: NCT00740805.

2583 General Poster Session (Board #7C), Mon, 8:00 AM-11:45 AM

A phase I imaging and pharmacodynamic trial of CS-1008 in patients (pts) with metastatic colorectal cancer (mCRC).

Marika Ciprotti, Niall C. Tebbutt, Fook Thean Lee, Sze Ting Lee, Dave C. McKee, Graeme J. O'Keefe, Sylvia J. Gong, Geoffrey Chong, Hui Kong Gan, Wendie Hopkins, Bridget Chappell, Fiona Elizabeth Scott, Martin W. Brechbiel, Archie N. Tse, Mendel Jansen, Manabu Matsumura, Rira Watanabe, Robert A. Beckman, Jonathan Greenberg, Andrew Mark Scott; Ludwig Institute for Cancer Research, Melbourne, Australia; Austin Health, Heidelberg, Australia; National Cancer Institute, Bethesda, MD; Daiichi Sankyo Co., Ltd., Edison, NJ; Daiichi Sankyo Co., Ltd., Gerrards Cross, United Kingdom; Daiichi Sankyo Co., Ltd., Tokyo, Japan

Background: Death receptor 5 (DR5) is a member of the TNFR superfamily that initiates the extrinsic apoptotic pathway. CS-1008 is a humanised, monoclonal IgG1 agonistic antibody (Ab) to human DR5 created by CDR grafting of the murine Ab TRA-8. The aim of this study was to investigate the impact of CS-1008 dose on biodistribution, quantitative tumor uptake and anti-tumor response in pts with mCRC. **Methods:** Pts with mCRC were treated with weekly IV CS-1008 in 5 non-sequential cohorts (Co). Different loading doses were used on days 1 and 8 (0.2 to 6 mg/kg), followed by a weekly dose of 2 mg/kg. D1 and D36 doses were trace-labeled with ^{111}In, followed by whole-body planar and regional SPECT imaging over 10 days. Primary endpoints: initial biodistribution, pharmacokinetic (PK) and tumor uptake following single infusion; changes in biodistribution, PK and tumor uptake following sequential doses. Secondary endpoints: tumor response; changes in tumor metabolism by FDG-PET; serum apoptosis biomarkers and tumor response markers. **Results:** 19 pts (median age 64 yrs; M:F 11:8; 2-6 prior chemotherapy regimens) were enrolled as follows: Co 1, n=2; Co 2, n=4; Co 3, n=5; Co 4, n=3; and Co 5, n=5. Tumor uptake was variable: 7 pts had no uptake, 11 pts had uptake in all sites of disease but liver, 1 pt showed liver uptake. Tumor uptake and PK were not affected by dose or repeated drug administration. No anti-CS-1008 Ab responses were detected. DR5 expression in archived samples did not correlate with uptake or response. ^{111}In-CS-1008 biodistribution showed gradual blood pool clearance and no abnormal uptake in normal tissue. Mean % change in SUVmax from baseline in lesions with uptake was higher than in those with no uptake. There were 8 SD, 1 PR and 10 PD. Duration of PR was 3.7 months (mo). Mean duration of SD was 4 mo. Disease control rate (SD + PR) in pts with uptake was 58% vs 28% of pts with no uptake. Lesions with no uptake were more likely to progress, with a PD risk of 3.4 times higher than those lesions with uptake. **Conclusions:** Tumor DR5 expression, assessed by ^{111}In-CS-1008 imaging, revealed real-time heterogeneous DR5 expression and appeared to be a promising predictive imaging biomarker of clinical benefit in pts with mCRC receiving CS-1008. Clinical trial information: NCT01220999.

2584^ General Poster Session (Board #7D), Mon, 8:00 AM-11:45 AM

Phase I study of ABT-888 in combination with carboplatin and gemcitabine in subjects with advanced solid tumors.

Katherine M. Bell-McGuinn, Heidi J. Gray, Gini F. Fleming, Mihaela C. Cristea, Diane M. Medina, Hao Xiong, Matthew W. Dudley, Martin Dunbar, Vincent L. Giranda, Yan Luo, Mark D. McKee, Lainie P. Martin; Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Obstetrics and Gynecology, University of Washington, Seattle, WA; Alliance for Clinical Trials in Oncology, Chicago, IL; City of Hope, Duarte, CA; AbbVie, Inc, North Chicago, IL; Fox Chase Cancer Center, Philadelphia, PA

Background: Veliparib (V) is an oral inhibitor of poly(ADP-ribose) polymerases (PARP)-1 and -2, which are essential for base excision repair of ssDNA breaks. BRCA deficient tumors are more sensitive to PARP inhibitors when used as monotherapy or in combination with DNA-damaging agents. The objectives of this study were to determine the maximum tolerated dose (MTD), pharmacokinetic interactions, and safety/tolerability profile of V in combination with carboplatin (C) and gemcitabine (G). **Methods:** Eligibility criteria included patients (pts) with metastatic or unresectable solid tumors for which C/G was a treatment option. During the study, eligibility was amended to limit prior chemotherapy regimens to ≤ 2. C AUC 4 /G 800 mg/m^{2}was given intravenously on Day 1 and G given on Day 8 of 21 day cycles. To assess tolerability of C/G prior to V, V was started in Cycle 2. When C/G was stopped, pts could stay on monotherapy V until progression. Dose-escalation used a Bayesian continual reassessment method. Results: 59 pts (51 female, median age 52) were enrolled. The most common tumor types were ovarian (n=39) and breast (n=10). Germline BRCA mutations were known in 24 ovarian pts. 58 pts had prior chemotherapy (1-6 regimens, median 2), and 51 had prior platinum. Grade 3/4 AEs in >10% of pts were neutropenia, thrombocytopenia, anemia, and leukopenia. Dose limiting toxicities were thrombocytopenia (n=3) and neutropenia at V 310 mg twice daily (BID) and thrombocytopenia at 250 mg BID. Other frequent AEs were nausea, constipation, and fatigue. Preliminary results showed co-administration of V did not affect C or G pharmacokinetics. Treatment cycles (range, median) were 1-28, 5 for V; 2-10, 5 for C; and 2-10, 4 for G. Day 8 G was stopped in some pts to improve tolerability. 28 pts stayed on monotherapy V (1-23 cycles). Partial and complete responses were seen in 11 and 2 pts. Response rates were 47% (8/17) in known BCRA deficient ovarian, 25% (3/12) in other ovarian, and 13% (2/15) in other evaluable pts. Conclusions: V combined with C and G was tolerated with a safety profile similar to C and G alone. The MTD was V 250 mg BID, C AUC 4.0, G 800 mg/m^2. Promising anti-tumor activity was observed in BRCA deficient ovarian pts. Clinical trial information: NCT01063816.

2585 General Poster Session (Board #7E), Mon, 8:00 AM-11:45 AM

A phase I dose-escalation and PK study of continuous oral rucaparib in patients with advanced solid tumors.

Rebecca Sophie Kristeleit, Geoffrey Shapiro, Patricia LoRusso, Jeffrey R. Infante, Michael Flynn, Manish R. Patel, Sara M. Tolaney, John Frederick Hilton, Alan Hilary Calvert, Heidi Giordano, Jeffrey D. Isaacson, Jennifer Borrow, Andrew R. Allen, Sarah S. Jaw-Tsai, Howard A. Burris; University College London, London, United Kingdom; Dana-Farber Cancer Institute, Boston, MA; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; Clovis Oncology, Inc., San Francisco, CA

Background: Rucaparib, a potent, oral small molecule inhibitor of poly (ADP-ribose) polymerase (PARP) 1 and -2, is being developed for treatment of homologous recombination repair deficient (HRD) ovarian cancer. This study evaluated oral rucaparib as monotherapy. Primary objectives were to define maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D), and PK of continuous oral rucaparib. **Methods:** A standard 3+3 dose escalation design was used. Intra-patient dose escalation was allowed. Patients (pts) aged ≥18 with advanced solid tumor that progressed on standard treatments were recruited. Rucaparib was taken orally qd or bid until disease progression. Plasma PK assessments included full profile, trough levels, and food effect. **Results:** 29 pts (median age 52 yrs [range 21-71]; 26 female; 15 ECOG PS=0; 17 breast cancer (BC), 7 ovarian/peritoneal cancer (OC), 5 other tumor) were enrolled in 6 dose cohorts to date (40, 80, 160, 300 and 500 mg qd, 240 mg bid). Evaluation of 360 mg bid rucaparib is nearly complete. No DLTs have occurred and no pts have discontinued treatment due to toxicity. Treatment-related adverse events (primarily CTCAE grade 1-2) reported in ≥2 of 29 pts include fatigue (n=5), anorexia (n=3), nausea (n=3), vomiting (n=3), and diarrhea (n=2). To date, two pts (1 OC, 1 BC; both $BRCA1^{mut}$) treated with 300 mg qd rucaparib achieved PR at wk 6; both are ongoing in wk 17. An additional 10 pts (5 OC, 4 BC, 1 CRC; 7 $BRCA^{mut}$, 2 $BRCA^{unk}$, 1 $BRCA^{wt}$) achieved best response of stable disease (SD) >12 wks thus far; 4 pts (3 OC, 1 BC) are ongoing at 17 (n=2) and 30 (n=2) wks. Overall disease control rate (CR+PR+SD>12 wks) in OC pts across all dose levels was 86% (6/7). Dose proportional PK was observed up to 500 mg qd with mean $t_{1/2}$ of 15 h (range 4.3 - 29 h). Following qd dosing, steady state was achieved by Day 8. As expected, bid dosing increased trough levels above 2 μM target with low interpatient variability. **Conclusions:** Continuous oral rucaparib is very well tolerated, with encouraging clinical activity, including objective responses and durable SD, observed during dose-escalation. Once confirmed, the RP2D will be evaluated in platinum-sensitive OC pts with a gBRCA mutation. Clinical trial information: NCT01482715.

2586 General Poster Session (Board #7F), Mon, 8:00 AM-11:45 AM

A phase I study of oral rucaparib in combination with carboplatin.

L Rhoda Molife, Patricia Roxburgh, Richard H. Wilson, Avinash Gupta, Mark R. Middleton, T. R. Jeffry Evans, Caroline Ogilvie Michie, Joaquin Mateo, Donna Crawford, Martin McKinlay Eatock, Wasir Saka, Nicola Cresti, Yvette Drew, Heidi Giordano, Darrin Despain, Dayna Simpson, Andrew R. Allen, Sarah S. Jaw-Tsai, Ruth Plummer; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Queen's University Belfast, Belfast, United Kingdom; Oxford University Hospitals NHS Trust, Oxford, United Kingdom; Northern Institute for Cancer Research, Newcastle University, Newcastle, United Kingdom; Clovis Oncology, Inc., San Francisco, CA

Background: Targeting poly (ADP-ribose) polymerase (PARP), an enzyme involved in DNA damage repair, may increase efficacy of DNA-damaging agents. This study evaluated the tolerability of oral rucaparib, a potent and selective PARP1/2 inhibitor, in combination with carboplatin (CP). **Methods:** Patients (pts) aged ≥18 with advanced solid tumors were included. Pts received lead-in doses of IV and oral rucaparib on Days -10 and -5, respectively, followed by CP on Day 1 and oral rucaparib on Days 1-14 q21 days. Treatment continued until disease progression. Pts with benefit could continue on rucaparib monotherapy once CP dosing was completed. Dose escalation was based on toxicities observed in Cycle 1 in cohorts of n=3-6. PK was assessed during Cycle 1. **Results:** 23 pts (median age 62 yrs [range 20 – 76]; 16 female; 9 ECOG PS=0; 6 ovarian/peritoneal cancer (OC), 5 breast cancer (BC), 2 NSCLC, 10 other tumor) were enrolled. Rucaparib doses of 80, 120, 180, 240, and 360 mg were administered with AUC3 CP, followed by 360 mg rucaparib with AUC4 CP, and currently with AUC5 CP. No DLTs have been reported. Median treatment cycles is 3 (range 1 – 15+). Treatment-related adverse events in ≥4 pts, all grades, include anemia (n=10), fatigue (n=9), nausea (n=7), thrombocytopenia (n=6), constipation (n=5), lethargy (n=5), neutropenia (n=5), and anorexia (n=4). One pt (OC, $BRCA^{wt}$, AUC3 CP/180 mg rucaparib) had a PR of 5.1 mo duration. Two patients (both with OC; 1 $BRCA^{unk}$, 1$BRCA^{wt}$) discontinued CP (after 4 & 8 cycles) and continued on rucaparib monotherapy (additional 5 and 7+ cycles, respectively). An additional 4 pts (all $BRCA^{unk}$) had stable disease (SD) >12 wks. Overall disease control rate (CR+PR+SD>12 wks) in OC pts across all dose levels was 50% (3/6). Dose-proportional increase in rucaparib exposure was observed with steady state achieved by Day 14 and mean $t_{1/2}$of 15 h. Oral bioavailability was 38% and dose-independent. Rucaparib exposure was not changed by CP co-administration. **Conclusions:** The combination of oral rucaparib and CP is well tolerated and exhibits activity at clinically relevant doses of each agent. Further studies in platinum-sensitive and homologous recombination repair deficient populations are warranted. Clinical trial information: NCT01009190.

2587 General Poster Session (Board #7G), Mon, 8:00 AM-11:45 AM

Phase I study of the HDAC inhibitor vorinostat in combination with capecitabine in a biweekly schedule in advanced breast cancer.

Edward Samuel James, Gina G. Chung, Michael DiGiovanna, Tara Beth Sanft, Erin Wysong Hofstatter, Noelle Sowers, Mary Beth Clark, Rebecca Lilian, Susan Chmael, Michelle Cappiello, Gineesha Abraham, Gary M Israel, Lajos Pusztai, Lyndsay Harris, Maysa M. Abu-Khalaf; Yale School of Medicine, New Haven, CT; Yale University School of Medicine, Yale Comprehensive Cancer Center, New Haven, CT; Yale Cancer Center, New Haven, CT; Yale Cancer Center/ Yale New Haven Hospital, New Haven, CT; Yale New Haven Hospital/ Diagnostic Radiology, New Haven, CT; Case Western/Seidman Cancer Center, Cleveland, OH

Background: Synergy between histone deacetylase inhibitors and 5-fluorouracil is thought to be due to down regulation of thymidylate synthase. Study objectives are to assess maximum tolerated dose (MTD), dose limiting toxicities (DLT) and objective response rate of vorinostat (V) in combination with capecitabine (C). Secondary aims are pharmacodynamics of V. **Methods:** Cohorts of 3-6 patients (pts) were enrolled on a 3+3 dose-escalation phase to assess MTD of escalating doses of oral C (1500/1800/2000mg) with V 200 mg BID on days 1-7 and 15-21 of a 28 d cycle. 10 pts enrolled on dose expansion phase and treated at MTD. Pts received a "run in" treatment of V for 5 d and pre/post V biopsy (bx) collected when feasible. DLT was defined as $\geq$ grade 3 non hematological toxicity, grade 4 thrombocytopenia, grade 4 neutropenia $>$ 5 d, grade 4 febrile neutropenia requiring hospitalization, QTc $>$500ms,or treatment delay $>$ 2 weeks from toxicity. Microarray analysis was performed using Illumina HT-12 gene arrays on pre/post bx from 4 pts. **Results:** 23 ptswith median age 51 (range 33-69) were treated: 8 pts at 1500/200mg, 5 pts at 1800/200mg, and 10 pts treated on dose expansion phase at 1500/200mg. Median # of prior lines of chemotherapy was 2 (range 0-7). 3 pts are still on study. Median # of cycles on study were 2 (range 1-42). Cycle 1 DLT was grade 3 fatigue in 2 pts treated on 1800/200mg, and in 1 pt treated on 1500/200mg. Other grade 3/4 toxicities are summarized in the Table. 14 pts are evaluable for response (12 pts at 1500/200mg and 2 pts at 1800/200mg). No objective responses were seen, 3 pts had stable disease $>$ 6 months (1 pt completed 42 cycles). Changes in pathways involved in extracellular matrix and TGFb pathway were noted. **Conclusions:** DLT of C concomitant with V was fatigue. MTD was 1500 mg C combined with 200 mg V BID. Combination has modest clinical activity. Consistent modulation of pathways involved in extracellular matrix and TGFb pathway, suggesting biomarkers of response to V. Clinical trial information: NCT00719875.

Adverse events	Grade 3 # pts	Grade 4 # pts
Thrombocytopenia	2	1
Leukopenia	3	0
Anemia	3	1
Mucositis	1	0
Hand-foot syndrome	2	0
Nausea/vomiting	2	0
Hypokalemia	1	1
Hyponatremia	1	0
Hypoalbuminemia	1	0
Syncope	1	0
Ataxia	1	0
Dyspnea	0	1
Bone pain	1	0
Infection	1	0

2588 General Poster Session (Board #7H), Mon, 8:00 AM-11:45 AM

Impact of *UGT1A4*, *UGT2B7*, and *UGT2B15* pharmacogenetics on tamoxifen (TAM) metabolism.

Joanne Siok-Liu Lim, Boian Ganchev, Onkar Singh, Thomas E Muerdter, Yoon Sim Yap, Raymond C.H. Ng, Nan Soon Wong, Matthias Schwab, Balram Chowbay; National Cancer Centre, Singapore, Division of Medical Sciences, Laboratory of Clinical Pharmacology, Singapore, Singapore; Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology and University of Tuebingen, Stuttgart, Germany, Stuttgart, Germany; Division of Medical Sciences, National Cancer Centre, Singapore, Singapore; National Cancer Centre Singapore, Singapore, Singapore; Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany; National Cancer Centre, Singapore, Singapore

Background: The aims were to characterize the genetic profiles of *UGT1A4*, *UGT2B7* and *UGT2B15*in Asian healthy populations (Chinese, Malay, Indians, N=80 each) and investigate the effects of these SNPs on the disposition of TAM in Asian breast cancer patients (N=202). **Methods:** Healthy Asian subjects and Asian breast cancer patients were genotyped for *UGT1A4*, *UGT2B7* and *UGT2B15* SNPs. Plasma levels of tamoxifen and its metabolites in Asian patients were determined via LC-MS/MS analysis. Genotypic-phenotypic differences were examined using non-parametric tests. Haplotypic effects were examined using haplotype-specific generalized linear model. **Results:** Screening of the 5′ upstream, exonic, exonic-intronic junctions and 3′ downstream regions identified 61, 77 and 47 SNPs in *UGT1A4*, *UGT2B7* and *UGT2B15*respectively. A total of 16, 14 and 20 tag-SNPs were identified in these genes respectively and genotyped in patients. Haplotypic analysis revealed associations between LD block 1 (-1548A>G, -1531C>T, -419G>A, -219C>T, -163G>A, 142T>G, 448T>C, 804G>A, IVS1+196T>C, IVS1+346T>G, IVS1+414A>G, IVS2+307A>G) and higher plasma Tam-N-Gluc level and $MR_{TAM\text{-}N\text{-}Gluc/TAM}$ after adjustment for significant covariates. The median (range) $MR_{TAM\text{-}N\text{-}Gluc/TAM}$ was 2.1- and 1.9-fold higher among patients carrying one and two copies of H2 (GCATAGCACTGG), respectively, compared to patients who carried two copies of H1 haplotype (ACGCGTTGTTAA) [H1/H1 vs H1/H2 vs H2/H2: 0.35 (0.11 - 2.09) vs 0.74 (0.19 - 3.60) vs 0.66 (0.52 - 1.66), $P < 0.0001$]. Similar association was observed between H2 and Tam-N-Gluc level [H1/H1 vs H1/H2 vs H2/H2: 0.75 (0.15 - 4.45) vs 1.29 (0.19 - 9.20) vs 1.66 (0.62 - 2.83) ng/ml, $P = 0.004$]. *UGT2B15* LD block 3 (1568A>C, *168C>T, *186A>T, *+630C>G and *+888A>G) was associated with modest decrease and increase in (*E*)-END and $MR_{Z\text{-}NDM\text{-}4\text{-}O\text{-}GLUC/E\text{-}END}$, respectively. *UGT2B7*haplotypes were not associated with O-glucuronidations of 4-OHT and END. **Conclusions:** This study highlights the involvement of *UGT1A4* haplotypes in the variability in TAM N-glucuronidation while *UGT2B7* and *UGT2B15* variants played limited role in the variabilities of O-glucuronidations of 4-OHT and END in Asian breast cancer patients. Clinical trial information: 0822570P.

2589 General Poster Session (Board #8A), Mon, 8:00 AM-11:45 AM

Can estimated glomerular filtration rate (eGFR) replace isotopic measurement of GFR for carboplatin dosing in stage 1 seminoma?

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Background: Accurate determination of GFR is essential for correct dosing of carboplatin, the standard adjuvant therapy for stage 1 seminoma. Isotopic methods (e.g. 51Cr-EDTA) remain the gold standard for determination of GFR. However, the use of eGFR could reduce the need for such isotope studies. As novel formulae to estimate GFR such as CKD-EPI and MDRD4 have improved the assessment of renal function in non-oncological settings, we investigated their utility for carboplatin dosing. **Methods:** 115 patients (pts) (mean age 40.3, std dev. 10.1) who received adjuvant carboplatin for stage 1 seminoma at our institution between 2007-2012 were identified. All pts underwent 51Cr-EDTA measurement of GFR with carboplatin dose calculated using the Calvert formula, based on GFR uncorrected for body surface area (BSA). Theoretical carboplatin doses were then calculated using eGFR values obtained using the CKD-EPI and MDRD4 formulae with additional calculation to uncorrect for BSA. Creatinine clearance was calculated by Cockcroft-Gault (CG) formula. For each pt the carboplatin doses calculated by eGFR were compared with the actual dose calculated by the gold-standard method; a difference of less than 10% was considered acceptable. **Results:** The Table shows the percentage of pts who would have received an equivalent carboplatin dose using each eGFR formula compared to the dose calculated using 51Cr-EDTA. The CKD-EPI formula performed best with 58.9% of pts receiving within 10% of the correct dose. Pts predicted to be underdosed by CKD-EPI eGFR were more likely to be obese (BMI >30) ($p=0.01$); there were no predictors of the 18.8% who would have received an excess dose. **Conclusions:** Our data support further evaluation of the CKD-EPI formula but highlight the clinically significant variances in carboplatin dosing when using non-isotopic methods of GFR estimation.

Comparison of carboplatin dose calculated using eGFR formulae versus 51Cr-EDTA.

eGFR formula	Same dose n (%)	Overdosed n (%)	Underdosed n (%)
MDRD4	27 (24.1)	10 (8.9)	75 (67.0)
CKD-EPI	66 (58.9)	21 (18.8)	25 (22.3)
CKD-EPI unadjusted	51 (45.9)	41 (36.9)	19 (17.1)
CG	45 (40.5)	61 (55.0)	5 (4.5)

2590 General Poster Session (Board #8B), Mon, 8:00 AM-11:45 AM

Involvement of compensatory CD44+ stem cells following BCL-2 suppression by antisense oligonucleotides.

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Background: Gene therapy is in theory specific but encounters difficulties in practice. Suitable targets are found in many pathways and tumors do express altered patterns of expression. However the actual activity of most regulatory genes are similar to normal. Resistance develops because biochemical pathways are complex, regulated by stimulatory and inhibitory factors, each possibly affected by therapy. It's suggested that tumors alter dependence on targeted gene products for growth by relying upon others, through compensation. Antisense oligos have targeted regulatory proteins in both *in vivo* and *in vitro* prostate cancer models. Cells treated with antisense directed against bcl-2 compensated by suppressing caspase-3 (an apoptosis promoter) and enhancing androgen receptor (AR), (co-activating) p300 and IL-6 expression. This suggests that in LNCaP a progression to increased androgen sensitivity accompanies bcl-2 suppression with a pattern of co-activation associated with more advanced prostate tumors. **Methods:** We evaluated mono- and bispecific oligos which targeted and equally suppressed bcl-2 expression in LNCaP cells. To further evaluate compensatory mechanisms related to tumor resistance we evaluated the level of CD44 expression employing RT-PCR and agarose gel quantification. Bands representing pcr product were photographed, converted to black and white and assessed by MIPAV software. **Results:** Comparable amounts of RNA from LNCaP cells treated with either mono- or bispecific oligos directed against bcl-2 (and EGFR in the bispecifics) were evaluated by RT-PCR using primers directed against CD44. When background intensity was subtracted, the relative intensity of the bands corresponding to CD44, and representing cells treated with MR_4, MR_{24} and MR_{42} (compared to controls) were respectively increased 3.0% $\pm$ 33.6 (NS), suppressed 16.4% $\pm$ 49.1 (NS) and suppressed 9.2% $\pm$ 26.5 (NS). These results were pooled from both duplicate PCR runs and gels, and indicate no significant changes in CD44 expression was produced by any oligo type. **Conclusions:** Stem cells expressing this marker were unaffected by treatment, suggesting this population is not altered by suppressive bcl-2 therapy.

2591 General Poster Session (Board #8C), Mon, 8:00 AM-11:45 AM

Dose-dependent pharmacokinetic (PK) interaction of pegylated liposomal doxorubicin (PLD) with escalating doses of veliparib in a phase I study.

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Background: PARP1 inhibition enhances the effects of DNA-damaging agents such as doxorubicin. We sought to investigate PK of PLD in a phase I study of veliparib (ABT-888, V) and PLD in patients (pts) with recurrent ovarian, fallopian tube, and primary peritoneal, and triple negative breast cancers. No prior PK interactions have been described in V clinical trials. **Methods:** Complete blood samples on day (D) 1 (pre-PLD and 1 hr post PLD), D 8, D 22 on cycle 1 and 2 of treatment in pts receiving PLD 40 mg/m2, day (D) 1 and V D1-14 at varying dose levels of 50,100,150, 200, 300, 350 mg twice daily, were collected in 25 of 31 pts enrolled to a previously reported dose finding phase I study of V and PLD (SGO2012). Plasma PLD levels were measured by HPLC methodology detailed by Gabizon et al Cancer Chemo Pharmacol 2008, 61:695. PK parameter estimates were obtained using non-linear modeling programs available in Winnonlin Ver 5.3. Affect of V dose on PK parameters was estimated with linear regression analysis. Due to a higher degree of GI toxicity with V dosages $>$ 200 mg, we utilized a cut-off of 200 mg for V. PK parameters in the group with dosages greater than or equal to 200 mg (high V, n=18) and those less than 200 mg (low V, n=7) were compared, utilizing an unpaired, 2 sided t-test. **Results:** PLD clearance (CL) was reduced, half-life (hL) was increased, and AUC/mg was increased with higher dosages of V when compared to historical published data. We noted a positive correlation of the auc/mg dose, p=0.001 and a negative correlation with the CL, p=0.001 and increasing V dose. When analyzed as low and high V groups, the mean $\pm$ SEM hL (hrs) was significantly lower in the low V when compared to the high V group, 83.2 $\pm$ 11.7 vs 108.6 $\pm$ 6.0(p =0.042) , and the mean PLD clearance (ml/h)was greater in the low V versus the high V group 35.9 $\pm$ 5.6 vs 14.2 + 1.0, P$<$.0001. Similarly the AUC/mg dose (mg x h/L) was significantly lower in the low vs high V groups, 35.0 $\pm$5.2 vs 74.9 $\pm$ 4.4, P$<$0.0001. **Conclusions:** Higher exposure of PLD is noted with V at doses greater than or equal to 200 mg twice daily. An expansion cohort with patients receiving PLD alone in cycle 1, and PLD + V 200 mg twice daily in subsequent cycles, will validate the presence of a PK interaction. Clinical trial information: NCT01145430.

2592 General Poster Session (Board #8D), Mon, 8:00 AM-11:45 AM

CYP3A4 phenotyping with midazolam to predict sunitinib exposure.

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Background: Patients treated with sunitinib show high inter-patient variability in drug exposure (40-60%), which is largely unexplained. Since sunitinib is metabolized by CYP3A4, variability in the activity of this enzyme may explain a considerable proportion of the observed variability. We therefore prospectively studied the relationship between CYP3A4 activity and systemic exposure to sunitinib. **Methods:** In fifteen patients treated with sunitinib in a four weeks "on" – two weeks "off" regimen the pharmacokinetics of sunitinib and its active metabolite SU12662 were assessed. To determine sunitinib+SU12662 steady-state exposure, samples were collected over 24hrs after at least 14 days of sunitinib therapy. To assess CYP3A4 activity, midazolam 7.5mg orally was administered on the final day of the two weeks "off". Plasma concentrations were measured over a period of 7hrs to determine midazolam exposure. Exposures (AUC) were calculated using a trapezoidal approach (Phoenix WinNonlin v6.3). The relationship between CYP3A4 activity (midazolam exposure) and sunitinib+SU12662 exposure was determined by linear regression analysis. The percentage of variability in sunitinib+SU12662 exposure that could be explained by CYP3A4 activity was calculated by Pearson's correlation. In addition, the correlation between sunitinib+SU12662 C_{trough} levels and sunitinib+SU12662 exposure was assessed. **Results:** A strong correlation between midazolam exposure ($AUC_{0\text{-}7hr}$) and steady-state sunitinib+SU12662 exposure ($AUC_{0\text{-}24hr}$) was found ($p=0.002$); CYP3A4 activity explained 55% of the observed inter-patient PK variability of sunitinib+SU12662. Furthermore sunitinib+SU12662 C_{trough} levels were highly predictive (96%) for overall sunitinib+SU12662 exposure ($AUC_{0\text{-}24hr}$). **Conclusions:** Midazolam as a phenotyping probe could be useful before start of sunitinib therapy to identify patients at risk for under- respectively overtreatment at a standard dosage regimen. Therefore, CYP3A4 phenotyping could be useful to individualize sunitinib therapy. Additionally, sunitinib+SU12662 trough levels are highly predictive for sunitinib+SU12662 exposure and thus can be used for monitoring and guiding sunitinib therapy in clinical practice. Clinical trial information: NCT01743300.

2593 General Poster Session (Board #8E), Mon, 8:00 AM-11:45 AM

A randomized, crossover phase I study to assess the effects of formulation and meal consumption on the bioavailability of dovitinib (TKI258).

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Background: Dovitinib (TKI258), an oral multitargeted receptor tyrosine kinase inhibitor, is being studied in a phase 3 trial for renal cell carcinoma. A previous study compared the bioavailability of 2 capsule formulations of dovitinib. Arm 1 of the current study compared relative bioavailability of the final market image (FMI) form (monohydrate tablets) with the clinical service form (CSF; anhydrate capsules) of dovitinib. Arm 2 assessed the effect of food on bioavailability of the FMI tablet in adult patients (pts) with advanced solid tumors. Both arms employed crossover designs. **Methods:** In arm 1, pts were randomized to receive a single 500-mg dose of dovitinib either as a CSF capsule or FMI tablet, followed by a single 500-mg dose of the other formulation after 7 days of rest. Plasma pharmacokinetic (PK) profiles were determined from blood samples. A linear mixed-effects model fitted to log-transformed PK parameters maximal concentration (C_{max}) and area under the curve ($AUC_{0\text{-}tlast}$) was used to determine the relative bioavailability of FMI vs CSF. In Arm 2, pts received 300 mg of the FMI formulation once daily for 22 days after being randomized to 1 of 6 meal sequences with 3 fed or nonfed states (no meal [NM], low-fat [LF] meal, or high-fat [HF] meal) on days 8, 15, and 22. The relative bioavailability of dovitinib under LF and HF vs NM state was determined using the same model as arm 1 for the PK parameters C_{max} and $AUC_{0\text{-}tlast}$. **Results:** The study accrued 21 pts to arm 1 and 42 pts to arm 2. Based on the interim analysis, PK was assessed in 17 evaluable pts in arm 1. The geometric mean ratios (GMRs; 90% CI) for C_{max} and $AUC_{0\text{-}tlast}$ comparing FMI vs CSF were 0.99 (0.91-1.08) and 0.96 (0.89-1.04), respectively. The FMI formulation was used in arm 2; PK was assessed in 19 pts. C_{max} GMR (90% CI) was 0.82 (0.71-0.94) and 0.90 (0.78-1.03) for HF/NM and LF/NM, respectively. $AUC_{0\text{-}tlast}$GMR (90% CI) was 0.91 (0.81-1.02) and 0.99 (0.88-1.10) for HF/NM and LF/NM, respectively. **Conclusions:** The oral bioavailability of the FMI tablet and CSF capsule were comparable, and there was no clinically relevant effect of food (HF or LF meals) on the bioavailability of the FMI tablet form of dovitinib. Clinical trial information: NCT01155713.

2594 General Poster Session (Board #8F), Mon, 8:00 AM-11:45 AM

Investigation of the pharmacogenetic influences of carbonyl reductase on doxorubicin and doxorubicinol in breast cancer patients.

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Background: The anthracycline doxorubicin (DOX) is widely used to treat breast cancer. Doxorubicin is associated with pharmacokinetic and pharmacodynamic variability and despite its use for several years there is limited understanding behind it. Hepatic carbonyl reductases (CBR1 and CBR3) catalyze the reduction of DOX into its main circulating C-13 metabolite doxorubicinol (DOXOL). Polymorphisms in *CBR1* and *CBR3* influence synthesis of DOXOL, and could potentially play a role in the pharmacokinetic (PK) variability seen with doxorubicin treatment. In this study, we examined the influence of genetic polymorphisms in *CBR1* and *CBR3* on DOX and DOXOL PK. **Methods:** DOX was administered IV to 79 breast cancer patients at 60 mg/m^2. Population PK modeling was performed on the parent concentration-time profiles with the following patient factors: [BSA (1.4-2.6 m^2), weight (40-140 kg), age (25-75), race (78% white), *CBR1* rs9024 (78% wild-type), *CBR3* V244M (47% wild-type), *CBR3* C4Y (20.5% wild-type); followed by model validation. Noncompartmental analysis (NCA) was performed for both DOX and DOXOL and the metabolic ratio was calculated as $AUC_{DOXOL0\text{-}24}$:$AUC_{DOX0\text{-}24}$. **Results:** A two-compartment model was used to describe DOX PK. Mean predicted (%SEM) clearance (CL), plasma volume (Vp), tissue volume and distribution clearance were 28.1 L/hr (7.72), 22.5 L (3.80), 257 L (13.8) and 13.6L (21.8), respectively. Interpatient variability on CL and Vp were 22.1% and 12.6%, respectively. BSA was found to be a significant predictor of the interpatient variability on CL. No other patient factors were found to be significant on parent drug PK. The metabolic ratio, assessing the conversion of DOX to DOXOL, was stratified by different polymorphisms of *CBR1* and *CBR3*. There were no significant differences in metabolic ratio due to *CBR1* and *CBR3* genotypes. **Conclusions:** A PK model was developed that was able to characterize DOX pharmacokinetics. *CBR1* and *CBR3* polymorphisms were tested as covariates but were not found to be significant contributors to the variable pharmacokinetic profiles of DOX and DOXOL.

2595 General Poster Session (Board #8G), Mon, 8:00 AM-11:45 AM

Application of pharmacokinetic (PK)-guided 5-fluorouracil (FU) in clinical practice.

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Background: Body surface area (BSA)-based dosing of FU results in up to 100-fold inter-individual PK variability. PK-guided FU compared to BSA-based dosing resulted in higher response rates and decreased rate of toxicities in two randomized clinical trials. A paucity of data exists on PK-guided FU dosing in the clinical setting. **Methods:** A total of 70 colorectal cancer (CRC) patients (pts) from 6 academic and community sites received mFOLFOX6 (FU 2,400 mg/m^{2}over 46 h every 2 wks) +/- bevacizumab. Peripheral blood was obtained 2-44 h after start of FU infusion and AUCs were estimated using an immunoassay at Myriad Genetics. FU doses for cycles 2-4 (C2-4) were adjusted algorithmically to target an area under the concentration-time curve (AUC) of 20-25 mg*h/L. The primary outcome was the % of pts within target AUC by C4, with a secondary outcome of toxicity rates compared to historical data. Comparisons between cycles were made using generalized linear models, accounting for repeated observations within pt. **Results:** The % of pts within target AUC post C1 and C4 was 30% (17/57, 95%CI: 18-43%) and 46% (24/52, 95%CI: 32-61%), respectively (OR=2.16, p=0.05). For each subsequent cycle, the odds of a pt being within range increases by 28% (p=0.04) (Table). The median dose needed to achieve target AUC at C4 was 2,580 (range 1,920-3,484) mg/m^2. The median AUC post C1 and C4 was 19 and 21 mg*h/L, respectively. Less grade 3/4 mucositis and diarrhea were seen compared to historical data (3 v 15% and 6 v 12%, respectively); however, no difference in grade 3/4 neutropenia was noted (27 v 33%). Nine pts were non-evaluable by protocol for PK analysis, largely due to sampling/processing errors. **Conclusions:** PK-guided FU resulted in a greater number of pts achieving the targeted AUC and fewer pts under-dosed at C4 compared to C1. Individualization of FU dosing in the front-line, community and academic, setting is achievable for the treatment of CRC; however, larger clinical trials are needed to define the clinical utility of PK-guided FU. Clinical trial information: NCT01164215.

Patients below, within, and above the target AUC at each cycle.

AUC mg*hr/L	C1(N = 57)	C2 (N = 57)	C3 (N = 53)	C4 (N = 52)
<20	30 (53%)	24 (42%)	25 (47%)	17 (33%)
20-25	17 (30%)	21 (37%)	21 (40%)	24 (46%)
>25	10 (17%)	12 (21%)	7 (13%)	11 (21%)

2596 General Poster Session (Board #8H), Mon, 8:00 AM-11:45 AM

CYP3A inhibitors and adverse outcomes in patients treated with docetaxel chemotherapy.

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Background: Docetaxel (D) is an anti-mitotic drug metabolized by the cytochrome P450 (CYP) 3A4 enzyme. While case reports have demonstrated a potential association of CYP3A inhibitor use with severe toxicity in D treated patients (pts), there are no data whether co-administration of CYP3A inhibitors with D increases the rate of hospitalization and/or death. **Methods:** A retrospective cohort of pts treated with D at the Mayo Clinic Rochester from 1/1/09-10/1/11 was identified. Information regarding D and concomitant chemotherapy (starting dose and dose reductions), type of CYP3A inhibitor, growth factor use, hospitalizations and deaths was abstracted. Time to event analyses (either hospitalization or death) were conducted using Kaplan-Meier estimates and proportional hazards modeling. **Results:** 384 pts (median age 63, range 20-93) received D as monotherapy (48%) or as multi-agent chemotherapy (52%) for a median of 4 cycles. 56 pts were co-administered CYP3A inhibitors (45 moderate, 11 strong). 90 pts were hospitalized during D chemotherapy and 15 died. The mean time to hospitalization was significantly shorter in pts treated with a mod/strong CYP3A inhibitor (186 days) vs not treated (408 days) ($p=0.02$) . While time to death was not significantly different based on inhibitor use (111 vs. 177 days, $p=0.49$), time to first event (hospitalization or death) varied significantly according to those on inhibitors (187 days) versus not (397 days) (HR: 1.78, $p=0.02$). Time dependent analyses indicated that use of multiage chemotherapy (combination vs D monotherapy; HR 1.96, $p= 0.002$) and chemotherapy dose reduction of either D (HR 0.54, $p<0.01$) or other chemotherapy (HR 0.61, $p=0.02$) were significantly associated with the risk of an event. In a multivariate analysis, moderate/strong CYP3A inhibitor use was associated with a higher risk of any event (HR 1.79, $p<0.02$), independent of the use or dose of either multi-agent chemotherapy or D dose. **Conclusions:** These are the first data to demonstrate that co-administration of CYP3A inhibitors with D increases the risk of hospitalization and/or death. Oncologists should reconcile medications prior to D administration and mod/strong CYP3A inhibitors should be avoided or used with caution.

2597 General Poster Session (Board #9A), Mon, 8:00 AM-11:45 AM

A pharmacogenetic model predicting low paclitaxel clearance based on the DMET platform.

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Background: Paclitaxel (PTX) is a commonly used cytotoxic agent. It is metabolized by P450 cytochrome iso-enzymes CYP3A4 and CYP2C8 and has high interindividual variability in pharmacokinetics (PK) and toxicity. Here, we present a genetic prediction model to identify patients with low PTX clearance (CL) using the new Drug-Metabolizing Enzyme and Transporter (DMET; Affymetrix) platform, capable of detecting 1,936 genetic variants (SNPs) in 225 genes. **Methods:** In a PK study, 270 Caucasian cancer patients were treated with PTX. PK parameters were determined using a limited sampling strategy. HPLC or LC-MS/MS were used to determine PTX plasma concentrations and non-linear mixed effects modelling (NONMEM) was used to estimate individual unbound CL from previously developed PK population models. Subsequently, the cohort of patients was randomly split into a training and validation set. In all patients, the presence of SNPs in metabolic enzymes and transporters was determined using the DMET platform. Selected SNPs were subsequently validated in the validation set. **Results:** Baseline characteristics were comparable in both sets. The mean CL of the total cohort was 488 $\pm$ 149 L/h and the threshold for low CL was set at 339 L/h (1 SD $<$ total mean CL). 14 SNPs were selected to be included in the prediction model and validated in the validation set. For none of these 14 SNPs, evidence for a biological plausible link to taxane metabolism exists. The developed prediction model had a sensitivity of 95% to identify low PTX CL, a positive predictive value of 22% and remained significantly associated with low CL after multivariate analysis correcting for age, gender and Hb levels at start of therapy ($P=0.024$). **Conclusions:** This is the first considerably-sized application of the DMET platform to explain PK variability of a widely used anti-cancer drug. Although this validated prediction model for PTX CL had a high sensitivity, its positive predictive value is too low to be of direct clinical use. Likely, genetic variability in DMET genes alone does not sufficiently explain PTX CL, as for example environmental factors may also influence PTX metabolism.

2598 General Poster Session (Board #9B), Mon, 8:00 AM-11:45 AM

Recommended phase (Ph) II dose (RP2D) selection for investigational Aurora A kinase (AAK) inhibitor MLN8237 (Alisertib; A) combined with paclitaxel (P): Clinical pharmacokinetics (PK), drug-drug interaction (DDI) assessment, and translational exposure-efficacy modeling.

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Background: Two maximum tolerated doses (MTDs) were reported for P/A combination in Ph 1 of NCT01091428 (Falchook, ASCO 2012). Here we report clinical PK/DDI results in the context of preclinical exposure-efficacy relationship for P/A to select RP2D. **Methods:** Pts with advanced ovarian/breast cancer received A (oral BID D1–3, 8–10, 15–17) with 60 or 80 mg/m^2 P on D1, 8, 15 in 28-D cycles, with 3+3 dose escalation of A. PK of P was assessed on cycle 1 D1 (P+A); during cycle 2, A doses were withheld on D1–3 allowing for PK of P to be determined in the absence of A on D1. Isobolographic analysis of the response surface relating area under the plasma concentration-time curve (AUC) of A and P to tumor growth inhibition in mice bearing MDA-MB-231 xenografts incorporated mouse-human ratios of plasma free fraction and maximum tolerated exposures, allowing rank ordering of predicted antitumor activity for combined P and A. **Results:** MTDs were 80 mg/m^2 P + 10 mg BID A (80P/10A) and 60 mg/m^2 P + 40 mg BID A (60P/40A), as grade 3/4 toxicities (diarrhea, stomatitis, neutropenia, febrile neutropenia) precluded further escalation. Co-administration with A resulted in a small increase in AUC of P (20–25% at 80P/10A; 10–19% at 60P/40A; Table). AUC of P at 60P/40A was below 80P alone. GeoMean D3 concentrations of A at 80P/10A (340 nM) and 60P/40A (1490 nM) were respectively below and within the reported range (590–6580 nM) for tumor AAK inhibition by A (Cervantes, CCR 2012) for 60P/40A. Exposures of A dosed with P were as expected from previous single agent population PK (Venkatakrishnan, ASCO 2012). Exposure-efficacy modeling and isobolographic analysis predicted a rank-order of efficacy at clinical exposures of P/A: 60P/40A > 80P/10A>80P=60P. **Conclusions:** Safety, PK, and modeling results support 60P/40A as RP2D, currently employed in Ph 2 of NCT01091428, which is enrolling pts with advanced ovarian cancer. Clinical trial information: NCT01091428.

GeoMean (%CV) AUC (ng.hr/mL) of P by treatment.

	N	AUC_{last}	AUC_{inf}
80P/10A	15	4,551 (29%) 3,683 (34%)	5,282 (27%) 4,377 (30%)
80P	14		
60P/40A	14	2,628 (24%)	3,072 (23%) 2,789 (21%)
60P	13	2,184 (28%)	

2599 General Poster Session (Board #9C), Mon, 8:00 AM-11:45 AM

Trastuzumab (T) and everolimus (E) pharmacokinetics (PK) in HER2 positive (+) primary breast cancer (BC) patients (pts): Unicancer RADHER trial results.

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Background: T has greatly modified the prognosis of HER2+ BC, but few studies have analyzed its PK. The RADHER study evaluated the interest of adding E to T as preoperative therapy for primary HER2+ BC. It also aimed at describing the PK of T and studying the impact of E with T in primary BC. **Methods:** Eligible pts with HER2+ operable primary BC were randomized to receive T alone (loading dose 4 mg/kg, then 2 mg/kg/week (W)) or T + E (10 mg/day (D)) for a 6-W pre-operative treatment. Blood samples were collected to measure T and E concentrations. For T, plasma samples were collected in all pts before each infusion, and at Hour (H) 1, D1, D3, W1, W2, W4, W8 and W12 after the last infusion. E concentrations were determined on whole blood collected at H0, H0.5, H1, H2, H4, H6, H12 and H24 after the first T infusion, and again after the last E intake. T and E PK were described using population compartment analyses. **Results:** From 82 pts randomized, 79 were evaluable for T and 22 for E PK. Mean estimated PK parameters of T were (interindividual coefficient of variation %): central (Vc) and peripheral (Vp) volumes of distribution = 2 L (24%) and 1.3 L (39%), systemic (CL) and intercompartment (Q) clearances = 0.22 L/day (19%) and 0.36 L/day, respectively. Vc increased with body weight and decreased with age, while CL increased with body weight and with tumor volume. Elimination half-life was 11 days, a value lower than that previously reported in metastatic BC (28 days). E PK was best described by a two-compartment model. Mean estimated PK parameters (RSE%) of E were: CL = 3.96 L/h (22%), Q = 29.1 L/h (7%), Vc = 119 L (11%), Vp = 1530 L (24%). E did not influence T PK. E PK was similar to that previously reported in other indications. **Conclusions:** This is the first study describing the PK of T and E in primary BC. Notably, T CL increases with tumor volume and the elimination half-life is only 11 days, lower than expected from previous results in metastatic BC. The differences in PK between primary and metastatic BC might lead to take a second look at trastuzumab dose regimen in primary BC. Clinical trial information: NCT00674414.

2600 General Poster Session (Board #9D), Mon, 8:00 AM-11:45 AM

Phase I clinical trials attrition related to central molecular prescreening.

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Background: The increasing trend to incorporate molecular assays as part of selection assessment in Ph1 trials is based on the potential to observe early antitumor activity. Nonetheless, its impact has been almost negligible to date and might affect time to achieve a recommended dose. We assessed the impact on recruitment of pursuing central mandatory molecular assessment of tumor samples on a state-of-the-art Ph1 unit. **Methods:** Two first-in-human Ph1 studies, requiring central laboratory biomarker assessment as inclusion criterion (DS6 IHC and FGFR mut/ampl, respectively), and a consecutive series of pts in our program for central tumor mutation screening (OncoCarta Panel v1.0) to participate in molecularly-driven Ph1 studies, were reviewed. **Results:** 13 (4.8%) out of 267 pre-screened pts were able to receive treatment within a targeted Ph1 trial. **Conclusions:** A vast majority of pts trying to participate in molecularly-driven trial central biomarker screening are not included due to negative results. Still 71.1% pts who were initially eligible and were positive in the central review fail to participate due to clinical and/or analytical deterioration during the time of central molecular assessment. New strategies including local sample pre-screening allowance, as well as anticipated massive molecular profiling in the conventional setting, are needed to reduce this time and improve feasibility of these trials. The derived current "impoverishment" of studies with non-targeted drugs (that lack patients with tumors with "hot" mutations) and of those with targeted drugs (that miss patients with nonmutated tumors) within the same Ph1 Programs, and the need of a joint approach to co-finance for wide-spectrum molecular profiling for different studies, would be discussed as well.

	DS6 study	FGFR study	OncoCarta panel
Informed consent	133	105	29
Withdrew consent	2	2	0
Insufficient sample (# in another study lab)	11 (3)	8 (3)	11 (0)
Positive test	24 (18%)	11 (10.5%)	10* (34.5%)
Not included in trial (Screening failure, worse ECOG, no slots)	18 (5, 4, 9)	5 (2, 2, 1)	9 (1, 2, 6)
Treated	6 (4.5%)	6 (5.7%)	1 (3.4%)(NRAS)
Time to inclusion, median days (range)	69,5 (22-266)	36 (29-173)	330

* BRAF (melan), FGFR (bladder), NRAS (melan), EGFR (NSCLC), KRAS x 6 (GI).

2601 General Poster Session (Board #9E), Mon, 8:00 AM-11:45 AM

Copper transporter CTR1 expression and tissue platinum concentration in NSCLC.

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Background: Platinum (Pt) resistance is a major limitation in the treatment of advanced non-small cell lung cancer (NSCLC). We previously demonstrated that low tissue Pt concentration in NSCLC tumor specimens was significantly associated with reduced tumor response and worse survival. Furthermore, low expression of the copper transporter CTR1, a transporter of Pt uptake is reported to be associated with poor clinical outcome following Pt-based therapy in NSCLC patients. However, a defect in CTR1expression as a causative factor in reduced Pt accumulation in NSCLC tissues is not well-established. We investigated the relationship between tissue Pt concentrations and CTR1 expression in NSCLC specimens. **Methods:** We identified paraffin-embedded NSCLC tissue blocks from 30 patients who underwent neoadjuvant Pt-based chemotherapy with known tissue Pt concentrations at MD Anderson Cancer Center. Expression of CTR1 was determined by immunohistochemistry with adequate controls; 0 = undetectable; 1+ = barely detectable staining; 2+ = readily appreciable staining; and 3+ = dark brown staining. Pt concentration was compared between different CTR1 expression groups. **Results:** Tissue Pt concentration significantly correlated with tumor response in 30 patients who received neoadjuvant Pt-based chemotherapy ($P<0.001$). There was an uneven distribution of CTR1 expression scores with a majority of specimens demonstrating scores of 2+ (N=15, 50%). There were 2 specimens with no detectable CTR1 expression (score of 0) and 6 patients with a score of 3+. Patients with undetectable CTR1 expression in their tumors had significantly lower Pt concentrations compared to those with scores of 3+ ($P=0.014$). Furthermore, those with undetectable CTR1 expression had reduced tumor response compared to those with scores of 3+ following Pt-based chemotherapy ($P=0.039$). **Conclusions:** To the best of our knowledge, this is the first study to correlate CTR1 expression in clinical specimens to both tumor Pt uptake and response. Patients with undetectable CTR1 expression in their tumors had significantly lower Pt concentration and reduced tumor response. Further evaluation with a larger sample size is required. (Supported by 2012 ASCO Young Investigator Award)

2602 General Poster Session (Board #9F), Mon, 8:00 AM-11:45 AM

Pharmacokinetics and safety of an oral ALK inhibitor, ASP3026, observed in a phase I dose escalation trial.

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Background: ASP3026 (3026) is a selective, potent, ATP-competitive, small molecule oral inhibitor of ALK receptor tyrosine kinase that has not previously been tested in humans. A Phase 1 dose-escalation trial, using a 3+3 design, evaluating 3026 as an oral single agent was conducted to investigate PK (Day 1 and Day 28), safety and clinical activity in patients (pts) with advanced malignancies (excluding leukemias) of ECOG PS 2 or less. **Methods:** 3026 was administered under fasting conditions on a continuous schedule to pts in successive dose-escalating cohorts at doses ranging from 25 mg QD to 800 mg QD. **Results:** Thirty pts were enrolled into the dose escalation part of the study. The MTD was determined based on DLT data from cycle 1. Three DLTs were observed: grade 2 nausea and vomiting leading to dose reduction at 525 mg QD; grade 3 rash leading to dose reduction, and grade 3 ALT/AST increase leading to study withdrawal at 800 mg QD. The most common AEs were constipation, vomiting, diarrhea, nausea and abdominal pain, and all AEs were manageable and reversible. Median AUC and Cmax increased proportionally with dose from 25 mg QD to 800 mg QD. There was no evidence of non-linear PK at ASP3026 doses >25 mg QD. The median terminal half-life was approximately 10 - 41 hours. Overall, A3026 appears well absorbed with median Tmax around 3 hours for both Day 1 and Day 28. Terminal $T_{1/2}$ appears adequate for one daily dosing with median values ranging from approximately 18 to 34 hours. Based on visual inspection of pre-dose (trough) values from Days 8, 15, 22, and 28 it appears that steady-state conditions are achieved by day 28. **Conclusions:** The MTD of 3026 is 525 mg QD. Treatment with 3026 resulted in a promising safety and PK profile in pts with advanced malignancies. Further evaluation of 3026 in pts with tumors harboring gene mutation or ALK fusion genes in the cohort expansion phase at the MTD is ongoing. Clinical trial information: NCT01401504.

2603 General Poster Session (Board #9G), Mon, 8:00 AM-11:45 AM

Exposure and clearance of bevacizumab in patients with first-line advanced gastric cancer.

Martina A. Sersch, Kelong Han, Mauricio Maia, Jin Jin, David Allison; Genentech, Inc., South San Francisco, CA

Background: Bevacizumab (BEV), rhuMAB VEGF, in combination with chemotherapy (CT) is currently approved in various types of cancer. Recently, BEV+CT was evaluated in 1st line advanced gastric cancer (AGC) in a double-blind randomized phase 3 trial (AVAGAST), but failed to meet the primary OS endpoint (HR=0.87; p=0.1002). BEV pharmacokinetics (PK) is well established by a reference population PK (PPK) model, and BEV PK is consistent across multiple cancer indications. However, BEV PK in AGC was never evaluated. We aimed to assess BEV exposure (EXP) and PK in AGC and to explore the influence of demographic, prognostic and biochemical (DPB) factors. **Methods:** BEV concentrations (Cp) were measured from plasma samples collected following disease progression from 182 patients (7.5mg/kg Q2W) in AVAGAST. Expected BEV Cp [median and 90% prediction interval (PI)] were simulated using the PPK model and compared to the observed BEV EXP. BEV clearance (CL) in AGC was estimated using NONMEM and compared between subgroups stratified by DPB factors. **Results:** All DPB factors of AGC are similar to those in other cancers except for lower body weight. No cachexia was observed. BEV Cp was detectable in 162 patients. 85% of observed BEV Cp was below the median BEV Cp simulated using PPK model and 38% below the lower limit of the 90% PI. Median BEV CL in AGC was 4.5 L/day/kg vs. 3 L/day/kg in other cancers. BEV CL was significantly higher (p=0.0012) in patients without prior gastrectomy (4.9 L/day/kg, n=120) than those with gastrectomy (4.1 L/day/kg, n=42). CL appeared to be higher in AGC patients with higher ECOG scores, lower albumin, more metastatic sites, poorer response and later stage AGC. Tumor location (GE Jct vs. Stomach), VEGF-A and ethnicity (Asian vs. Non-Asian) did not correlate with BEV CL. **Conclusions:** Overall, AGC patients exhibited significantly lower BEV EXP due to a 50% increase in BEV CL vs. other cancers. In addition, BEV is cleared significantly faster in patients without prior gastrectomy. The low BEV EXP in AGC could potentially reduce the effect of BEV in AGC. The underlying mechanism for faster BEV CL in AGC is unknown and warrants further research and potential BEV dose modifications.

2604 General Poster Session (Board #9H), Mon, 8:00 AM-11:45 AM

Phase I clinical trial of lenalidomide with temsirolimus in patients with advanced cancer.

Prasanth Ganesan, Sarina Anne Piha-Paul, Aung Naing, Gerald Steven Falchook, Jennifer J. Wheler, Filip Janku, Ralph Zinner, Shell Laday, Merrill S. Kies, Apostolia Maria Tsimberidou; Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Investigational Cancer Therapeutics (Phase I Program), University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Lenalidomide (immunomodulatory and antiangiogenic drug) and temsirolimus (mTOR inhibitor) are potentially synergistic (Raje N, Blood 2004;104(13):4188). We conducted a phase I study of the combination in patients with advanced cancers. **Methods:** During the escalation phase, lenalidomide (PO days 1-21) and temsirolimus (IV, Q weekly) were given at the following respective doses: level 1 (10 mg, 15mg); level 2 (10 mg, 20 mg); level 3 (20 mg, 20 mg); and level 4 (20 mg, 25 mg) (1 cycle = 28 days). A "3+3" study design was used. The maximum tolerated dose, dose-limiting toxicity, and response were assessed. **Results:** Forty- three patients were treated (median age: 58 (21-80) years; male/female: 26:17). The most common diagnoses were colorectal cancer (N=5), sarcoma (N=5) and adenoid cystic carcinoma (N=4). Overall, 121 cycles (median: 2) were administered. No dose limiting toxicities were observed. The maximum tested dose (level 4) was used for expansion. Grade 3-4 toxicity (all reversible) occurred in 19 (44%) patients: neutropenia (N=12), thrombocytopenia (N=6), and infection (N=1). Of 43 patients, 31 (72%) received anticoagulation prophylaxis. There were no thrombotic events. Of 36 patients who were evaluable for response, PR was noted in 1 (2.7%), and stable disease (SD) was noted in 17 (47%) patients (SD ≥6 months: 17%). Tumors with SD≥6 months were soft tissue sarcoma, 2/5 (40%), adenoid cystic carcinoma, 1/4 (25%), parotid ca, 1/2 (50%), adrenocortical ca 1/3 (33%), and neuroendocrine ca, 1/4 (25%) (Table). The median progression-free survival was 2.2 months (95% CI, 1.5-2.9) and overall survival was 7.8 months (95% CI, 5.1-10.6). **Conclusions:** Lenalidomide and temsirolimus combination was well tolerated and had antitumor activity in selected participants with advanced cancer. Clinical trial information: NCT01183663.

Dose level	Age/Sex/ ECOG PS	Diagnosis	Disease sites (N)/ Prior Rx (N)	Best RECIST response (%)	Cycles (N)	PFS (months)	Progression/ Death	Survival (months)
4	63/M/1	Parotid	2/2	-10	6	7.6	Yes/No	13.8+
4	30/M/1	Sarcoma	4/1	-8	11	10.9	Yes/Yes	13.5
4	72/F/1	Adrenal	4/3	-2	5	6	No/No	14.5+
4	60/F/0	Adenoid cystic	1/1	0	9+	12.4+	No/No	12.4+
4	62/M/1	Sarcoma	3/3	-21	8	8.5	Yes/No	11.6+
4	71/F/1	Neuro-endocrine	2/2	-51	8	8.2	Yes/Yes	13.1

2605 General Poster Session (Board #10A), Mon, 8:00 AM-11:45 AM

Phase Ib dose-escalation trial of the AKT inhibitor (AKTi) MK2206 in combination with paclitaxel (P) and trastuzumab (H) in patients (pts) with HER2-overexpressing (HER2+) cancer.

Amy Jo Chien, Thach-Giao Truong, Michelle E. Melisko, Mark M. Moasser, Robin Katie Kelley, Michael Korn, Andrew H. Ko, Norma Pantoja, Anne Reinert, Jennifer A. Grabowsky, Mark Jesus M Magbanua, Hope S. Rugo, Pamela N. Munster; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; University of California, San Francisco, San Francisco, CA

Background: AKT plays a key role in the survival, resistance, and overall aggressive pathogenesis of HER2+ malignancies, suggesting that AKTis may be of therapeutic value. MK2206 is a selective allosteric AKTi that has demonstrated synergy in combination with both H and P in preclinical studies. **Methods:** We conducted a phase 1b study of MK2206 in combination with weekly P 80 mg/m2 and H 2 mg/kg in pts with HER2+ solid tumors. MK2206 was given orally at a starting dose of 135 mg once a week (QW). Dose escalation was performed using a modified Ji method. The maximum tolerated dose (MTD) was defined as the dose level resulting in 3 or fewer dose limiting toxicities (DLTs) in 11 pts, then confirmed in 4 additional pts. Circulating tumor cells and PK samples were collected for all pts. **Results:** A total of 17 pts were enrolled, and 15 pts were evaluable for toxicity. All pts had HER2+ tumors (11 breast, 3 gastric, 1 esophageal). Based on interim toxicity data from other studies, the dose of MK2206 was not escalated beyond 135 mg QW. All 15 pts were treated at this dose level which was determined to be tolerable. Two DLTs were observed including grade 3 rash and grade 3 neutropenia resulting in a $>$7 day treatment delay. There were no severe adverse events (AEs) related to study treatment. Other grade 3/4 AEs were neutropenia (6 pts), febrile neutropenia (1 pt), peripheral neuropathy (1 pt), and depression (1 pt). The most common all-grade AEs include rash (13 pts), hyperglycemia (13 pts), neutropenia (13 pts), peripheral neuropathy (10 pts), diarrhea (9 pts), fatigue (9 pts), anorexia (9 pts), stomatitis (7 pts). Of the 14 pts evaluable for response, 9 pts (64%) had tumor response (2 CR, 7 PR), and 4 pts had SD. The median duration of response was 5.5 months. Pts were heavily pretreated (median lines of prior therapy 3, 11 prior taxane, 12 prior H). **Conclusions:** MK2206 at a dose of135 mg QW in combination with weekly P and H is safe and well-tolerated. 135 mg QW is the recommended phase 2 dose for this combination. Preliminary data indicate significant clinical activity in pts with HER2+ tumors despite extensive prior therapy. MK2206 is now being tested in the neoadjuvant ISPY2 trial. Clinical trial information: NCT01235897.

2606 General Poster Session (Board #10B), Mon, 8:00 AM-11:45 AM

Phase I expansion trial of an oral TORC1/TORC2 inhibitor (CC-223) in advanced solid tumors.

Andrea Varga, Monica M. Mita, Jennifer J. Wu, John J. Nemunaitis, Timothy Francis Cloughesy, Paul S. Mischel, Johanna C. Bendell, Kent C. Shih, Luis G. Paz-Ares, Amit Mahipal, Jean-Pierre Delord, Robin Katie Kelley, Jean-Charles Soria, Lilly Wong, Shuichan Xu, Angela James, Xiaoling Wu, Rajesh Chopra, Kristen Hege, Pamela N. Munster; Institut Gustave Roussy, Villejuif, France; Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA; NYU Cancer Institute, New York, NY; Mary Crowley Cancer Research Center, Dallas, TX; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; SCRI/Tennessee Oncology, PLLC, Nashville, TN; Hospital Universitario Virgen del Rocío, Seville, Spain; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Institut Claudius Regaud, Toulouse, France; Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; Celgene Corporation, San Diego, CA; Celgene Corporation, Summit, NJ; Celgene Corporation, Basking Ridge, NJ; Celgene Corporation, San Francisco, CA; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Background: CC-223 is an ATP-competitive inhibitor of the mTOR kinase, including both TORC1 and TORC2. CC-223 was selected to address resistance of rapamycin analogues mediated by TORC2 activation. **Methods:** Following establishment of the MTD (reported at ASCO 2012), subjects with select advanced, refractory solid tumors, including NSCLC, HCC, NET, GBM and breast were enrolled in expansion cohorts of up to 20 evaluable subjects. CC-223 was dosed at 45 mg once daily in 28 day cycles until disease progression. **Results:** As of 09 January, 2013, 101 solid tumor subjects have been treated, including NSCLC (26), HCC (25), NET (23), breast (14), and GBM (13). Results from the NSCLC, HCC, and GBM cohorts are reported here; NET results are reported separately. The most common ($>$ 20%) related adverse events (all grades) were fatigue, rash, stomatitis, hyperglycemia, anorexia, nausea, vomiting and diarrhea. In addition, related serious adverse events included infection (1), pneumonitis (4), renal insufficiency (2) and pancreatitis (2). CC-223 dose reduction was required in $>$ 50% of subjects with NSCLC and HCC, usually during cycle 1 or 2. Exposure-dependent TORC1 (p4EBP1) and TORC2 (pAKT) inhibition was observed across cohorts. mTOR pathway inhibition and/or decreased proliferation was demonstrated in paired tumor biopsies, but results were inconsistent. Reduction in glucose uptake ($>$ 25% decrease in SUV) on PET imaging at day 15 was observed in 78% (14/18) of NSCLC and 69% (11/16) of HCC subjects. Partial tumor responses were observed in evaluable subjects with NSCLC (1/17; confirmed, treatment duration 36 weeks) and HCC (3/15; 1 confirmed, treatment duration 15 – 26 weeks). Disease control rate in the overall NSCLC cohort was 42% (11/26) and in the HCC cohort, 40% (10/25). GBM subjects underwent salvage resections on study and none were progression-free at 6 months. CC-223 was present in all (11/11) resected GBM tumors with plasma:tumor ratios of 16 - 77%, confirming transit across the blood-brain barrier. **Conclusions:** Encouraging signals of biomarker and clinical activity were observed in HCC and NSCLC. Due to the frequency of dose reductions, select additional cohorts will be enrolled at a starting dose of 30 mg QD. Clinical trial information: NCT01177397.

2607 General Poster Session (Board #10C), Mon, 8:00 AM-11:45 AM

A phase I study of MK-2206 in combination with lapatinib in patients (pts) with advanced solid tumors.

Kari Braun Wisinski, Amye Tevaarwerk, Maria Bell, Mark E. Burkard, Jens C. Eickhoff, George Wilding, Noelle K. LoConte, Anne M. Traynor, Tien Hoang, Jennifer Heideman, Jill Kolesar, Glenn Liu; University of Wisconsin Carbone Cancer Center, Madison, WI; Sanford Health USD Medical Center, Sioux Falls, SD; Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI

Background: The AKT protein kinase is a key mediator of signaling in the human epidermal growth factor receptor-2 (HER2) pathway. HER2 inhibition can result in feedback regulation of signaling, leading to high AKT activity. Preclinical studies demonstrate activity of combined HER2 and AKT inhibition. Lapatinib is an oral tyrosine kinase inhibitor of HER2. MK-2206 is an oral selective inhibitor of AKT with a maximum tolerated dose (MTD) of 60mg qod. Both agents cause rash and diarrhea. This study was designed to determine the MTD, dose limiting toxicities (DLTs), adverse events (AEs), clinical activity and pharmacokinetic (PK) parameters of the combination. **Methods:** This phase I study evaluated the safety of MK-2206 (30-60 mg qod) and lapatinib (1000-1500 mg qd) continuously. Cycles were 28 days, except cycle 1 (35 days), due to a 1 week MK-2206 lead-in to evaluate for PK interactions. Because of the continuous nature of therapy, protocol-specified intolerable grade 2 AEs were considered DLTs during cycle 1. **Results:** 23 pts (median age 59 [range 22-72];15 female:8 male) were enrolled. The most common malignancies were colorectal (8 pts), lung (4 pts), and breast (3 pts). 4 pts were unevaluable per protocol; 19 evaluable pts were on study a median of 8 weeks (range 3-35). 3 pts experienced DLTs. At dose level one, 1 pt had grade (gr) 3 hyponatremia and fatigue. At dose level four, 1 pt had gr 4 hyponatremia, gr 3 rash and hypocalcemia and 1 pt had intolerable gr 2 mucositis with delivery of $<75\%$ of drug. The most common AEs at least possibly related to therapy included diarrhea (gr 3-4 in 3 pts; gr 1-2 in 16 pts), nausea (gr 3 in 2 pts; gr 1-2 in 14 pts) and rash (gr 3 in 2 pts; gr 1-2 in 12 pts). The MTD was 45mg po qod of MK-2206 with 1500 mg po qd of lapatinib, exceeding biologically active doses for each agent. One pt with adrenal cortical carcinoma was on study for 6 months with stable disease (SD) and 1 pt with colorectal cancer was on study for 5 months with significant tumor marker decline and SD. PK analyses are ongoing. **Conclusions:** MK-2206 in combination with lapatinib is well-tolerated at biologically active single agent doses. Anti-tumor activity will be evaluated further in a dose expansion cohort in pts with advanced HER2-positive breast cancer. Clinical trial information: NCT01245205.

2608 General Poster Session (Board #10D), Mon, 8:00 AM-11:45 AM

A first-in-human phase I trial of AR-12, a PDK-1 inhibitor, in patients with advanced solid tumors.

Joaquin Mateo, Johann Sebastian De Bono, Ramesh K. Ramanathan, Maryam B. Lustberg, Andrea Zivi, Dawn Basset, Matthew Ng, Anna-Mary Young, Michelle Garrett, Shaun Decordova, Florence I. Raynaud, Timothy Anthony Yap, Alexander A. Zukiwski, Stefan Proniuk, Charles L. Shapiro; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Virginia G. Piper Cancer Center Clinical Trials at Scottsdale Healthcare/TGen, Scottsdale, AZ; The Ohio State University, Columbus, OH; ARNO Therapeutics, Flemington, NJ

Background: AR-12 (OSU-03012) is an oral celecoxib analogue lacking COX-2 inhibitory activity that inhibits pyruvate dehydrogenase kinase isoenzyme 1 (PDK-1), AKT and impacts the endoplastic reticulum stress pathway. Preclinical studies indicate antitumor activity of AR-12 in various models and enhanced activity in combination. We completed a first in human clinical trial to determine its safety and tolerability, maximum tolerated dose (MTD) and recommended phase II dose (RD). Secondary objectives included assessment of tumor response, pharmacokinetics (PK) and pharmacodynamics (PD) including food effect. **Methods:** Patients (pts) with advanced solid tumors, ECOG PS 0-1, and adequate organ function were recruited in a modified 3+3 dose-escalation study. Pts received a run-in dose of AR-12 to analyze PK-PD and food effect, followed by continuous daily (QD) dosing in 28-day cycles. A twice daily (BID) cohort was initiated based on safety data. PD analysis was performed in platelet-rich plasma (PRP) and paired tumor biopsies when feasible. **Results:** 35 pts received at least one dose of study drug; 30 were evaluable for dose limiting toxicities (DLT) at dose ranges 100-3200mg QD and 800-1600mg BID. No DLT were observed in the QD cohort; DLT in the BID cohort are listed in table 1. Drug-related events (NCI-CTCAE v3) included rash (G2-2pts; G3-1pt), fatigue (G2-2pts; G3-4pts), nausea (G2-7pts; G3-1pt) and bloating (G2-1pt). Cmax after single dose was dose-proportional but high PK variability was observed, likely due to inadequate disintegration and dissolution of the formulation in the stomach. At RD, partial GSK3ß inhibition in PRP after 4 hours suggests AKT-pathway modulation. Best response (RECIST v1.0) was stable disease >6 cycles for 2 pts. **Conclusions:** The RD based on safety data is 800mg BID. Signs of pathway modulation were observed in concordance with the expected mechanism of action but were short-lasting. Considering limited drug absorption and PK variability, a new formulation of the drug will be developed to overcome these limitations. Clinical trial information: NCT00978523.

Dose-limiting toxicities (BID cohort).

Dose (mg; BID)	Patients with DLT	DLT
1600	4/7	G3 fatigue, G3 rash, G3 dizziness, G2 nausea (dose delay >3d)
1200	2/4	G3 fatigue
800	0/7	-

2609 General Poster Session (Board #10E), Mon, 8:00 AM-11:45 AM

A phase I study of MM-121 in combination with multiple anticancer therapies in patients with advanced solid tumors.

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Background: MM-121 is a fully human monoclonal antibody targeting the epidermal growth factor receptor family member ErbB3. ErbB3 has been implicated in driving cancer growth and in the development of resistance to conventional chemotherapies across multiple malignancies. Here we present results of an open-label, Phase 1, multicenter, non-randomized, dose-escalation trial which recently completed enrollment evaluating MM-121 in combination with one of the following chemotherapies: Gemcitabine (Arm A, n=11), carboplatin (Arm B, n=11), pemetrexed (Arm C, n=10), or cabazitaxel (Arm D, n=11). **Methods:** Patients were treated in a dose escalation "3+3" design to assess the safety, tolerability and pharmacokinetics (PK) of MM-121 administered weekly in combination with anticancer therapies in subjects with advanced cancer. Doses were escalated until the maximum tolerated dose (MTD) was identified or the combination was shown to be tolerable at the highest planned doses. Secondary objectives included: Determining the objective response rate, clinical benefit rate, PK and immunogenicity of MM-121. Data summarized are as of 1/17/2013 from a live database. **Results:** Overall, 43 patients, [22 (51%) female and 21 (49%) male] have been treated with a median treatment duration of 57 days (range 1-302). The median age was 59 years (range 42-84) and patients had received a median of four prior lines of therapy (range 0-13). Common (>20%) adverse events of any grade and causality across all arms included diarrhea (74%), nausea (54%), fatigue (51%), anemia (44%), vomiting (33%), hypokalemia (30%), decreased appetite (26%), thrombocytopenia (26%), peripheral edema (23%), neutropenia (21%), and constipation (21%). Four DLTs were observed: Two in combination with carboplatin (G4 thrombocytopenia and G3 rash), one with gemcitabine (G4 thrombocytopenia), and one with pemetrexed (G4 hyperuricemia). Overall 38 (88%) patients were evaluable for response and the overall clinical benefit rate (PR or SD >18 weeks), is 32% (12/38). **Conclusions:** MM-121 can be combined at its recommended single agent dose with standard doses of gemcitabine, pemetrexed, and cabazitaxel and adapted doses of carboplatin. Clinical trial information: NCT01447225.

2611 General Poster Session (Board #10G), Mon, 8:00 AM-11:45 AM

Phase I trial of sorafenib, bevacizumab, and temsirolimus in advanced solid tumors.

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Background: Pathway crosstalk and emergence of drug resistance have limited the activity of targeted therapies, including anti-angiogenic agents and mTORC1 inhibitors. However, this vulnerability may be addressed by rationally combining targeted therapies to improve outcomes. We sought to determine the MTD/recommended phase II dose and define the pharmacokinetics (PK) of the combination of sorafenib (S), bevacizumab (B), and temsirolimus (T) in patients with advanced solid tumors. **Methods:** S was given once or twice daily, B was given intravenously every three weeks, and T was given intravenously weekly. Doses were escalated in a stair-step dose escalation with 6 planned dose levels (DL) in a standard 3+3 design. Responses were defined using RECIST 1.1. **Results:** To date, 51 patients have been enrolled. Three patients withdrew consent after only one dose. One dose-limiting toxicity (DLT) occurred at DL 5 (grade 4 fatigue, pain) and one DLT occurred at DL 6 (G3 headache). However, 5/6 patients required dose reduction on DL6 (G2 nausea, fatigue, hand/foot syndrome, rash). Thus, DL5 (B 10mg/kg, T 20mg, S 200mg twice daily) is being explored in dose expansion (N=10) and tumor expansion cohorts as the recommended phase II dose. The most common adverse events (>10%) were fatigue (69%; G3/4 6%), nausea (38%, G3/4 2%), pain (35%, G3/4 10%), thrombocytopenia (33%, G3/4 8%), mucositis (33%, 0%), constipation (29%, G3/4 0%), hand/foot syndrome (23%, G3/4 0%), rash (19%, G3/4 0%), hypertension (17%, 0%), neuropathy (17%, G3/4 0%), diarrhea (15%, G3/4 6%), vomiting (15%, G3/4 2%), headache (12%, G3/4 2%), and hypertriglyceridemia (10%, G3/4 2%). Of 34 patients evaluable for response, 4 had PR including ovarian (-57%, +6m), gastric (-46%, +5m), colorectal (-32%, +5 m), and thyroid (-31%, +6m) cancer. Eight patients had SD for greater than 4 months including ovarian (0%, +7m), colorectal (-5%, +8m), endometrial (-26%, +5m; -16%, +4m; -15%, +6m), leiomyosarcoma (-5%, +6m), squamous lung cancer (-6%, +6m), and triple negative breast (-15%, +4m) cancer. **Conclusions:** The combination of S, B, and T is well tolerated and demonstrates preliminary evidence of tumor activity in a variety of solid tumors. PK studies at the recommended phase II dose are ongoing. Clinical trial information: NCT01187199.

2612 General Poster Session (Board #10H), Mon, 8:00 AM-11:45 AM

Protein pathway activation mapping guided biomarker development to identify optimal combinations of MEK inhibitor with PI3K/mTOR pathway inhibitors for the treatment of triple-negative breast cancer.

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Background: Activated MAPK and PI3K pathway signaling are associated with poor prognosis in triple negative breast cancer (TNBC). Although some TNBC cell models are sensitive to MEK inhibition, feedback activation of the PI3K pathway mediates resistance. Thus, suppression of both arms of the MAPK/PI3K/mTOR network is a rational approach to targeting TNBC. Here we explore the anti-tumor efficacy of combinations of MEK inhibitor with PI3K, AKT, or mTOR inhibitors with a focus on biomarker development. **Methods:** Combinations of the MEK inhibitor PD-0325901 with the PI3K inhibitor GDC-0941, AKT inhibitor MK-2206, dual mTORC 1/2 inhibitor Torin 1, or the rapalog temsirolimus were evaluated in TNBC cell lines. Synergy was assessed using the combination index method of Chou and Talalay. We utilized reverse-phase protein array to map the signaling architecture of the treated lines to verify target suppression and identify pharmacodynamic biomarkers. **Results:** All combinations demonstrated synergy that was mediated by both suppression of proliferation and cell death in a dose-dependent manner. Cell death was delayed, peaking at least 96 hours post-dosing, and was associated with sustained suppression of target proteins in both pathways, including $pERK^{T202/Y204}$, $pS6rp^{S235/236}$, $p4EBP\text{-}1^{S65}$, and $pPRAS40^{T246}$. However, suppression of pAKT (at T308 or S473) was variable and not consistently required for cell death. Pathway mapping identified a protein network 'signature' specific to all combination therapies that emerged at 72 hours and was associated with cell death. Thus, all combinations appear to share common downstream effectors. All combinations showed promising efficacy and will be evaluated in a human-in-mouse model of TNBC. **Conclusions:** These data support therapeutic strategies for TNBC that simultaneously inhibit both arms of the MAPK/PI3K/mTOR signaling network. For continued biomarker development, we stress the importance of studying the delayed effects of combination therapy. This strategy coupled with a protein network based approach uncovered a unique functional signaling 'signature'.

2613 General Poster Session (Board #11A), Mon, 8:00 AM-11:45 AM

A combination of dual PI3K-mTOR inhibitor, GDC-0980, with PARP inhibitor plus carboplatin blocked tumor growth of BRCA-competent triple-negative breast cancer cells.

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Background: PARP is a promising target in the TNBC. The PI3K pathway, in addition to its pro-proliferative effects on tumor cells, also controls the repair of DSB (Kumar, 2010; Friedman, 2009; Juvekar, 2012; Ibrahim, 2012). We hypothesize that the growth of TNBC tumor will be blocked due to the inhibition of (1) HR / NHEJ, and (2) PI3K-mTOR pathway mediated survival signals following GDC-0980 (G), when combined with PARP inhibitor (impaired DNA-SSB-repair), and carboplatin (C) (increased DNA-DSB). **Methods:** We tested the in vivo efficacy of a combination of G with ABT888 (A) plus C in BRCA-competent TNBC cells, and compared the triple combination arm (A+C+G) with a combination arm of A+C+ pan PI3K inhibitor GDC-0941 in mice xenograft (MDA-MB231) model. Mechanistically, we tested, (1) cell survival/ proliferation (5-7 BRCA-wt and mutant cell lines) using MTT assay, CelltiterGLO, and cell cycle analyses, (2) anchorage independent and dependent clonogenic growth (3D ON-TOP and soft-agar assay), (3) apoptosis, and (4) cell signaling marker(s). **Results:** (1) G alone decreased the tumor growth by 40-50%. (2) The G + A + C combination blocked the growth of established tumors by 90% as compared to control(s). (3) Interestingly, G + A + C combination had markedly higher percentage of inhibition of tumor growth than the inhibition observed in the A+C+GDC-0941 arm (36%). (4) G treatment time-dependently increased cl-caspase 3, 9, and cl-PARP and increased AnnexinV positivity both time (24 and 48 hrs) and dose dependently (50 and 200 nM) in cells. (5) G when combined with A+C was most effective in inducing apoptosis in PIK3CA-mutated BT20 cells. (6) The triple combination (50 nM G+10 μM A + 10 μM C) inhibited clonogenic growth of MDA-MB231, MDA-MB468 and BT20 cells. (7)Treatment of G decreased downstream effectors of PI3K-mTOR pathway, pAKTS473, pP70S6K and pS6RP. **Conclusions:** Tumor growth of BRCA-competent TNBC cells is blocked by a combination treatment of G with A+C. The profound anti-tumor effect of this triple combination can be explained by the anti-proliferative and pro-apoptotic actions of the drugs. The combination of G with A+C merits further investigation in TNBC.

2614 General Poster Session (Board #11B), Mon, 8:00 AM-11:45 AM

A first-in-human phase I study of ER-α36 modifier icaritin in patients with advanced solid tumors.

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Background: ER-α36 was recently identified to be expressed in varieties of cancers and may play important roles in carcinogenesis and tumor progression. Icaritin, a natural prenylflavonoid derived from the Chinese herb Epimedium, is a first of its kind ER-α36 modifier, which demonstrated potent anti-tumor effect in multiple cancer cell lines and their xenograft models. This study aims to determine its safety, tolerability, pharmacokinetics (PK), and potential antitumor activity. **Methods:** This phase I study comprises phase Ia and Ib. In phase Ia part, patients with advanced breast cancer (ABC) were treated with escalating doses of Icaritin orally once daily on a continuous 28-day dosing schedule. In phase Ib part, dosing was fixed to 600 or 800mg twice daily and expansion was made to other selected malignancies including hepatocellular cancer (HCC), colorectal cancer (CRC) and intrahepatic cholangiocarcinoma (ICC) to further explore PK parameters and efficacy. **Results:** 24 patients were enrolled to receive Icaritin at six dose levels ranging from 50mg to 1600mg per day in phase Ia. No dose limited toxicity (DLT) was found even in the highest dose defined in the protocol, thus the maximum tolerated dose (MTD) was not reached. Only grade 1 drug-related adverse events were observed including neutropenia, ALT elevation, hypercholesteremia, fatigue, anorexia, hypertriglyceridemia, proteinuria, myalgia, hot flash and rash. PK data from the fed dosing showed 3-fold increase of Cmax and AUC compared with the fast dosing. Half life was around 2-7 hours. Among 22 evaluable subjects, no complete or partial response (CR or PR) was detected, 5 patients had stable disease(SD)for 3 months or longer. For phase Ib study, 24 patients had been enrolled. One ABC, 2 CRC and 3 ICC patients progressed after 2 months of medication. Among 7 HCC patients already evaluated, 1 obtained PR and progressed after one year of treatment and 2 remained in the study, stable for 5 months. Similar drug related toxicity profile was noted in phase Ib. **Conclusions:** Icaritin was generally well-tolerated without DLT across tested dose levels. Evidence of promising antitumor activity was observed in ABC and HCC. Final results will be presented at the meeting. Clinical trial information: NCT01278810.

2616 General Poster Session (Board #11D), Mon, 8:00 AM-11:45 AM

Final results of a phase I study of lapatinib (LAP) and cetuximab (CET) in patients with CET-sensitive solid tumors.

John F. Deeken, Hongkun Wang, John Marshall, Deepa Suresh Subramaniam, Jimmy J. Hwang, Aiwu Ruth He, Corinne Ramos, Rosemarie A. Hardesty, Kenneth Steadman, Louis M. Weiner, Michael J. Pishvaian; Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; Lombardi Comprehensive Cancer Center, Washington, DC; Theranostics Health, Rockville, MD

Background: Acquired resistance to anti-EGFR MoAb therapy may be via EGFR-ErbB2 heterodimerization and pathway reactivation. Dual anti-EGFR treatment was recently found to be active in colon cancer. We performed a phase I trial of CET and LAP to determine the DLTs, MTD, and clinical activity of the combination. **Methods:** Pts received CET at 400mg/m2 then 250 mg/m2 weekly, combined with daily LAP in a 3+3 dose escalation trial. LAP dose levels (DL) were (1) 750mg, (2) 1000mg, and (3) 1250mg. Cycles lasted 3 weeks, toxicity was assessed through C2, and pts were restaged every 2 cycles. Baseline and post-C1 tumor biopsies were analyzed for phosphoprotein activation in 36 EGFR/ErbB2 pathway proteins. Germ-line pharmacogenetic (PGx) variations were correlated with efficacy and toxicity. **Results:** Between 10/2010 and 10/2012, 22 pts were enrolled - colon (8), lung (8), head and neck (4), and anal cancers (2) - and 59% had prior anti-EGFR therapy. 18 pts were evaluable for toxicity, and 18 for response. Mean treatment was 3.8 cycles (range 1 - 12); 3 patients are still on trial. One DLT occurred at DL1 (gr 3 rash) and DL2 (gr 3 diarrhea). No pt on DL3 experienced a DLT. No pt experienced a gr 4 toxicity; gr 3 toxicities anytime on therapy included rash (17%), diarrhea (6%), fatigue (6%), lymphopenia (6%), and hypomagnesemia (6%). Rash was experienced by 94% of pts (gr 1=50%, gr 2=28%, and gr 3=17%). Partial responses (PR) occurred in 4 pts (22%), stable disease (SD) in 8 (44%), and disease progression in 6 (33%), for a clinical benefit rate of 67%. Seven of 13 (54%) pts on prior EGFR therapy had SD or PR. Down-regulation of phosphorylated EGFR/ErbB2 pathway components correlated with response; distinct pathway components were up-regulated in non-responders, including PI3K, Jak/Stat, MAPK, and IGF. PGx variants in FcRII correlated with response ($p=0.045$); no variants correlated with toxicity. **Conclusions:** The RP2D is CET 250 mg/m2 weekly and LAP 1250mg daily. Treatment was well tolerated with few grade 3 toxicities and a significant 67% clinical benefit rate. Non-responders showed up-regulation of EGFR pathway components – components which are druggable, warranting further study. A trial in colorectal cancer is ongoing. Clinical trial information: NCT01184482.

2617 General Poster Session (Board #11E), Mon, 8:00 AM-11:45 AM

Results of two phase I dose escalation studies of the oral heat shock protein 90 (Hsp90) inhibitor SNX-5422.

Todd Michael Bauer, Jeffrey R. Infante, Ramesh K. Ramanathan, Glen Weiss, Jasgit C. Sachdev, Howard A. Burris, James M Hinson, Everardus O Orlemans; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; Virginia G. Piper Cancer Center at Scottsdale Healthcare/TGen, Scottsdale, AZ; Unicorn Pharma Consulting, Brentwood, TN; Esanex Inc, Indianapolis, IN

Background: SNX-5422 is a prodrug of SNX-2112, a highly potent, non-geldanamycin analog, HSP90 inhibitor with preclinical anti-tumor activity in multiple tumor models. These phase 1 studies were designed to evaluate safety and tolerability, determine dose limiting toxicities, maximum tolerated doses (MTDs), and describe pharmacokinetics of SNX-2112 and SNX-5422. **Methods:** Two phase 1, open-label, 3 + 3 dose-escalation studies evaluated SNX-5422 when given daily (QD) or every-other-day (QOD) during the first 30 days of treatment in patients (pts) with advanced solid tumors or lymphoma. Plasma concentrations of SNX-2112 and SNX-5422 were measured after the first and 11^{th} (steady state) doses. Tumor assessments were performed every 8 weeks. **Results:** In both studies, pts received SNX-5422 QOD, 3 wks on/1 wk off, with doses ranging from 4 to 133 mg/m^2 QOD. In one study, pts also received QD doses from 50 to 89 mg/m^2, 3 wks on/1 wk off, and 50 mg/m^2 QD continuously. Fifty-six pts (34M/22F; mean age 62 years) were enrolled. Treatment-related adverse events were mainly low grade (G), including diarrhea (64%), nausea (39%), vomiting (29%), fatigue (27%), abdominal pain (14%), and anorexia (14%). Reversible G 1 blurry vision, and G 1-2 blurry vision/vision darkening were reported by 1 pt on 100 mg/m^2 QOD, and 4 pts treated with 50 to 89 mg/m^2 QD. G 3 diarrhea was dose limiting in 2 of 3 pts (89 mg/m^2 QD; 133 mg/m^2 QOD). MTDs for the QOD and QD schedules were declared at100 mg/m^2 and 67 mg/m^2, respectively. The QD schedule was associated with higher incidences of treatment related adverse events. 38 pts were evaluable for response including 1 confirmed durable complete response, 1 unconfirmed partial response, and 17 with stable disease. Activity was seen in adrenal, lung, liver, neuroendocrine, GIST, and prostate. All but 2 were seen with the QOD schedule. **Conclusions:** SNX-5422 mono-therapy was generally well tolerated and showed promising signs of efficacy in pts with advanced solid tumors. Given the superior benefit-risk profile of QOD dosing over QD dosing based on these preliminary clinical findings, 100 mg/m^2 QOD has been selected for further clinical testing. Clinical trial information: NCT00506805 and NCT01611623.

TPS2618 General Poster Session (Board #11F), Mon, 8:00 AM-11:45 AM

A phase Ib study of combined angiogenesis blockade with REGN910 (SAR307746), a selective monoclonal antibody (MAb) against angiopoietin-2 (Ang2) and ziv-aflibercept in patients with advanced solid tumor malignancies.

Lieve Adriaens, Kyriakos P. Papadopoulos, Donna M. Graham, Amita Patnaik, Albiruni R.A. Razak, Anthony W. Tolcher, Lillian L. Siu, Drew Warren Rasco, Pamela Trail, Carrie M. Brownstein, Israel Lowy; Regeneron Pharmaceuticals, Inc., Tarrytown, NY; START Center for Cancer Care, San Antonio, TX; Princess Margaret Cancer Center, Toronto, ON, Canada; Princess Margaret Hospital, Toronto, ON, Canada; South Texas Accelerated Research Therapeutics (START), San Antonio, TX

Background: REGN910 is a selective, fully human Angiopoietin-2 (ANG-2) MAb, which potently blocks signaling through the Tie2 receptor. Ziv-aflibercept (ZAFL) is a recombinant human fusion protein that acts as a decoy receptor for vascular endothelial growth factor (VEGF)-A, VEGF-B, and placental growth factor (PlGF), thereby preventing the interaction of these ligands with their receptors. In several mouse xenograft models, combination of the 2 anti-angiogenic compounds, REGN910 and ZAFL, demonstrated significantly enhanced tumor growth inhibition relative to either agent alone, suggesting that dual angiogenic blockade is worth exploring in cancer patients. **Methods:** This phase 1b study employs a standard 3+3 dose escalation design exploring 5 different combination treatment dose levels of REGN910 and ZAFL. Once the recommended phase 2 dose (RD) of the combination treatment is determined, additional patients will be enrolled in a safety expansion cohort, for a planned total enrollment of up to 40 patients. The primary study objectives are to evaluate the safety and determine the RD of the 2 drugs in combination when both are administered IV every 2 weeks in patients with advanced solid tumors. Secondary endpoints include characterization of the PK and potential immunogenicity of REGN910 and ZAFL when given in combination, evaluation of correlative PD biomarkers related to REGN910 and ZAFL, and identification of antitumor activity. Enrollment to cohorts 1 and 2 has been completed without DLT. Enrollment to cohort 3 opened in December 2012. Updated enrollment status will be presented. Reference: ClinicalTrials.gov Identifier: NCT01688960. Clinical trial information: NCT01688960.

TPS2619 General Poster Session (Board #11G), Mon, 8:00 AM-11:45 AM

Phase I study of VGX-100, an anti-VEGF-C monoclonal antibody, with or without bevacizumab, in patients (pts) with advanced solid tumors.

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Background: The vascular endothelial growth factor C (VEGFEC) induces angiogenesis via activation of both VEGFRE2 and VEGFRE3, as well as lymphangiogenesis via activation of VEGFRE3. VGX-100 is a novel fully human $IgG_1\lambda$ neutralizing monoclonal antibody directed against human VEGFEC. Synergism between the VEGF-A inhibitor, bevacizumab and VGX-100 has been documented pre-clinically. It is thought that tumoral escape and relapse following VEGF-A inhibition, may in part be due to increased VEGF-C that signals through VEGFR-2 and VEGFR-3. Therefore the premise of this study is that administration of VGX-100 in conjunction with bevacizumab would block the two key ligands for VEGFRE2 along with blocking VEGFR-3-mediated tumor angiogenesis and lymphangiogenesis, and thus this drug combination will be clinically synergistic. This study (NCT01514123) is enrolling at MD Anderson and UCLA. **Methods:** Objectives:establish the safety and toxicity, MTD, pharmacokinetic and pharmacodynamic / biomarker profiles, as well as preliminary anti-tumor activity in refractory pts. Eligibility: pts with advanced solid tumors, good organ function, ECOG PS 0-1, any number of prior therapies, no CNS or cerebrovascular haemorrhage, no MI or reversible posterior leukoencephalopathy syndrome associated with prior anti-VEGF/anti-VEGFR therapy. Design: This is an open-label phase I dose escalation study with a standard "3+3" design. The study has two arms: safety data from the 28 day DLT period from Arm A (VGXE100 monotherapy at 6 cohort dose levels: 1, 2.5, 5, 10, 20 and 30 mg/kg, QW) will be available prior to starting the equivalent dose level in Arm B (VGXE100 at 5 cohort dose levels: 2.5, 5, 10, 20 and 30 mg/kg QW with bevacizumab at doses of either 5 or 10 mg/kg, Q2W). Accrual has completed in Cohorts A1 to A5 and B1 to B2. Accrual is underway for Cohort A6 and B3. Clinical trial information: NCT01514123.

TPS2620 General Poster Session (Board #11H), Mon, 8:00 AM-11:45 AM

A phase I/IB study of paclitaxel in combination with VS-6063, a focal adhesion kinase (FAK) inhibitor, in patients (pts) with advanced ovarian cancer.

Suzanne Fields Jones, Kathleen N. Moore, Manish R. Patel, Jeffrey R. Infante, Anne Poli, Mitchell Keegan, Mahesh Padval, Howard A. Burris; Sarah Cannon Research Institute, Nashville, TN; Sarah Cannon Research Institute/University of Oklahoma Health Sciences Center, Oklahoma City, OK; Sarah Cannon Research Institute; Florida Cancer Specialists, Sarasota, FL; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; Verastem, Inc., Cambridge, MA

Background: Blockade of FAK reduces tumor growth and metastasis through inhibition of tumor cell survival, proliferation and invasion as well as tumor angiogenesis. Furthermore, treatment with FAK inhibitors reduces the proportion of cancer stem cells (CSCs) in a dose dependent manner while paclitaxel treatment enriches for CSCs. (Kolev VN San Antonio Breast Cancer Symposia 2012 abstr P6-11-09). The ability of CSCs to survive exposure to chemotherapy but remain susceptible to novel drugs suggests a unique therapeutic approach whereby standard of care chemotherapy may be sequentially combined with targeted drugs to kill surviving CSCs and thus prevent tumor recurrence and metastasis. VS-6063 (previously PF-04554878) is a potent oral inhibitor of FAK and proline-rich tyrosine-kinase -2. The phase I first-in-man trial explored doses ranging from 12.5 -750 mg twice daily (BID). (Jones SF J Clin Oncol 2011 29:1 suppl; abstr 3002) Dose-limiting toxicities consisted of headache, fatigue, and unconjugated hyperbilirubinemia at various dose levels. A maximum tolerated dose was not defined, but doses $>$ 100 mg BID consistently yielded concentrations above the preclinically predicted minimal efficacious concentration. Seven pts demonstrated stable disease lasting approximately 6 months or greater, including 3 heavily-pretreated ovarian cancer pts (2 platinum resistant). **Methods:** Pts with advanced or refractory ovarian cancer ($\leq$ 4 prior regimens) will be enrolled. In the phase I portion, VS-6063 is administered continuously at a starting dose of 200mg BID with paclitaxel 80 mg/m^2 on days 1, 8, and 15 every 28 days, and will be escalated to 400mg BID if tolerated. Pharmacokinetics will be analyzed. An additional 15 pts with biopsiable disease will be enrolled at the recommended dose. A 10-day run-in with VS-6063 alone will be used to obtain paired tumor biopsies in order to examine the effects on pFAK expression, CSCs, and other biomarkers. Patients will continue treatment until disease progression. Clinical trial information: NCT01778803.

TPS2621 General Poster Session (Board #12A), Mon, 8:00 AM-11:45 AM

A phase I dose-escalation study of TKM-080301, a RNAi therapeutic directed against polo-like kinase 1 (PLK1), in patients with advanced solid tumors: Expansion cohort evaluation of biopsy samples for evidence of pharmacodynamic effects of PLK1 inhibition.

Donald W. Northfelt, Solomon I. Hamburg, Mitesh J. Borad, Mahesh Seetharam, Kelly Kevelin Curtis, Peter Lee, Brynne Crowell, Linda Vocila, Paul Fredlund, Mark J. Gilbert, Catherine Patricia Mast, Sean C. Semple, Adam D. Judge, Ian MacLachlan, Ramesh K. Ramanathan; Mayo Clinic, Scottsdale, AZ; Tower Cancer Research Foundation, Beverly Hills, CA; Arizona Oncology-Scottsdale Medical Oncology & Hematology, Scottsdale, AZ; Translational Drug Development (TD2), Scottsdale, AZ; Tekmira Pharmaceuticals Corporation, Burnaby, BC, Canada; Virginia G. Piper Cancer Center at Scottsdale Healthcare/ TGen, Scottsdale, AZ

Background: TKM-080301 is a lipid nanoparticle formulation of a small interfering RNA (siRNA) directed against PLK1, a serine/threonine kinase that regulates multiple critical aspects of cell cycle progression and mitosis. Anti-tumor activity, RNA interference and pharmacodynamic effects of PLK1 inhibition have been conclusively demonstrated in preclinical models. Demonstration of pharmacodynamic effects of PLK1 inhibition in patient biopsy samples is an exploratory objective of this first-in-human study. **Methods:** TKME080301 is being evaluated in an open-label, non-randomized, dose-escalation study in patients with advanced solid tumors or lymphoma. Sequential cohorts of 3 to 6 patients receive TKME080301 as a 30-minute intravenous infusion on Days 1, 8 and 15 of a 28-day cycle. Treatment can continue until disease progression, based on overall clinical benefit. Tumor response is determined according to RECIST criteria. Primary study objectives include determination of safety, maximum tolerated dose and dose limiting toxicities. Secondary objectives include characterization of pharmacokinetics and the preliminary assessment of anti-tumor activity. Five cohorts have been enrolled and a tentative Phase 2 dose has been identified. An expansion cohort of 10 patients began enrolling in February, 2013. The focus of the expansion cohort will be to collect additional safety and pharmacokinetic data at the tentative Phase 2 dose, as well as pharmacodynamic data from mandatory biopsy samples. Pre- and post-dose biopsy samples will be evaluated for potential evidence of PLK1 inhibition using 5' RACE (rapid amplification of cDNA ends) polymerase chain reaction (to identify the predicted PLK1 mRNA cleavage product), histology (to assess for the presence of aberrant mitotic figures) and immunohistochemistry. An update on enrollment and pharmacodynamic evaluations will be presented. Clinical trial information: NCT01262235.

TPS2622 General Poster Session (Board #12B), Mon, 8:00 AM-11:45 AM

Phase II, multicenter, open-label, proof of concept study of tasquinimod in patients with advanced/metastatic hepatocellular (HCC), ovarian (OC), renal cell (RCC) and gastric (GC) carcinomas.

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Background: Treatment resistance and disease progression are common in HCC, OC, RCC and GC. Tasquinimod is an oral, quinoline-3-carboxamide derivative that binds to S100A9, resulting in immunomodulatory, anti-angiogenic and anti-metastatic effects involving downregulation of chemokine receptor type 4 and hypoxia-inducible factor. Tasquinimod significantly improves PFS (7.6 v 3.3 mo) in patients with metastatic hormone-resistant prostate cancer (Pili, R. *et al*. 2011. *JCO* 29:4022-8) and is in an ongoing phase III program. Its unique mode of action (MOA) makes tasquinimod attractive for other indications. The primary study objective is to determine the clinical activity of tasquinimod in advanced/metastatic HCC, OC, RCC and GC. Tasquinimod has been shown to delay disease progression with limited tumor shrinkage, therefore an innovative design was proposed, with PFS rate as the main endpoint. **Methods:** Design: Phase II, multinational, exploratory proof of concept study to evaluate tasquinimod activity in 4 independent cohorts of patients (HCC, OC, RCC and GC) with progressive disease after standard therapy. An innovative design (Litwin S. 2007. *Stat Med* 26:4400-15) based on the proportion of patients who have not progressed nor died at predefined timepoints (PFS rate) will be used in each cohort independently. Patients: 110–200 patients (dependent on outcome of futility analyses) aged ≥18 yr, ECOG performance status 0 or 1 will be enrolled. Patients must have histologically confirmed and documented HCC, OC, RCC or GC and demonstrable disease progression on standard therapy. Recruitment is ongoing. Dosage: Tasquinimod will be administered as a starting dose of 0.5 mg/day, in each cohort. After 2 wks, the dose will be increased to 1 mg/day based on individual safety and tolerability. Primary endpoint: PFS rate, defined as the proportion of patients who have neither progressed nor died at 12 wks (GC), 16 wks (HCC, RCC) or 24 wks (OC). Secondary endpoints: Include OS, response rate, safety, pharmacokinetics, inflammatory and specific target biomarkers to explore comprehensively the MOA according to each disease type. Clinical trial information: NCT01743469.

TPS2623 General Poster Session (Board #12C), Mon, 8:00 AM-11:45 AM

Phase I study of pazopanib (PAZ) in combination with PCI-24781 (PCI) in patients (pts) with metastatic solid tumors with new tumor proliferation imaging correlates in renal cell carcinoma (RCC) and sarcoma.

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Background: PAZ is a multi-targeted tyrosine kinase inhibitor of VEGFR, PDGFR, and C-KIT, approved for metastatic RCC and refractory sarcoma based on phase III data showing prolonged PFS (*JCO* 2010;28:1061-8 and *Lancet* 2012;379:1879-86). PCI is a potent pan-HDAC inhibitor (pan-HDACi), observed in cell lines to change regulation of genes involved in cell signaling, apoptosis, proliferation, differentiation, and angiogenesis (*Anticancer Res* 2011;31:1115-23). Pre-clinical models suggest epigenetic modification with an HDACi potentiates PAZ's efficacy by causing chromatin instability and gene expression changes involved in drug resistance (*Can Res* 2005;65:3815-22 and *BJC* 2009;100:758-63). We therefore designed a Phase Ia/b clinical trial combining PCI with PAZ in pts with advanced solid tumors, with an expansion cohort for preliminary efficacy in RCC and sarcoma. **Methods:** Primary objective of this phase Ia/b study is to evaluate the safety and tolerability of the combination of PAZ and PCI to determine the MTD and RP2D. In phase Ia, we utilized an accelerated phase I design. The phase Ib portion will include up to 20 pts per expansion cohort, for up to 32-70 pts enrolled. In phase 1a, pts receive run-in PCI alone on C1D-7 to D-4. Starting with C1D1, pts receive oral PCI on D1-5, 8-12, 15-19 BID 4 hrs apart and PAZ daily (D1-28) q28D cycle. CORRELATIVES: Pre- and post-treatment (Tx) H3 & H4 acetylation and HDAC activity in PBMCs. In phase Ib, these will also be studied in tumor biopsies. We will measure expression of VEGF, VEGFR, RAD51, HIF, Ki67; and analyze SNPs through genomic profiling. We will correlate response with pre- and post-Tx tumor thymidine uptake using 18F-fluorothymidine (FLT-PET) PET. Current Status: This is the 1st trial exploring the combination of an HDACi with PAZ in RCC and sarcoma, where there is an unmet need for new tolerable therapies. It will study FLT-PET, an imaging correlate that captures tumor proliferation and may have a role as a predictive biomarker. We are currently in phase Ia. Enrollment in the 3rd cohort exploring higher doses of PAZ will begin in Feb 2013. Clinical trial information: NCT01543763.

TPS2624 General Poster Session (Board #12D), Mon, 8:00 AM-11:45 AM

A phase I study of the BCR-ABL tyrosine kinase inhibitor nilotinib and cetuximab in patients with solid tumors that can be treated with cetuximab.

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Background: Therapeutic blockade of Epidermal Growth Factor Receptor (EGFR) signaling with the monoclonal antibody cetuximab is clinically effective in the treatment of patients with metastatic squamous cell carcinoma of the head and neck or *KRAS* wildtype colorectal cancer. However, these patients eventually become resistant to this therapy. An exploration of the EGFR signaling network using an EGFR network-focused small interfering RNA library identified potential regulators of resistance to EGFR-targeted therapies. The ABL1 gene was identified as a central node to target in this complex genomic pathway. In a preclinical EGFR-expressing cancer cell line model, targeting c-abl, the gene product of ABL1, using nilotinib was found to be highly synergistic in decreasing cell survival when combined with anti-EGFR targeted therapy. **Methods:** We have initiated an open-label Phase I study for patients who progressed after standard therapies for metastatic *KRAS* wildtype colorectal cancer or metastatic head and neck squamous cell carcinoma. Enrolled patients must have adequate performance status and organ function. Treatment consists of cetuximab 400 mg/m^2 on day 1, then 250 mg/m^2 once weekly, and nilotinib twice daily, starting on day 1, according to a traditional 3+3 dose escalation, from 200mg to 300mg BID. Patients are restaged every 2 cycles (every 8 weeks). The primary endpoint is the maximum tolerated dose (MTD) of nilotinib when used in conjunction with cetuximab. Secondary endpoints are clinical benefit rate (defined as rates of stable disease, partial response, and complete response) and response rate. Additionally, biopsies of metastases obtained prior to and after initiation of therapy will be used to establish primary tumor cell cultures using conditional cellular reprogramming to permit the dynamic study of signaling and drug sensitivity through an evaluation of evidence of a drug effect on EGFR signaling and on Antibody-Dependent Cell-Mediated Cytotoxicity. An additional 10 colorectal cancer patients will be treated as an expansion cohort at the MTD. This expansion cohort data may be used to plan a Phase II trial in the future.

TPS2625 General Poster Session (Board #12E), Mon, 8:00 AM-11:45 AM

Evesor: The first phase I trial combining multiple dose/dosing schedules—Pharmacodynamic assessments and mathematical modeling to optimize the benefit/toxicity ratio of everolimus and sorafenib association.

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Background: In 2004, FDA declared the abandon rate of new oncology drugs was too high and new trial designs should be developed. The combination of everolimus (EVE) and sorafenib (SOR) is rational, and has been studied in 11 phase I studies, where approved monotherapy regimens have been used (EVE qd and SOR bid). Although promising efficacy outcomes were found, the combination may be abandoned due to metabolical and skin toxicity. The best doses and dosing schedules of EVE and SOR associated with the optimal benefit/toxicity ratio may be identified using mathematical modeling of data from an adequately designed multiparameter trial. **Methods:** This academic study is composed of 4 arms with different dosing schedules of EVE and SOR (qd; 1 week/2; 3 days-on . . .), and dose escalations. Patients with different tumor types potentially sensitive to the combination are enrolled. Multiparameter assessments include: pharmacokinetics (PK); pharmacodynamics (PD) with control of signaling pathway inhibition (ERK, AKT, S6K) in 2 tumor biopsies & repetitive PBMC assays; kinetics of circulating tumor DNA kinetics & angiogenesis markers; tumor angiogenesis changes using repeated DCE-ultrasounds; and radiological/clinical effects. These data enrich a translational multiscale model meant to quantify the relationships between drug dosing modalities, PK, PD, radiological and clinical effects, developed in parallel. The doses and dosing schedules of EVE and SOR which enable maximization of benefit/toxicity ratio (utility function) will be searched using simulations, and then tested. The protocol was approved by ethic committee in 2012. Two patients a month have been enrolled in 2 centers since January 2013. Expected results: Mathematical modeling of the relationships between dosing modalities; PK; PD; radiological and clinical effects based on the data from an adequately designed trial may help determine the optimal doses and dosing schedules of EVE and SOR (with the best benefit/toxicity ratio), and avoid the combination abandon. EVESOR study may embody the proof of concept of this new model-based trial design. Clinical trial information: 2012-002818-39.

TPS2626 General Poster Session (Board #12F), Mon, 8:00 AM-11:45 AM

FGFR: Proof-of-concept study of AZD4547 in patients with FGFR1 or FGFR2 amplified tumours.

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Background: Genetic modifications of the *FGFR* family of transmembrane tyrosine kinase growth factor receptors are described in a range of cancers. Amplification of *FGFR*2 is detected in up to 10% of oesophagogastric cancers where it is associated with poor prognosis. *FGFR*1 amplification has also been demonstrated in 10% of breast cancers, is more common in luminal B ER positive tumors, and is also associated with inferior survival outcomes. Finally, *FGFR*1 amplification has been described in up to 22% of squamous cell lung cancers. AZD4547 is a potent and selective inhibitor of FGFR-1, 2 and 3 receptor tyrosine kinases. Preclinically, AZD4547 potently inhibits growth in *FGFR* amplified gastric and lung cancer cell lines and induces dose dependent tumor growth inhibition and regression in *FGFR* amplified tumour xenograft and patient derived explant models. **Methods:** This is an open label, phase II non-randomised multi-centre study to assess the efficacy of AZD4547 monotherapy and resulting molecular changes in serial biopsies in pts with previously treated *FGFR1* amplified advanced breast cancer, *FGFR2* amplified advanced oesophagogastric cancer, or *FGFR1* amplified advanced squamous lung cancer. Eligibility include centrally verified *FGFR* amplified tumour (ratio $>$2.2), PS$=$0-2, ability to comply with the collection of tumor biopsies (mandatory at baseline and on days 10-14), calcium and phosphate within normal limits, measurable disease (RECIST 1.1), and no history of significant eye disease. Pts may be prescreened for *FGFR* amplification on archival tissue while undergoing first line or adjuvant chemotherapy. Sixteen pts will be enrolled per cohort. All pts will receive AZD4547 80mg bd on a two week on, one week off schedule. The primary endpoint is correlation between change in pERK in pretreatment and day 10-14 biopsy and change in tumour diameter on week 8 CT. Secondary endpoints include ORR, DCR and PFS. Multiple exploratory translational endpoints are also planned. The study is currently open at the Royal Marsden Hospital and will open at 15 selected UK cancer centres. This study is sponsored by the Royal Marsden Hospital, funded by AstraZeneca and has been adopted to the UK National Cancer Research Network (NCRN) portfolio. Clinical trial information: 2011-003718-18.

TPS2627 General Poster Session (Board #12G), Mon, 8:00 AM-11:45 AM

A phase I, dose-escalation, safety, pharmacokinetic, pharmacodynamic study of thioureidobutyronitrile, a novel p53 targeted therapy, in patients with advanced solid tumors.

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Background: Thioureidobutyronitrile, kevetrin, has demonstrated anti-tumor activity in several wild type and mutant p53 human tumor xenografts without evidence of genotoxicity. In wild type p53 models, kevetrin induces cell cycle arrest and apoptosis through activation and stabilization of wild type p53, resulting in increased expression of p53 target genes p21 and PUMA. Kevetrin also alters processivity of MDM2, and induces monoubiquitination of wild type p53, enhancing its stability (AACR 2011 abstract 4470). Mutant p53 is a complex target since it is an array of mutant proteins with oncogenic properties. Kevetrin induces degradation of oncogenic mutant p53 and induces apoptosis (AACR 2012 abstract 2874). Kevetrin therefore has the unique ability to target both wild type and mutant p53 tumors thereby controlling tumor growth in a wide range of preclinical tumor models. **Methods:** Adults with refractory locally advanced or metastatic solid tumors, acceptable liver and kidney function, and hematological status were eligible. Objectives include determination of DLT, MTD, recommended phase 2 dose, pharmacokinetics (PK), pharmacodynamics (PD), and evaluating preliminary evidence of antitumor activity. Kevetrin is given as a 1-hour intravenous infusion once weekly for 3 weeks in 28-day cycles. The starting dose was 10 mg/m^2. In a 3+3 design, groups of 3-6 patients are evaluated for toxicity at each dose level. Dose escalation is based upon the number and intensity of adverse events in cycle 1. Kevetrin PK is characterized for the first and last doses given in cycle 1. Kevetrin induced expression of p21 in lymphocytes in preclinical studies; therefore p21 expression in peripheral blood mononuclear cells will be measured as a PD biomarker. Antitumor activity by RECIST 1.1 criteria and serum tumor markers will be assessed. The p53 status of tumors of selected patients will be determined. The second cohort is currently under evaluation. Conclusion: In preclinical models, Kevetrin has activity against tumors harboring both wild type and mutant p53 by diverse mechanisms. A first-in-human dose escalation trial is underway. Clinical trial information: NCT01664000.