PHASE II ACTIVITY OF THE HSP90 INHIBITOR AUY922 IN PATIENTS WITH ALK-REARRANGED ALK+ OR EGFR-MUTATED ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)


1Medical Oncology, Vall d’Hebron University Hospital, Barcelona, SPAIN, 2Medical Oncology Service, Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, SPAIN, 3Multidisciplinary Oncology and Therapeutic Innovations Department & Centre Investigation Clinique, Aix Marseille University, Marseille, FRANCE, 4Oncology, Dana-Faber Cancer Institute, Boston, UNITED STATES OF AMERICA, 5Medicine, Massachusetts General Hospital, Boston, MA, UNITED STATES OF AMERICA, 6Oncology, Asan Medical Center, Seoul, KOREA, 7Pulmonary Diseases, University Hospital Groningen (UMCG), Groningen, NETHERLANDS, 8Department of Medicine, Institute Gustave Roussy, Villejuif, FRANCE, 9Department of Internal Medicine, Seoul National University Hospital, Seoul, KOREA, 10Department of Pulmonary Diseases, Vrije Universiteit Medical Centre, Amsterdam, NETHERLANDS, 11Translational Medicine, Novartis Pharma AG, Basel, SWITZERLAND, 12Oncology Translational Medicine, Novartis Pharmaceuticals, East Hanover, NJ, UNITED STATES OF AMERICA, 13Biometrics and Data Management, Novartis Pharma AG, Basel, SWITZERLAND, 14Oncology, Novartis Oncology, Florham Park, NJ, UNITED STATES OF AMERICA, 15Translational Oncology Research, David Geffen School of Medicine at UCLA, Los Angeles, UNITED STATES OF AMERICA

Background: AUY922 is a highly potent, non-geldanamycin, HSP90 inhibitor. HS9PO is a chaperone of client proteins relevant in NSCLC pathogenesis, including ALK and EGFR. Oncogenic fusion genes giving constitutive ALK activity (ALK+) occur in up to 6% of NSCLCs, and EGFR mutation (mut) occurs in 10–20% of cases. We report data from a Phase II study of AUY922 in patients (pts) with previously treated, advanced NSCLC, stratified by molecular status.

Methods: Pts with advanced NSCLC who progressed following ≥1 prior line of chemotherapy, received AUY922 (70 mg/m2) a sao n c e - w e e k l y , 1 - h ri n f u s i o n . Pts were stratified by prior crizotinib therapy. Eight pts discontinued (7 disease progression, 1 investigator decision). The most frequent adverse events (AEs) were: diarrhea (74%), fatigue (77%), eye disorders (77%), nausea (43%) and vomiting (38%). No treatment-related serious AEs were observed. The most common grade 3 AEs were: diarrhea (9), fatigue (5), nausea (3), vomiting (3), and infection (3). The most common grade 4 AEs were: neutropenia (1). The most common grade 1–2 treatment-related AEs were: diarrhea, fatigue, nausea, vomiting and constipation. The most frequent severe AEs associated with treatment were: fatigue (7), diarrhea (7), nausea (5), vomiting (3) and constipation (3).

Results: On 6 April 2012 cutoff, 121 pts had been treated (ALK+ [n = 22; both crizotinib (CRZ) treated and naive], EGFR-mut [n = 35], KRAS-mut [n = 28], EGFR/ KRAS/ALK wild-type [n = 33], undetermined [n = 5]); pts were heavily pretreated (61% had received ≥3 prior regimens). Clinical activity of AUY922 was seen in pts with ALK+ and EGFR-mut NSCLC, with partial responses in 8/22 (36%) and 7/35 (20%) pts, respectively. 4/6 ALK+ responders were CRZ-naive and 2/6 were pretreated. Estimated median PFS rates (FAS) were 43% and 34% at 18 wks in ALK+ and EGFR mut pts, respectively. In EGFR mut pts who had progressed just after crizotinib-naïve therapy, median PFS rate was 18% at 18 wks vs 21% in pts who had not received a TKI as their immediate pre-AUY922 therapy.

Conclusions: AUY922 had an acceptable safety profile. Activity was demonstrated in pts with ALK+ and EGFR-mut NSCLC; clinical activity observed in pts naïve to or failing prior crizotinib. The phase 2 expansion will include 4 cohorts: 1) crizotinib-naïve ACUP pt). Anti-tumor activity at 120 mg remains to be evaluated. In summary, AP26113 is a novel, synthetic, orally-active tyrosine kinase inhibitor (TKI) that potently inhibits mutant activated forms of anaplastic lymphoma kinase (ALK+) and epidermal growth factor receptor (EGFRm), as well as TKI resistant forms including L1196M (ALK) and T790M (EGFR). AP26113 does not inhibit native EGFR. This is the initial report of a phase 1/2 open-label, multicenter study of AP26113. The dose finding phase (3 + 3 design) is ongoing in pts with advanced malignancies (except leukemia) refractory to available therapies or for whom no standard treatment exists. Initial dosing is once daily. As of 07 May 2012, 15 pts were enrolled: 30 mg n = 3, 60 mg n = 3, 90 mg n = 5, 120 mg n = 2; 67% female, median age 65 (41–77) yrs. Diagnoses were: 11 non-small cell lung cancer (NSCLC), 4 other (1 pancreatic, 1 colon, 1 cholangiocarcinoma, 1 unknown primary [UP]), 4 ALK+ (n = 3, 2 CRZ naïve and 1 naïve to all TKIs), and 3 EGFRm NSCLC that is resistant to EGFR-targeted therapy; 4) other cancers with abnormalities in ALK or other AP26113 targets. ClinicalTrials.gov: NCT01449461.

Disclosure: G.J. Weiss: GWJ has received funding and other support related to participation in this clinical trial from ARIAD Pharmaceuticals, Inc. through his employer, Scottsdale Healthcare. GWJ has served on Speakers Bureaus for Genentech, Pfizer, and Eli Lilly. N.I. Narasimhan: NIN is an employee of ARIAD Pharmaceuticals, Inc. D.J. Dorer: DJD is an employee of ARIAD Pharmaceuticals, Inc. V.M. Rivera: VMR is an employee of ARIAD Pharmaceuticals, Inc. J. Zhang: JZ is an employee of ARIAD Pharmaceuticals, Inc. T. Clackson: TC is an employee of ARIAD Pharmaceuticals, Inc. F. Halushka: FH is an employee of and owns stock in ARIAD Pharmaceuticals, Inc. A.T. Shaw: ATS has received consulting fees/honorarium from ARIAD, Pfizer, Chugai, and Daiichi. ATS has received support in the form of grants paid to her employer by Novartis and AstraZeneca. D.R. Camidge: DRC has received consulting fees/honorarium from ARIAD and has served on advisory boards for Pfizer, Chugai, Novartis, and ARIAD. All other authors have declared no conflicts of interest.
RESULTS OF A FIRST-IN-HUMAN PHASE I STUDY OF THE ALK INHIBITOR LDK378 IN ADVANCED SOLID TUMORS


1Medicine, Harvard Medical School, Boston, MA, UNITED STATES OF AMERICA, 2School of Medicine, University of Colorado, Denver, CO, UNITED STATES OF AMERICA, 3Oncology, Vall d’Hebron University Hospital, Barcelona, SPAIN, 4Center for Investigational Therapeutics, Huntsman Cancer Institute, Salt Lake City, UT, UNITED STATES OF AMERICA, 5Department of Medical Oncology, National Cancer Center, Singapore, SINGAPORE, 6Department of Internal Medicine, Seoul National University Hospital, Seoul, SOUTH KOREA, 7Medical Oncology Unit of Respiratory Tract and Sarcomas, Istituto Europeo di Oncologia, Milano, ITALY, 8Respiratory Oncology Unit (pulmonology), University Hospital Gentofte, Copenhagen, DENMARK, 9Department of Medical Oncology and Hematology, Istituto Clinico Humanitas, Rozzano, ITALY, 10Ontario Cancer Institute, Princess Margaret Hospital, Toronto, ON, CANADA, 11Novartis Institutes for BioMedical Research, Novartis Pharmaceuticals, Cambridge, MA, UNITED STATES OF AMERICA, 12Oncology Clinical Pharmacology, Novartis Pharmaceuticals, East Hanover, NJ, UNITED STATES OF AMERICA, 13Clinical Research, Novartis Institutes for Biomedical Research, Inc, Cambridge, MA, UNITED STATES OF AMERICA, 14Department of Developmental Therapeutics, Fox Chase Cancer Center, Philadelphia, PA, UNITED STATES OF AMERICA

Background: Translocations of the anaplastic lymphoma kinase (ALK) gene occur in 3–8% of NSCLC. LDK378 is a novel, potent small molecule ALK inhibitor that produces tumor regressions in preclinical models driven by ALK (N372T) NSCLC translocations. A Phase I study is being conducted with the primary objective of determining the MTD and safety profile in patients (pts) with ALK+ cancers. Other objectives are to assess safety, PK, and antitumor activity in pts with ALK+ NSCLC, either previously untreated with ALK inhibitors, or relapsing following ALK inhibitor treatment, and other ALK-positive cancers.

Methods: LDK378 was administered orally once-daily on a continuous 21 day schedule, in adults pts with advanced malignancies harboring a genetic alteration in ALK who progressed on standard therapy or for whom there was no effective therapy. Dose escalation was guided by a Bayesian logistic regression model to determine the MTD, and toxicity at 50 mg/d.

Results: As of 25 April 2012, 56 pts (primary site: lung 50 pts [37 with prior crizotinib]; breast 4 pts; other 2 pts; median age 53 [22–76] years; 88% ECOG PS 0/1) had received LDK378 at doses of 50–750 mg/day. Of 47 pts evaluable for response (per investigator), there were 24 (51%) responses. All responses were in ALK+ NSCLC (PSI positive in ≥51% of tumor cells). Four pts with NSCLC who had progressed following crizotinib treatment were at ≥200 mg/day there were 21 (81%) responses. Dose limiting toxicities (DLTs) have occurred in 2/14 pts at 400 mg/day, 2/9 pts at 600 mg/day, and 1/9 pts at 750 mg/day. DLTs included diarrhea, vomiting, nausea, dehydration, and altitude. The MTD was 750 mg/day. At the cutoff date, 36 (64%) pts remain on treatment. Discontinuations were due to adverse events (AEs) in 1 (2%), and disease progression in 19 (34%) pts. The most frequent AEs (all grades) were nausea (33 [59%]), vomiting (30 [54%]), and diarrhea (27 [48%]) pts. The most frequent Grade 3/4 AE was diarrhea (5 [9%]) pts. Oral absorption of LDK378 was rapid with peak levels at 5–6 hours, and half-life was about 36 hours.

Conclusions: Daily oral LDK378 is well tolerated and the MTD was 750 mg/day. Striking activity was seen in ALK+ NSCLC pts treated at doses ≥200mg, who had previously progressed following crizotinib.


PIK402

PI3K KINASE INHIBITOR GSK2126458 (GSK458): CLINICAL ACTIVITY IN SELECT PATIENT (PT) POPULATIONS DEFINED BY PREDICTIVE MARKERS (STUDY P3X112826)


1Medicine, Division of Hem/Onc, University of California, San Francisco, San Francisco, CA, USA, 2Oncology, Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, NETHERLANDS, 3Department of Medical Oncology, University Medical Center Utrecht, Utrecht, NETHERLANDS, 4University of Washington Division of Medical Oncology, Fred Hutchinson Cancer Research Center, Seattle, WA, UNITED STATES OF AMERICA, 5Department of Internal Medicine, Division of Hematology, Utrecht University School of Medicine, Salt Lake City, UT, UNITED STATES OF AMERICA, 6Developmental Therapeutics Working Group, U_NC Linneberger Cancer Comprehensive Cancer Center, Chapel Hill, NC, UNITED STATES OF AMERICA, 7Division of Medical Oncology, University of Maryland School of Medicine, Baltimore, MD, UNITED STATES OF AMERICA, 8Division of Medical Oncology, University of Washington, Seattle, WA, UNITED STATES OF AMERICA, 9Department of Pharmacology, The Netherlands Cancer Institute, Amsterdam, NETHERLANDS, 10Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, UNITED STATES OF AMERICA, 11Department of Investigational Cancer Therapeutics, UT MD Anderson Cancer Center, Houston, TX, UNITED STATES OF AMERICA, 12Research and Development, Oncology, GlaxoSmithKline Research Triangle Park, NC, UNITED STATES OF AMERICA, 13Research and Development, Oncology, GlaxoSmithKline, Collegeville, PA, UNITED STATES OF AMERICA

Background: GSK458 is an oral, potent inhibitor of PI3K (α, β, γ, δ), mTORC1, and mTORC2. Cell lines with activation of the PI3K pathway are more likely to be sensitive to GSK458.

Methods: Pts with advanced solid tumors received GSK458 until disease progression or intolerable toxicity. Dose escalation with once (QD) and twice daily dosing (BID) was explored. Pharmacodynamics (PD) (tumor biopsies and FDG-PET) in untreated populations, and clinical activity in specific populations (PIK3CA-mutant and wild-type [WT]) bladder cancer, renal cell carcinoma, PIK3CA-mutant metastatic breast cancer, and KRAS-WT endometrial cancer) were evaluated.

Results: 170 pts (49% female; 14% had ECOG PS 0/1) treated across doses ranging from 0.1 to 3 mg, the MTD for both QD and BID was 2.5 mg. The median (range) time above the target plasma concentration (20 ng/mL) was longer in BID versus QD dosing: 21 hours (IQR 14.8–24) vs 8 hours (IQR 0.3–9.9; n = 18), respectively. Dose limiting toxicities were Grade 3/4 events were diarrhea (28%), fatigue (24%) and nausea (23%). A dose expansion was based on a phase II trial of GSK458 at 3 mg (74% response rate). GSK458 plasma concentrations were modestly correlated with decreases in tumor burden in CDK4+/5+ breast cancers treated with GSK458 (−0.42) (p = 0.002).

Conclusions: GSK458 is a potent, orally bioavailable PI3K inhibitor with a well tolerated toxicity profile. The PI3K pathway is a target for multiple solid tumors.
Purpose: The cell surface receptor tyrosine kinase c-Met and its ligand, hepatocyte growth factor (HGF), mediate cell migration, survival and proliferation. EMD 1214063 is a highly selective, reversible and ATP-competitive c-Met inhibitor that causes growth inhibition and regression of HGF-dependent and HGF-independent tumors in pre-clinical models.

Methods: This is a first-in-man dose-escalation study to establish the MTD of EMD 1214063. Eligible pts had advanced solid tumors not amenable to standard therapy. Following a 3 + 3 dose escalation scheme, pts were treated with once-daily oral EMD 1214063 according to two 21-day-cycle schedules, either days 1-14 followed by a 7-day washout (regimen L [RI]), or continuous 21-day therapy (regimen S). The initial optimized formulation was introduced in August 2011. Pd markers were evaluated in paired tumor biopsies using immunohistochemistry (IHC) and a Luminescence based assay.

Results: Until 3 November 2011, 50 pts had been treated; 27 in R1 and 23 in R2. The initial regimen was escalated from 30 mg to 230 mg/day in R1 and to 115 mg/day in R2 with the initial formulation. For the optimised formulation, data are available for 30 mg and 60 mg/day in R1, and for 60 mg/day in R2. Cmax and AUC increased with dose. The optimised formulation showed higher oral bioavailability. Two DLTs were reported, a Grade 4 and 3 amylase elevation in 1 pt in R1 at 115 mg/day, and a G3 lipase elevation in R2 at 115 mg/day. No treatment-related SAEs were observed. Treatment-related AEs of ≥G2 included nausea (n = 1), vomiting (n = 1), decreased appetite (n = 2), diarrhea (n = 1), and fatigue (n = 1) in R1, and neutropenia (n = 1) and fatigue (n = 1) in R2. Forty-four patients (88%) had no drug-related AE ≥G1. Analysis of pre- and on-treatment biopsies showed decreased phospho-c-Met staining intensity under treatment on IHC and >80% reduction in phospho-c-Met levels on the Luminescence assay. Preliminary anti-tumor activity included an unconfirmed PR in 1 pt and an SD in 7 pts. Overall, the regimen showed promising activity in bladder cancer and multiple MET copies due to polysomy of Chr 7 achieved SD for 2 + 5 months (a confirmed PR). The drug was safe and did not cause dose limiting hematologic or non-hematologic toxicities. This is encouraging for further clinical development of this first-in-class c-Met inhibitor.

Conclusion: The MTD has not yet been reached and dose escalation of EMD 1214063 continues. Updated results will be presented.

Disclosure: G.S. Falchook: Honoraria, travel reimbursement and relationship with EMS Serono, received research funding of EMD Serono, received travel reimbursement from EMD Serono. H.M. Amin: Received research funding of EMD Serono.M. Klevesath: Merck KGaA employee, V. Jego: Merck Serono employee, A. Johne: Merck Serono employee, S. Stinchi: Merck Serono employee, R. Kurzrock: received research funding of EMD Serono and Merck KGaA other authors have declared no conflicts of interest.

444PD CLINICAL ACTIVITY AND PHARMACOKINETICS (PK) OF CABOZANTINIB (XL184) IN PATIENTS WITH PROGRESSIVE MEDULLARY THYROID CARCINOMA (MTC)


1Dept of Medicine, University of Chicago Medical Center, Chicago, IL, UNITED STATES OF AMERICA, 2Department of Endocrinology, University of Pisa, Pisa, ITALY, 3Medical Imaging, Institut de Cancérologie de L’Ouest de la France, Rennes, FRANCE, 4Klinik und Poliklinik für Nuklearmedizin, Universitätshilikonlinik Essen, Essen, GERMANY, 5Department of General Medical Oncology, University Hospitals Leuven, Leuven, BELGIUM, 6Dept of Medicine, University of Pennsylvania Health System, Philadelphia, PA, UNITED STATES OF AMERICA, 7College of Medicine, Ohio State University, Columbus, OH, UNITED STATES OF AMERICA, 8Nonclinical Development, Exelixis, Inc., South San Francisco, CA, UNITED STATES OF AMERICA, 9Department of Endocrine Neoplasia and Hormonal Disorders, University of Texas MD Anderson Cancer Center, Houston, TX, UNITED STATES OF AMERICA

Background: Cabozantinib (cabo) is a potent oral therapy that inhibits MET, VEGFR2, and RET. In a phase I study, cabo demonstrated anti-tumor activity in patients with MTC, and a long terminal half-life of 120 hours. We report clinical activity and PK analyses from a Phase 3 study of cabo versus placebo (P) in patients with progressive, unresectable, locally advanced or metastatic MTC.

Methods: Patients with MTC and documented RECIST progression within 14 months (mo) of screening were randomized 2:1 to receive cabo (140 mg freebase qd, n = 219) or placebo (n = 111). Blood samples for PK were collected on days 1 and 29. In a population-PK analysis, moderate inter-subject variability in PK was identified which would require dose adjustment, and PFS for cabo-treated patients was superior in cabo vs placebo. Based on these results, cabo is superior to placebo and has a long half-life of 120 hours.

Conclusion: Cabozantinib is a potent oral therapy that inhibits MET, VEGFR2, and RET. In a phase I study, cabo demonstrated anti-tumor activity in patients with MTC, and a long terminal half-life of 120 hours. We report clinical activity and PK analyses from a Phase 3 study of cabo versus placebo (P) in patients with progressive, unresectable, locally advanced or metastatic MTC.


444PD PHASE I DOSE-ESCALATION STUDY OF ORAL SELECTIVE C-MET INHIBITOR EMD 1214063 IN PATIENTS WITH ADVANCED SOLID TUMORS

G.S. Falchook1, D.S. Hong1, H.M. Amini1, S. Fu1, S.A. Pha-Paul1, M.E. Klevesath2, V. Jego3, A. Johne4, S. Stinchi4, R. Kurzrock5

1Department of Investigational Cancer Therapeutics, UT MD Anderson Cancer Center, Houston, TX, UNITED STATES OF AMERICA, 2Department of Hematopathology, UT MD Anderson Cancer Center, Houston, TX, UNITED STATES OF AMERICA, 3Global Early Development Unit - Oncology, Merck KGaA, Darmstadt, GERMANY, 4Biostatistics Geneva, Merck Serono, Geneva, SWITZERLAND, 5Clinical Pharmacology, Merck KGaA, Darmstadt, GERMANY, 6Istituto Di Ricerca Biomediche, Merck Serono RBM, Colleferro Giacosa, ITALY

Purpose: The PHASE I dose-escalation study to establish the MTD of EMD 1214063 in patients with advanced solid tumors. EMD 1214063 continues. Updated results will be presented.

Disclosure: All authors have declared no conflicts of interest.

444PD PHARMACODYNAMIC (PD) – PHARMACOKINETIC (PK) STUDY OF FITICLATUZUMAB(D), A MONOClonAL Antibody (mAb) DIRECTED TO THE HEPATOCYTE GROWTH FACTOR (HGF) IN PATIENTS (PTS) WITH ADVANCED SOLID TUMORS WHO HAVE LIVER METASTASES (METS)

E. Elez1, J. Tabernero1, L. Prudkin2, S. Agarwal2, M. Han3, M. Credi4, W. Yin5, N. Kugiyama6, J. Basioglu7

1Medical Oncology, Vall d’Hebron University Hospital, Barcelona, SPAIN, 2Oncology Department, Vall d’Hebron University Hospital Medical Oncology Service, Barcelona, SPAIN, 3Pathology, Vall d’Hebron University Hospital, Barcelona, SPAIN, 4Aveto Pharmaceuticals, Inc, Cambridge, MA, UNITED STATES OF AMERICA, 5Hematology/Oncology, MGH Cancer Center, Massachusetts General Hospital, Boston, MA, UNITED STATES OF AMERICA

Background: fituclatuzumab(D) is a humanized IgG1 mAb directed to HGF that inhibits activation of the c-Met receptor, with potential anti-tumor activity. This study was to define the optimal dose using PD and PK assessments.

Methods: Pts with solid tumors and liver mets, with phospho-(p)-Met expression were sequentially enrolled into 2, 10, or 20 mg/kg (RP2D, defined in a previous study), of fituclatuzumab(D) in a single dose escalation design. At each dose level, 6 pts were evaluated and 6 were evaluated in the next dose level to define the PK. PK at steady-state (Day 29) relative to baseline was assessed. At least 2 pts were evaluable at each dose level. PD markers were evaluated in biopsies of liver mets: p-Met, p-Akt, p-ERK, phospho-c-Met staining intensity under treatment on IHC and >80% reduction in phospho-c-Met levels on the Luminescence assay. The PK and PD results of this study were consistent with that reported previously. Increase in post-dose serum HGF and HGF/F complex levels indicates target engagement. At RP2D, a majority of pts experienced decreases in key cell signaling PD markers. This study supports the recommended schedule for GSK458 monotherapy. Surrogate PD markers (insulin) in patients with progressive, unresectable, locally advanced or metastatic MTC.

Conclusion: Based on its superior pharmacokinetic profile, BID is the recommended schedule for EMD 1214063 monotherapy. Updated results will be presented.

Disclosure: G.S. Falchook: Honoraria, travel reimbursement and relationship with EMS Serono, received research funding of EMD Serono, received travel reimbursement from EMD Serono. H.M. Amin: Received research funding of EMD Serono.M. Klevesath: Merck KGaA employee, V. Jego: Merck Serono employee, A. Johne: Merck Serono employee, S. Stinchi: Merck Serono employee, R. Kurzrock: received research funding of EMD Serono and Merck KGaA other authors have declared no conflicts of interest.
Background: Inhibiting multiple signalling pathways with the combination of afatinib, an oral irreversible ErbB Family Blocker, and nintedanib, an oral triple angiokinase inhibitor of VEGFR, PDGFR and FGFR, may lead to better efficacy.

Methods: This Phase I study used a modified 3 + 3 design to determine the maximum tolerated dose (MTD) of afatinib, with dose escalating from 10 to 40 mg qd given in 2 schedules: continuous (C) or intermittent (I) (every other week), in combination with fixed-dose nintedanib (200 mg bid reduced to 150 mg bid after protocol amendment) in a 28-day cycle. Secondary endpoints were safety, efficacy, pharmacokinetics (PK), and circulating tumour cells (CTC) analysis. Treatment continued until disease progression or intolerability.

Results: 45 pts with heavily pretreated advanced solid tumours were included: 26 men; median age 56 years (range 37–73); main cancer types: lung (NSCLC), colorectal, breast, melanoma and ovary. Main adverse events were diarrhoea, asthenia, nausea, vomiting and transaminase elevation. Two MTDs were established: afatinib 40 mg qd (I) plus nintedanib 150 mg bid and afatinib 30 mg qd (C) plus nintedanib 150 mg bid (Table). Efficacy data showed evidence of antitumour activity with partial responses (RECIST) observed in 2 pts (HER2-negative breast cancer, and head & neck squamous cell carcinoma) and stable disease in 27 pts (lasting >3 months in 8 pts). Preliminary PK data showed no drug-drug interaction. CTC analysis will be presented.

Conclusions: Twenty pts were evaluable for dose-limiting toxicity (DLT). Two of 6 pts at doses 5 mg and 10 mg daily combined with S 400 mg bid were not tolerable in patients. S toxicity appeared accentuated by E co-administration with no drug-drug interaction observed. Efficacy was observed in uterine carcinosarcoma but no significant efficacy in GR-PanCa. Median PFS was 6.8 mo (95%CI 0, 6.8 mo). No PK interaction between S and E was observed.
Background: Dysregulation of the Hh pathway is a principal event in the carcinogenesis of multiple tumor types, including basal cell carcinoma. TAK-441 is an investigational, orally-available inhibitor of the G protein-coupled receptor Smoothened, a component of the Hh signalling cascade.

Methods: This study (NCT01204073) was designed to determine safety, maximum tolerated dose (MTD) and maximum feasible dose (MFD) in patients with advanced solid tumors. Cycles consisted of 3 weeks continuous dosing, with a single dose-cycle 1 lead-in, followed by 7 drug pharmacokinetics (PK). Dose escalation (DE) proceeded in a modified 3 + 3 fashion. Radiographic tumor assessments were performed after cycles 2, 4, and every 4 cycles thereafter.

Results: Thirty-two patients were enrolled in the DE phase, median age 59 y (range 28–82), and treated with doses from 50–1600 mg daily. TAK-441 concentrations were quantifiable in plasma after the starting 50 mg dose, with total exposure increasing dose-proportionally to 800 mg. Maximum plasma concentration typically was reached 3 h post-dose. The median terminal disposition half-life was 15 h (range 6–35 h). DLTs of Gr 3 fatigue and muscle spasm were observed in 1 pt at the 1600 mg dose. Six subjects discontinued due to an adverse event (AE) including a patient who suffered a fatal cerebral hemorrhage in cycle 4 related to 50 mg TAK-441. Most common treatment-emergent AEs were muscle weakness (44%), dyspnea (41%), nausea (41%), fatigue (38%) and constipation (28%). The MFD is 1600 mg and the MTD has not been reached. Four patients remained on trial for >10 cycles, and 3 patients continue on treatment. Response and PK/PD data will be presented.

Conclusions: TAK-441 was well-tolerated up to an MFD of 1600 mg taken once daily. A dose expansion cohort has been initiated at 800 mg in patients with untreated basal cell carcinoma.

Disclosure: All authors have declared no conflicts of interest.
A PHASE 1B STUDY TO EVALUATE THE SAFETY AND PHARMACOLOGY OF THE DUAL PI3K- mTOR INHIBITOR GDC-0980 IN COMBINATION WITH A FLUOROPYRIMIDINE, OXALPLATIN, AND BEZ235 (BKM120) IN PATIENTS WITH ADVANCED SOLID TUMORS

L.S. Rosen1, J. Goldman1, S. Stewart2, J.M. Hubbard2, M. Roos2, W. Lin3, G. Shankar4, J. Capdevila5, E. Freas6, S. Leong6
1Division of Hematology Oncology, UCLA, Santa Monica, CA, UNITED STATES OF AMERICA, 2Oncology, Mayo Clinic, Rochester, MN, UNITED STATES OF AMERICA, 3Biotechnology Early Development, Genentech Inc, South San Francisco, CA, UNITED STATES OF AMERICA, 4Bioconjugate Clinical Development, Genentech Inc, South San Francisco, CA, UNITED STATES OF AMERICA, 5Medical Oncology, Hospital Vall d’Hebron, Barcelona, Spain, 6Medicine/oncology, University of Colorado, Denver, CO, UNITED STATES OF AMERICA

Background: PI3K signaling is altered in many cancer types. In colorectal cancer (CRC), ~30% of the tumors harbor PI3KCA mutations, and ~20% of tumors have PTEN loss. GDC-0980 has demonstrated synergy with fluoropyrimidines, a common therapeutic agent in colorectal and advanced breast cancers.

Methods: This was a standard 3+3 dose escalation design to determine the recommended phase 2 dose (RP2D) of GDC-0980 with capcitabine (CPC) (Arm A) or with mFOLFOX6 + Bev (Arm B) in patients (pts) with advanced solid tumors. In Arm A, GDC-0980 + CPC were given daily for 14 consecutive days in each 21-day cycle. In Arm B, GDC-0980 is given for 7 consecutive days in a 14-day cycle with mFOLFOX6 given on the first day. Bev is given on Day 1 starting in Cycle 2 during the dose escalation stage. 

Results: In Arm A 6 pts received 25mg GDC-0980 + 1650mg/m2 bid of CPC (A1); 3 pts received 40mg GDC-0980 and 1650mg/m2 CPC (A2); and 9 pts received 40mg GDC-0980 and 2000mg/m2 CPC (A3). Common adverse events (AEs) in ≥20% pts were nausea, fatigue, decreased appetite, hyperglycemia, vomiting, diarrhea, stomatitis, mucositis and rash. One dose limiting toxicity (DLT) of G3 AST/ALT was observed in A1. The RP2D in Arm A is 40mg GDC-0980 + 2000mg/m2 CPC. One pt in A2 with HNSCC experienced a confirmed partial response (cPR, 26mo). In Arm B, 4 pts received 25mg (B1) and 6 pts received 40mg GDC-0980 (B2) in combination with mFOLFOX6 and Bev (10 mg/kg). The RP2D in Arm B is 40mg GDC-0980 + mFOLFOX6 + Bev. Common AEs in ≥20% pts were nausea, vomiting, decreased appetite, diarrhea, fatigue, peripher neuropathy. One DLT of G4 thrombocytopenia was observed in cohort B2. Cohort expansion with CPC in pts in Arm B is ongoing. Two pts in cohort B1 (cholangiocarcinoma, anal cancer) experienced cPRs (>6mo). In Arm B 6 pts received 25mg GDC-0980 and 1650mg/m2 bid of CPC

Disclosures: G.D. Rosen: Research support received from Genentech, the study sponsor. All other authors have no conflicts of interest.

ANNALS OF ONCOLOGY

Volume 23 | Supplement 9 | September 2012 doi:10.1093/annonc/mds395 | i1x57

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PHASE IB DOSE-ESCALATION STUDY OF BEZ235 OR BKM120 IN COMBINATION WITH PAACLITAXEL (PTX) IN PATIENTS WITH ADVANCED SOLID TUMORS

1Clinical Trials Oncology, Sint Augustinus Hospital, Antwerp, Belgium, 2Department of Medical Oncology, University Hospitals ZNA St. Luc, Brussels, Belgium, 3Medical Oncology, Kantonsspital St. Gallen, St. Gallen, Switzerland, 4Medical Oncology, Vall d’Hebron University Hospital, Barcelona, Spain, 5Oncology, Hospital Vall d’Hebron, Barcelona, Spain, 6Medical Oncology, University Hospital Virgen del Rocio, Seville, Spain, 7Medicinische Onkologie und Hämatologie, Kantonsspital Graubünden, Chur, Switzerland, 8Oncology, Novartis Pharma AG, Basel, Switzerland, 9Medical Oncology, Vall d’Hebron University Hospital, Barcelona, Spain.

Background: The pan-PI3K inhibitor BMK120 and the dual PI3K/mTOR inhibitor BEZ235 have demonstrated preclinical and clinical antitumor activity as single agents and in combination with other drugs. Here, we report interim results of BMK120 or BEZ235 + PTX in pts with advanced solid tumors.

Methods: In the first 2 arms of this 4-arm Phase Ib dose-escalation study, pts with metastatic or locally advanced solid tumors received once-daily oral BMK120 or BEZ235 + weekly IV PTX. Dose-escalation was guided by a Bayesian logistic regression model with overdose control. The primary objective was to determine the MTD of BMK120 or BEZ235 + PTX.

Results: 33 pts were treated with BMK120 (mg/d) + PTX (mg/m2) at 6 dosing levels: 40/10 (1 pt); 40/80 (5 pts); 60/80 (3 pts); 80/80 (1 pt); 100/80 (16 pts); and 120/80 (4 pts). DLTs were observed in 4 pts (1/16 at 100/80 and 3/12 at 200/80), including asthenia, hyperglycemia, and depression. The MTD of BMK120/PTX was declared as 100/80. Most common G3/4-suspected study treatment-related AEs (5%) were neutropenia, hyperglycemia, and anemia. For the BEZ235 arm, 29 pts were treated with BEZ235 (mg/d) + PTX (mg/m2) at 4 dosing levels: 400/70 (2 pts); 400/80 (3 pts); 600/80 (4 pts); and 800/80 (20 pts). DLTs were observed in 4 pts (3/20 at 800/80 and 1/4 at 600/80), including GI events, peripheral neuropathy, and febrile neutropenia. The MTD of BEZ235/PTX was declared as 800/80. Most common G3/4-suspected study treatment-related AEs (>10%) were fatigue, diarrhea, and anemia. As of Feb 29, 29 pts were evaluable for response in each arm. In the BMK120/PTX arm, 1 CR (penea carcinoma Ca), 4 PRs (breast and ovarian Ca pts, each with multiple lines of prior therapy), 3 PRs and progression on prior PTX; cervical

45SP

ANTI-PROGRAMMED DEATH-1 (PD-1) (BMS-936558/MDX-1105/ONO-4538) IN PATIENTS (PTS) WITH ADVANCED SOLID TUMORS: CLINICAL ACTIVITY, SAFETY, AND MOLECULAR MARKERS

1Clinical Trials Oncology, Sint Augustinus Hospital, Antwerp, Belgium, 2Department of Medical Oncology, Cliniques Universitaires Saint-Luc, Bruxelles, Belgium, 3Medical Oncology, Kantonsspital St. Gallen, St. Gallen, Switzerland, 4Medical Oncology, Vall d’Hebron University Hospital, Barcelona, Spain.

Purpose: Blockade of PD-1, a co-inhibitory receptor expressed by activated T cells, can overcome immune resistance and mediate tumor regression. This study describes the activity and safety of BMS-936558, an anti-PD-1 monoclonal antibody, in pts with advanced cancers.

Methods: Pts received BMS-936558 IV q2wk at 0.1 to 10mg/kg during dose escalation and/or cohort expansion. Tumors were assessed by RECIST v1.0. Pts received up to 12 doses (4 doses/cycle) or until unacceptable toxicity, confirmed progressive disease, or complete response.

Results: As of Feb 24, 2012, 296 pts with melanoma (MEL, n = 104), non-small cell lung (NSCLC, n = 122), renal cell (RCC, n = 34), colorectal (n = 19), and prostate (n = 17) cancer were treated. Median duration of therapy was 16 wks (range 2.0 – 121.7 wks). MTD was not reached. Grade ≥3 drug-related AEs occurred in 14% of pts. AEs of special interest included pneumonia, vitiligo, colitis, hepatitis, hypothyroidism, and thyroiditis. There were 3 deaths due to pneumonia. In evaluable pts, objective responses (ORs) or prolonged stable disease was observed in MEL, RCC, and NSCLC (Table). Some had a persistent reduction in overall tumor burden in the presence of new lesions and were not categorized as responders. To assess PD-1 up-regulation (PD-L1) as a potential predictive molecular marker, immunohistochemistry was performed on pretreatment tumor biopsies from 42 pts. Of 25 pts with PD-L1+ tumors, 9 (36%) achieved OR vs 0/17 with PD-L1-.

Conclusions: BMS-936558 produces durable activity in advanced NSCLC, MEL, and RCC, warranting further clinical development. Preliminary data suggest a relationship between PD-L1 expression status on tumor cells and OR. Additional long-term follow-up data will be reported.
Disclosure: BKIM120 or BEZ235 + PTX were generally well tolerated and showed preliminary signs of efficacy. The MTDs of BEZ235/PTX and BEZ235/PTX were reached. For BKIM120, the MTD in combination with PTX was the same as the single-agent MTD. Arms 3 and 4 will determine the MTD of BEZ235 or BKIM120 + PTX and trastuzumab in pts with advanced HER2+ breast Ca.

Disclosure: M. Schuler is an advisor for Novartis, and receives research funding from Novartis. J. Michals: Jean-Pascal Machies is on an advisory board for Boehringer, and receives a research grant from Sanofi. D. Hess: Dagmar Hess owns <30,000 swiss francs of Novartis stocks. N. Steeghs: Neeljee Steeghs receives research funding from Novartis. L. Paz-Ares: Luis Paz-Ares has been an advisor for Lilly, Baver, Roche and Pfizer. He has also received honoraria from all of the above. R. von Moos: Roger von Moos is a participant of advisory boards for Amgen, Novartis, Roche, BMS, and MSD, and receives unrestricted research grants and speaker honoraria from Amgen and Roche. B. Rabault: Bertrand Rabault is an employee of Novartis and owns stock in novartis pharma. All other authors have declared no conflicts of interest.

**455P**

**EVOLUTION OF CLINICAL TRIAL DESIGN IN EARLY DRUG DEVELOPMENT: THE USE OF EXPANSION COHORTS (ECS) IN PHASE I CANCER TRIALS (PITS)**


1Drug Development Program, Division of Medical Oncology and Hematology, Princess Margaret Hospital, Toronto, ON, CANADA, 2Medical Oncology, Princess Margaret Hospital, Toronto, ON, CANADA

Background: ECS are frequently used to optimize the yield of PITS. However, their rationale and value have yet to be evaluated. Here, we explore the prevalence, characteristics and objectives of ECS in single-agent PITS.

Methods: We conducted a systematic review using MEDLINE and EMBASE to identify all adult single-agent PITS published after 2006. Eligibility assessment and data extraction were performed by 2 reviewers. The primary endpoint was the proportion of PITS with ≥ 1 ECS. Additional endpoints included factors associated with ECS inclusion and whether the ECS objectives were stated and achieved.

Results: 4557 articles were reviewed and 591 trials met eligibility criteria. 139 (24%) included ≥ 1 ECS. Of ECS in single-agent PITS increased between 2006 and 2011 (12.2% to 35.7%, Spearman’s rho 0.20, p < 0.001). In PITS with ECS, a median of 22 and 17 subjects were enrolled in the dose-escalation cohorts (DECs) and ECS, respectively. In unadjusted analysis, PITS were more likely to include an ECS if they were multi-center (OR 2.41, 95% CI 1.52-3.82, p < 0.001), industry-sponsored (OR 1.80, 95% CI 1.12-2.91, p = 0.02), and evaluating non-ctotoxic agents (OR 2.12, 95% CI 1.30-3.47, p = 0.003). In multivariable analysis, these factors retained statistical significance except for industry sponsorship. Geographical location of study and tumor type were not significant. ECS objectives were reported in 74% of trials and included safety (83%), efficacy (45%), pharmacokinetics (28%), pharmacodynamics (23%), and patient enrichment (14%). Among ECS assessing safety, the MTD was modified in 14% and new toxicities defined in 33%. Among ECS designed to assess efficacy, only 24 of 46 (52%) reported ECS efficacy separately; of these, only 3 (13%) reported tumor responses in ECS subjects not previously observed in the DEC.

Conclusions: The utilization of ECS in PITS has increased with time and is more common for multi-center trials of non-ctotoxic agents. Safety and efficacy are common objectives but 26% failed to report explicit aims. Although the majority of ECS supplement PITS with meaningful safety data, their role in assessing preliminary efficacy requires better definition.

Disclosure: All authors have declared no conflicts of interest.

**457P**

**MULTICENTER, DOSE-ESCALATION STUDY OF THE INVESTIGATIONAL DRUG TAK-733, AN ORAL MEK INHIBITOR, IN PATIENTS (PTS) WITH ADVANCED SOLID TUMORS: PRELIMINARY PHASE 1 RESULTS**


1Medicine Oncology, Roswell Park Cancer Institute, Buffalo, NY, UNITED STATES OF AMERICA, 2Oncology, Stanford University Medical Center, Nashville, TN, UNITED STATES OF AMERICA, 3Oncology, University of California Los Angeles, Los Angeles, CA, UNITED STATES OF AMERICA, 4Department of Medical Oncology, Erasmus University Medical Center, Rotterdam, NETHERLANDS, 5Medical Oncology, Vall d’Hebron University Hospital, Barcelona, SPAIN, 6GI Oncology Research/Drug Development Unit, Sarah Cannon Research Institute, Nashville, TN, UNITED STATES OF AMERICA, 7Oncology, University of California Los Angeles, Los Angeles, CA, UNITED STATES OF AMERICA, 8Medical Oncology, MGH Cancer Center, Massachusetts General Hospital, Boston, MA, UNITED STATES OF AMERICA

Background: TAK-733 is an investigational, orally available, selective, non-ATP-competitive, allosteric inhibitor of MEK1/2 shown to have anti-tumor activity in multiple xenograft models. In this first-in-human ph 1 study (NCT00948467), we evaluated safety, pharmacokinetics (PK), pharmacodynamics (PD), maximum tolerated dose (MTD) and efficacy of TAK-733 in pts with advanced solid tumors.

Methods: Pts aged ≥18 y, with ECOG PS 0–2 and radiographically or clinically evaluable tumors were eligible. Pts received TAK-733 QD on d 1–21 in 28-d cycles; doses escalated in a modified 3 + 3 design based on dose-limiting toxicities (DLTs) in cycle 1 to determine MTD. Plasma and blood samples for PK and PD analysis were collected pre-dose on d 1, 8, 15 and 21 and post-dose d 1 and 21 in cycle 1.

Results: Of 35 pts, 44 pts median age 58 yr (range 24 – 75) and 50% male, received TAK-733 (dose mg: [n]: 0.2; [1]; 0.4; [1]; 0.8; [2]; 1.6; [2]; 3.2; [4]; 4.4; [4]; 6; [4; 8; 9]; 11.8; [6]; 16; [9]). 2 pts had DLTs (11.8 and 16.0 mg; both Grade 3 acneiform rash); MTD has not been reached. Pts received a median of 2 cycles (range 1-11, 6 pts ≥6 cycles). Safety and PK data are shown in the Table. Maximum inhibition (I_{max}) of ERK phosphorylation peripheral blood lymphocytes ranged from 21-95% (TAK-733; 0.2-16 mg QD), median I_{max} were 63%, 78%, and 92% at 8.4, 11.8, and 16 mg, respectively. In 32 evaluable pts, 1 pt (16 mg dose) with melanoma (BRAF L597R) had partial response confirmed at cycle 6 (RECIST v1.1) and is still on treatment at cycle 8; 12 pts had a best response of stable disease.

Conclusions: These preliminary data indicate that TAK-733 is generally well tolerated and pharmacodynamically active with signs of anti-tumor activity in pts with advanced non-hematologic malignancies. Dose escalation is continuing to determine the MTD.

AEs, NCI-CTCAE v4.0

<table>
<thead>
<tr>
<th>AE</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-related AE, n (%)</td>
<td>37 (84)</td>
</tr>
<tr>
<td>≥ Grade 3</td>
<td>≥ 15</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>19 (43)</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>8 (18)</td>
</tr>
<tr>
<td>Grade ≥3 drug-related AE, n (%)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>≥ Grade 3</td>
<td>≥ 15</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Creatine phosphokinase evaluation</td>
<td>N = 41</td>
</tr>
<tr>
<td>PK data</td>
<td>&lt;50</td>
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</tbody>
</table>

Disclosure: P.M. LoRusso: Consultancy or advisory board (Millennium Pharmaceuticals Inc.), Research Funding (Millennium Pharmaceuticals Inc.). A. Ribas: Consultancy or advisory board (Millennium Pharmaceuticals Inc.), Honoraria (Millennium Pharmaceuticals Inc.). J.A. Sosman: Consultancy or advisory board (Millennium Pharmaceuticals Inc.), Honoraria (Millennium Pharmaceuticals Inc.). B. Chmielowski: Consultancy within past 2 years (GSK, Genentech, Prometheus, Cytrix, Morphotek). Membership on Board of Directors, Speakers Bureau, Advisory Committee (BMS, Genentech, Prometheus). P. Lipman: Employment (Millennium Pharmaceuticals Inc.). X. Zhou: Employment (Millennium Pharmaceuticals Inc.). Y. Bezöin: Employment (Millennium Pharmaceuticals Inc.). All other authors have declared no conflicts of interest.
measured at $C_{\text{min}}$ (2-4 hrs post-dose) on Day 1 in 72 pts. Pathway phosphorylation in surrogate tissue was investigated in 51 paired skin samples by correlating changes in pS6 (baseline to Day 28) with the mean dose of BKM120 administered in each pt. In 8 pts where pre/post-treatment biopsies could be obtained, pS6, pAKT, and Ki67 were quantified within limits of tissue availability.

Results: Blood C-peptide at $C_{\text{min}}$ on Day 1 increased as a function of the 1st dose administered, with no change after 12.5 mg and mean increase of 72% (range: 56–84%) after 150 mg. Inhibition of pS6 on Day 28 (range: 20–60%) was observed in tumor tissue from 5 out of 8 pts. 4 of these 5 pts also demonstrated a decrease in either pAKT (range: 30–70%) or pEKB1 (range: 27–35%) with 1 pt displaying a mean 30% decrease in all 3 markers. A decrease in proliferation as measured by Ki67 was observed in 21% of pts (range: 13–60%) suggesting a potential impact in response to PI3K pathway inhibition. Inhibition of pS6 in skin increased moderately with the mean administered dose of BKM120 (mean inhibition of –28, –37, and –40%, for 12.5–60 mg, ±60–90 mg, and ±90 mg dose ranges, respectively) suggesting a relationship between treatment dose and the degree of PI3K pathway inhibition.

Conclusion: This analysis supports the notion that daily BKM120 not only has the ability to induce inhibition of the immediate effecter of PI3K (pAKT) but also to downregulate the pathway further downstream (pS6) at MTD.

Disclosure: F. Eskens: Membership on an advisory board. Participant of LEAD summit meetings (Novartis). E. In Tomase: Employee of Novartis. D.W. Sternberg: Employee of Novartis. L. Wang: Employee of Novartis. C. Sarr: Employee of Novartis. Stock Ownership in Novartis Pharmaceuticals. J. Baslega: Novartis Scientific Ad Board (Novartis/BM120); other pan-Pi3K inhibitors: Consulting for Exelixis; SL147; Boehringer Genentech Scientific Ad Board; GDC9941. All author relationships have CA in place which conform to the Partners/Harvard COI Policies. All other authors have declared no conflicts of interest.
knowing HLA-A status double-blindly, and the HLA genotype will not be key-opened until the final analysis point. The endpoints evaluate between HLA-A*0201 positive (24+), n = 60 and HLA-A*0201 negative (24-), n = 40 group, because the frequency of A*0201 positive forecasts about 60%.

Results: In PI study, the total numbers of peptide specific response were 2 in 3 pts at 0.5mg, 6 in 3 pts at 1.0 mg, and 37 in 12 pts at 3.0 mg. We decided that the RD was 3.0 mg. One patient experienced a CR and 6 pts revealed SD. The median OS was 15.2 months. The overall response rate (above 15%; p = 0.0022) and CRP (below 0.008) were primitive but important biomarkers to predict OS. In the low CRP group, pts with 3 or more pepitides specific responses at 8 weeks survived longer than others(p = 0.032). In PI study, 86 pts were enrolled. The PFS of all pts without HLA key-open was seemed to be improved as compared to NO16966 study 9 month after the initial therapy. This result indicated the delayed effect which is characteristic in vaccine therapy.

Conclusions: The PI study demonstrated that Lymphocyte%, CRP and CTL responses were predictive biomarkers for vaccination. The interim report about PI study will be presented at the meeting.

Disclosure: All authors have declared no conflicts of interest.

MLN8237 (ALISERTIB), AN INVESTIGATIONAL AURORA A KINASE INHIBITOR, IN PATIENTS (PTS) WITH NON-SMALL CELL LUNG CANCER (NSCLC), SMALL CELL LUNG CANCER (SCLC), BREAST CANCER (BRC), HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC), AND GASTROESOPHAGEAL CANCER (GE); EMERGING PHASE (PH) 2 RESULTS

B. Melichar1, P. Lee2, R.H. Alvarez3, M. Degardin4, J. Bennouna2, C. Schöffski2,1, B. Zhang5, E. Benaïm6, P. Rosen3
1Oncology, University Fakultät Nenchemes Olomouc – Onkologické Klinika, Olomouc, CZECH REPUBLIC; 2Oncology, Tower Cancer Research Foundation, Beverly Hills, CA, UNITED STATES OF AMERICA; 3Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX, UNITED STATES OF AMERICA; 4Département de Cancérologie Cervico-faciale, Centre Oscar Lambret, Lille, FRANCE; 5Pharmacology and Clinical Oncology, Institut de Cancérologie de l’Ouest, Nantes, FRANCE; 6Clinical, Millennium Pharmaceuticals, Inc., Cambridge, MA, UNITED STATES OF AMERICA; 7Biostatistics, Millennium Pharmaceuticals, Inc., Cambridge, MA, UNITED STATES OF AMERICA; 8Clinical Development, Millennium Pharmaceuticals, Inc., Cambridge, MA, UNITED STATES OF AMERICA; 9Hematology and Medical Oncology, Providence Saint Joseph Medical Center, Burbank, CA, UNITED STATES OF AMERICA

Background: Aurora A Kinase plays a key role in centrosome maturation and spindle formation in mitosis, and is frequently amplified or overexpressed in various human cancers. MLN8237 is an investigational, oral, selective AAK inhibitor being evaluated in pts with hematologic and non-hematologic malignancies. Here we report ph 2 results from an ongoing multicenter ph 1/2 trial of MLN8237 in pts with advanced solid tumors (NCT01045421).

Methods: Pts aged ≥18 y with relapsed/refractory NSCLC, SCLC, BRC, HNSCC, or GE adenocarcinoma, EOCG PS 0-1, measurable disease by RECIST, and ≤5 prior cytotoxic chemotherapy regimens (≤4 in BRC) were eligible. Ph 2 enrollment followed a two-stage Simon’s design; to proceed to the second stage, at least two responses were required in the first 20 response-evaluable pts enrolled in that tumor cohort. The primary and secondary ph 2 objectives were overall response rate and safety profile, respectively. Response was assessed by RECIST v1.1. MLN8237 was administered orally as an enteric-coated tablet at the MTD of 50 mg BID for 7 d followed by 14-d rest in 21-d cycles (determined in RECIST v1.1). MLN8237 was administered orally as an enteric-coated tablet at the MTD of 50 mg BID for 7 d followed by 14-d rest in 21-d cycles (determined in ph 1).

Results: As of March 29, 2012, 226 pts have been treated in ph 2: HNSCC (n = 54), BRC (n = 53), GE adenocarcinoma (n = 53); SCLC (n = 40), and NSCLC (n = 26); median age was 61 y (range 30-88). Best responses achieved are: partial response in 17 pts (BRC, n = 6; SCLC, n = 4; GE, n = 3, NSCLC, n = 1), and stable disease in 92 pts. Median cycles of treatment is 2 (range: 1-15). 89% of pts reported drug-related adverse events (AEs); the most common included neutropenia (44%), fatigue (38%), alopecia (38%), diarrhea (30%), and anemia (27%). Grade ≥3 drug-related AEs were seen in 53% of pts and included neutropenia (36%), leukopenia (10%), and anemia (10%). 21 pts (9%) discontinued due to AEs; there were 19 on-60dly deaths (none drug-related).

Conclusions: These emerging ph 2 data suggest antitumor activity for MLN8237, and further support a developing safety profile that is generally well tolerated across a range of solid tumors.


A PHASE IB CLINICAL STUDY WITH 10F-FDG-PET RESPONSE EVALUATION OF THE COMBINATION OF TEMSIROLIMUS (T) AND PEGLYTATED LIPOSOMAL DOXORUBICIN (PLD) IN BREAST, ENDOMETRIAL AND OVARIAN CANCER

M.J. Sonderegger1, I.M.E. Desar1, L. De Geus-Oei2, W.T.A. van der Graaf2, W.J.G. Oyen2, P.B. Ottevanger2, C.M.L. van Herpen3
1Department of Medical Oncology/452, Radboud University Medical Centre Nijmegen, Nijmegen, NETHERLANDS; 2Department of Nuclear Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, NETHERLANDS

Background: PLD is active in metastatic breast, endometrial and ovarian cancer. Preclinical data suggest that mTOR inhibitors can reverse resistance to doxorubicin. Therefore, the combination of T and PLD is promising.

Methods: This phase I study assessed the MTD, safety and activity of the combination of T and PLD in advanced or recurrent breast, endometrial or ovarian cancer. After a 2 wk run in period with T iv once weekly, PLD iv once every 4 wks was added. The MTD was defined as the highest dose at which ≤1 DLT had been observed among 6 pts. FDG PET scans were performed at baseline (B), after 2 and 6 wks to assess the effect on tumor metabolism. A CT scan was performed as RECIST evaluation at B and after 10 wks. PET scans were evaluated by SUV analysis and total lesion glycolysis (TLG). The fractional change in SUV and TLG between the first, second and third FDG-PET was calculated.

Results: 20 pts were enrolled. On the 4th dose level with 20 mg T and 40 mg/m2 PLD 2 DLT’s occurred in 6 pts, a grade 3 thrombocytopenic bleeding and a grade 3 skin toxicity. Thus the MTD was assessed at 15 mg T and 40 mg/m2 PLD. AEs occurring most frequently were all grds/grd 3-4 (%) fatigue (84/5), nausea (84/16) and mucositis (79/21). 3 pts showed PR and 9 SD (>3 months). The mean PFS was 4.9 months with 2 pts still on treatment. The fractional decrease in TLG from the first to the second FDG-PET for PR pts differed from those who had not (p = 0.018 for ΔTLG50). The fractional change in SUVmax from the second to the third FDG-PET differed between pts who had PD and those who had not (+14.0 versus -15.8, p = 0.034). The degree of decrease in SUVmax between the FDG-PET made after 2 and 6 wks was associated with better PFS (HR 1.068; p = 0.013).

Conclusions: The combination of T and PLD is safe and tolerable. The MTD was assessed at PLD 40 mg/m2 once every 4 wks and T 15 mg weekly. Early response evaluation with FDG-PET could predict PR and PD early after start of treatment. The activity of this combination in breast, endometrial and ovarian cancer pts is promising and warrants further studies with FDG-PET evaluation.

Disclosure: All authors have declared no conflicts of interest.

DEVELOPMENT OF CANCER STEM CELLS THERAPEUTICS

A.A. Epenetos1, C. Kousparou2, M. Deonarain1, S. Stylianou2
1Life Sciences, Imperial College London, London, UNITED KINGDOM; 2Cancer Research, Trojantec, Nicosia, CYPRUS

Cancer Stem Cells, (CSCs), are responsible for the initiation, metastasis and recurrence of a variety of cancers and may be a key reason for the failure of current therapies. Cancer Stem cells operate through similar signaling pathways as normal stem cells such as Notch, Hedgehog,Wnt and others. Notch signaling is abnormal in many, if not all cancers as shown in cancer stem cell development. Furthermore, it may be that some cancers are 'addicted' to Notch signaling. This presents opportunities for tumour-specific intervention. As all the signaling cascades converge on the Notch transcriptional complex (NTC) in the nucleus, we have developed a novel synthetic protein acting as a Notch inhibitor operating at nuclear level. This protein is based on the cell penetrating protein (CPP) antenapedia (Amn) produced together with a dominant-negative truncated mastermind-like protein (DN-MAML) called TrA. TrA has been shown in vitro and in vivo to have anti-Notch and anti-cancer activity with similar potency to many of the gamma-secretase inhibitors or monoclonal antibodies being developed by others against this pathway, but it is completely specific for the NTC. In summary, a specific Notch inhibitor has shown anti-cancer activity and could now be considered for clinical development.

Disclosure: A.A. Epenetos: Receive directors fees from Trojantec ltd. All other authors have declared no conflicts of interest.
A PHASE I STUDY OF DAILY AFatinib, AN IRREVERSIBLE ERBB FAMILY BLOCKER, COMBINED WITH WEEKLY Paclitaxel and 2-WEEKLY BEvacizumab in PATIENTS WITH ADVANCED SOLID TUMOURS

1Department of Oncology, King’s College School of Medicine and Guy’s Hospital, London, UNITED KINGDOM, 2Drug Development Unit, Royal Marsden Hospital NHS Foundation Trust, Sutton, UNITED KINGDOM, 3Drug Development Unit, Royal Marsden Hospital, Sutton, UNITED KINGDOM, 4Clinical Development & Medical Affairs, Boehringer Ingelheim, Biberach, GERMANY, 5Clinical Research Unit, Royal Marsden Hospital, Sutton, UNITED KINGDOM, 6Translational Medicine, Boehringer Ingelheim, Biberach, GERMANY, 7Translational Research / Oncology, Boehringer Ingelheim, Bracknell, UNITED KINGDOM, 8Statistics, Boehringer Ingelheim, Bracknell, UNITED KINGDOM, 9Translational Medicine, Boehringer Ingelheim, Biberach, GERMANY, 10Drug Development Unit, Royal Marsden Hospital NHS Foundation Trust, Surrey, UNITED KINGDOM

Background: The clinical efficacy of cytotoxic agents can be enhanced both by ErbB inhibition and by bevacizumab (Bev). The primary objective of this study was to determine the maximum tolerated dose (MTD) of afatinib (A), an oral, irreversible ErbB Family Blocker, in combination with paclitaxel (P) and Bev.

Methods: A Phase 1 open-label 3 x 3 design dose-escalation trial was undertaken to determine safety, pharmacokinetics (PK), and antitumour efficacy of A combined with P (fixed dose 80 mg/m² on Days 1, 8 and 15 of a 4-week cycle), and Bev (5 mg/kg starting dose to be escalated to 10 mg/kg) administered on Days 1 and 15 in patients (pts) with advanced solid tumours. After at least 6 cycles of triplet combination therapy, pts benefiting and tolerating treatment were eligible to continue treatment with A and Bev. The PK data of P and Bev (± A) were presented.

Results: Twenty-nine pts were enrolled (12 male; median age: 58 years [range: 21–73]; ECOG PS 0–1 for 93% of pts). The MTD dose previously established for 40 mg/day in combination with P only (above schedule; Spicer et al. ESMO 2008) had to be de-escalated to 30 mg and then to 20 mg after 2/6 pts developed dose-limiting toxicities (DLTs) at 40 mg A and 2/5 at 30 mg A when combined with Bev and P 5 mg/kg. No significant antagonist activity was observed with ANA up to 1000 nM. In binding experiments, the affinity of ghrelin and ANA for ghrelin receptors were evaluated and resulted in a Kd of 58 nM and 0.7 nM, respectively. In the in vivo experiments, ANA (3, 10, 30 mg/kg p.o.) significantly (p < 0.05 vs vehicle) increased FI and BW gain. The effect on FI was stable from Day 2 to Day 7 of treatment. ANA at the same doses increased GH AUC0-24h and induced an increase in plasma GH levels. The effect was dose-dependent, and GH AUC0-24h at 10 and 30 mg/kg p.o. were significantly higher (p < 0.05) than vehicle-treated animals.

Conclusion: Anamorelin is a potent ghrelin agonist endowed with significant orexigenic activity demonstrating both an increase of FI and BW after subchronic treatment in rats. Plasma GH levels were increased after a single administration of ANA. These results support the continued investigation of Anamorelin as a potential treatment of cancer cachexia/anorexia.


THE SAFETY AND EFFICACY OF SORAFENIB COMBINED WITH TRANSARTERIAL CHEMOEMBOLIZATION FOR PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA

W. Shao, N. Cong, J. Song
Interventional Therapy, Shandong Cancer Hospital and Institute, Jinan, CHINA

Background and aim: Transarterial chemoembolization (TACE) is widely used for unresectable hepatocellular carcinoma. However, the hypoxia caused by TACE in surviving tumor cells leads to release of angiogenic and growth factors contributing to poor outcome. Sorafenib can block tumor cell proliferation and angiogenesis. The hypothesis is that patients with unresectable HCC may benefit from sorafenib in combination with TACE.

Methods: This is a retrospective study involving patients with unresectable HCC who had received at least one TACE session. Patients received sorafenib 400 mg twice per day and were monitored monthly. Dose reduction from 400mg to 200mg of sorafenib bid was permitted. The primary outcome is safety. The second outcome is overall survival.

Results: Twenty-one patients (mean age, 58 years; Child-Pugh class A, 100%; ECOS PG 0, 100%; BCLC B, 36.8%; BCLC C, 63.2%) were included from April, 2009 to February, 2011. The mean TACE sessions prior to or after sorafenib administration were 4.3 ± 2.9 and 5.0 ± 0.4 respectively. All patients were treated with sorafenib despite radiographic progression until there was deterioration in patient’s Child-Pugh class C or had intolerant adverse events or death. Two patients qualified the study for intolerant diarrhea and withdrew of consent, respectively. Of the other 19 patients, no grade 3 or 4 adverse events were observed. The most common toxicities were dermatologic adverse effects (94.7%), diarrhea (63.2%) and alopecia (26.3%). Sorafenib dose was reduced temporarily in 14 patients (73.7%). Most of toxicities could be relieved after dose reductions and not aggravated again the dose of sorafenib resumed to 400 mg bid. Five patients remained on sorafenib as of February 29, 2012, and were censored at that time point. The median survival was 12 months (9.2-14.8 months).

Conclusion: The combination of sorafenib and TACE for unresectable HCC is safe providing that dose adjustment is permitted. The survival benefit is promising.

Disclosure: All authors have declared no conflicts of interest.

THE PRECLINICAL PHARMACOLOGICAL PROFILE OF ANAMORELIN/ONO-7643, A NEW GHRELIN RECEPTOR AGONIST FOR THE TREATMENT OF CANCER CACHEXIA

C. Pietra, Y. Takeda, N. Tazawa-Ogata, M. Minami, X. Yuanfeng, E. Duus, R. Northrup
1Research and Preclinical, Helsinn Healthcare SA, Pambio Noranco, 2Division of Thoracic Oncology, National Cancer Center Hospital, Tokyo, JAPAN, 3Division of Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo, JAPAN, 4Division of Translational Medicine, Boehringer Ingelheim, Biberach, GERMANY, 5Clinical Development Unit, Royal Marsden Hospital NHS Foundation Trust, Surrey, UNITED KINGDOM

Introduction: Ghrelin is the only known circulating orexigenic hormone which acts as the endogenous ligand for the ghrelin receptor (GRLR), and is considered a potential agent to treat cancer cachexia/anorexia. The aim of this study was to evaluate the in vitro and in vivo pharmacological activities of Anamorelin/ONO-7643 (ANA), a new synthetic ghrelin receptor agonist, on food intake (FI), body weight (BW) and GH in rats.

Material and methods: HEK293 cells expressing human recombinant ghrelin receptor were utilized in a Fluorescent Imaging Plate Reader (FLIPR), along with Flu-2 dye to signal intracellular calcium. Ghrelin and ANA were incubated (0.001-1000 nM) to generate a concentration response increase of Ca²⁺. Binding experiments were also performed by using [125I]Ghrelin. In vivo experiments were performed on male SD rats after subcutaneous treatment of ANA or vehicle. FI and BW were measured daily from Day 1 up to Day 7 of once-daily treatment. In other experiments, blood samples were collected at different time intervals up to 6 hours post single dose for GH measurements.

Results: Ghrelin and ANA showed a significant agonist activity on the ghrelin receptor in the FLIPR assay, with EC50 values of 0.67 nM and 0.74 nM, respectively. No significant antagonist activity was observed with ANA up to 1000 nM. In binding experiments, the affinity of ghrelin and ANA for ghrelin receptors were evaluated and resulted in a Kd of 0.58 nM and 0.70 nM, respectively. In the in vivo experiments, ANA (3, 10, 30 mg/kg p.o.) significantly (< 0.05 vs vehicle) increased FI and BW gain. The effect on FI was stable from Day 2 to Day 7 of treatment. ANA at the same doses increased GH AUC0-24h and induced an increase in plasma GH levels. The effect was dose-dependent, and GH AUC0-24h at 10 and 30 mg/kg p.o. were significantly higher (< 0.05) than vehicle-treated animals.

Conclusion: Anamorelin is a potent ghrelin agonist endowed with significant orexigenic activity demonstrating both an increase of FI and BW after subchronic treatment in rats. Plasma GH levels were increased after a single administration of ANA. These results support the continued investigation of Anamorelin as a potential treatment of cancer cachexia/anorexia.

Disclosure: All authors have declared no conflicts of interest.
Acquired-resistance to EGFR inhibitors may result from the activation of HER3 and/or HER2, which share overlapping the signaling pathways. U-3287 is a fully human anti-HER3 monoclonal antibody that has demonstrated anticancer activity in preclinical models. In a preceding US phase I study, the tolerability of U-3287 was evaluated up to the dose of 20 mg/kg without dose-limiting toxicities (DLTs). In this study, we evaluated the tolerability, pharmacokinetics (PK) and potential antitumor activities of U-3287 in Japanese patients with solid tumors up to the dose of 18 mg/kg.

Methods: Patients received U-3287 at a dose of 9 mg/kg or 18 mg/kg intravenously every 3 weeks (q3w). Tumor response, incidence of anti-U-3287 antibodies (HAHA), and level of soluble HER3 (sHER3) were also evaluated.

Results: Nine patients, 3 at 9 mg/kg and 6 at 18 mg/kg, were enrolled. Five patients were male and median (range) age of 67 (56-69) years. Tumor types were lung (2), colorectal (2), esophageal (2), breast (1), cervical (1), and sarcoma (1). No DLTs were reported. U-3287-related AEs were ALT increase (3 patients), thrombocytopenia, diarrhea, stomatitis, chills, rash, and AST increase (2 each). Plasma disappearance was bi-phasic and terminal half-life at the dose of 18 mg/kg was approximately 9 days. PK profiles were similar to those in the US phase I study. Four patients had best responses of stable disease. All patients tested were negative for HAHA formation. Level of sHER3 unexpectedly increased about four times in all patients. Mean sHER3 concentrations at baseline and day 15 were 3.8 ng/mL and 16.5 ng/mL, respectively. These changes did not correlate with clinical response (at day15 in SD and PD patients: 16.7 ng/mL and 16.9 ng/mL, respectively).

Conclusions: U-3287 was well tolerated up to 18 mg/kg in Japanese patients with solid tumors. This data support a dose regimen of 18 mg/kg q3w in future studies.

Disclosure: All authors have declared no conflicts of interest.

Table: 468P

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Table: 469P

**THE CLINICAL UTILITY OF A CHANGE IN THE ROYAL MARSDEN HOSPITAL PROGNOSTIC SCORE (RMHPS) IN PATIENTS (PTS) PRIOR TO PHASE I CLINICAL TRIAL THERAPY**

C.O. Michal1, M. Ong1, J. Matoe1, A.M. Young1, D. Ormos2, J.E. Ang1, T.R. Mollie3, U. Banerji4, J.S. de Bonoi1, S.B. Kaye1

1Drug Development Unit, Royal Marsden Hospital, Sutton, UNITED KINGDOM, 2DOU/Prostate Unit, Royal Marsden Hospital/HF Foundation Trust, Sutton, UNITED KINGDOM

Background: Previously we developed and validated the RMHPS to aid patient selection for phase I clinical trials. However, its sensitivity in predicting short-term outcome is limited. Here we assessed whether, prior to trial entry, a worsening of RMHPS during screening improves specificity.

Methods: Pts treated in phase I trials between Sep 09-11 at RMH Drug Development Unit were identified from a prospectively-collected database. RMHPS was calculated at 2 distinct timepoints; ≤1 wk prior to start of therapy and at an earlier timepoint ≤8 wk previously. RMHPS of 0-1 and 2-3 were denoted low and high respectively. Pts were divided into 4 groups based on the sequential RMHPS: low-low; low-high; high-low; and high-high. Median overall survival (OS) and time to study withdrawal were estimated by Kaplan-Meier method and prognostic variables compared by multivariate Cox regression analysis.

Results: One hundred and thirty one pts were identified. The most common tumours were colorectal, ovary and breast. Median age and lines of prior chemotherapy was 57y and 2 respectively. 99% of pts had ECOG PS 0/1 at baseline while 8% had distant metastases. Pts were treated on study for a median of 70 days (d), with 74.8% discontinuing for progression, 8.4% for toxicity and 12.2% for other reasons. Study withdrawal <30d was 17.6%. The proportion of pts in RMHPS groups were: low-low (62.6%); low-high (9.2%); high-low (6.1%); and high-high (22.1%). Pts in the low-high group had the worst median OS compared with the low-low, high-high and high-high groups (145 vs 358, 291 and 253d respectively, p < 0.0001). In multivariate analysis, the new RMHPS low-high category conferred significantly worse prognosis (HR 6.53, 95% CI 3.09-13.79) compared to other groups. Deterioration from low-high was 95.3% specific with a positive likelihood ratio of 6.47 for predicting 30-day trial discontinuation.

Conclusions: Deterioration in RMHPS ≤ 8 weeks prior to phase I trial treatment was highly predictive of early trial withdrawal and death, with a median time on study of 28 days. This simple, dual timepoint assessment potentially increases the clinical utility of the validated RMH prognostic model, identifying a specific population who would benefit from earlier trial withdrawal. We therefore recommend a 2nd RMHPS is repeated in pts of uncertain suitability for phase I trials. 1 Olmos, JCO 2012

Disclosure: All authors have declared no conflicts of interest.

**COMPARATIVE PHARMACOKINETICS OF TRASTUZUMAB SUBCUTANEOUS FORMULATION ADMINISTERED USING A PROPRIETARY SINGLE-USE INJECTION DEVICE, OR MANUALLY USING A SYRINGE**

C. Wynne1, D.S. Vaaika1, R.B. Ellis-Pegler2, C. Schwabe1, M. Lehie1, D. Hennizmann1, R. Mangat3, C. Li4, L.A. Hernandez-Baranda5, B.L. Lumi6

1Christchurch Clinical Studies Trust, Christchurch Clinical Studies Trust, Christchurch, NEW ZEALAND, 2Auckland Clinical Studies, Auckland, NEW ZEALAND, 3Clinical Science, F. Hoffmann-La Roche Ltd, Basel, SWITZERLAND, 4Clinical Pharmacology, Genentech Inc, South San Francisco, CA, UNITED STATES OF AMERICA

Background: Intravenous (IV) trastuzumab, alone or with chemotherapy, is the standard of care for HER2-positive breast cancer and metastatic gastric cancer. The
A PHASE I, DOSE-ESCALATION STUDY OF MGCD265, A MULTITARGETED ORAL TYROSINE KINASE INHIBITOR, FOR TREATMENT OF ADVANCED SOLID TUMORS


1Division of Hematology and Oncology, Duke University Medical Center, Durham, NC, UNITED STATES OF AMERICA, 2BCCA Vancouver Cancer Centre, University of British Columbia Division of Medical Oncology, Vancouver, BC, CANADA, 3Clinical Affairs, Methylgene, Inc, Montreal, QC, CANADA, 4Oncology, Dana-Farber Cancer Institute, Boston, MA, UNITED STATES OF AMERICA

Background: MGCD265 is a multikinase inhibitor with activity against Met, VEGFR family of receptors, PDGFRs, EGFR, and Akt. The primary goal of the study was to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of MGCD265. The secondary goal was to evaluate pharmacokinetics, pharmacodynamics, and antitumor activity of MGCD265.

Methods: Patients with advanced malignancies were enrolled in a phase I, open-label, dose-escalation study. Oral MGCD265 was administered daily over a 3-wk cycle, up to 5 cycles. Dose escalation was performed using a 3+3 design, starting at a dose of 24 mg/m2 once daily. Dose-limiting toxicities were defined as any grade 3 to 5 toxicity occurring during treatment with MGCD265. PK and safety were assessed using single-dose and continuous administration.

Results: A total of 54 patients were enrolled, with 28 patients evaluable for safety and 25 evaluable for efficacy. The MTD was determined to be 250 mg/m2 administered 3 times daily for 21 days. The most common DLTs were fatigue, diarrhea, and lipase elevation, pituitary hemorrhage (all grade 3) and hypertension (grade 2, one patient). All patients had a measurable disease, and 45% of patients achieved a clinical benefit. Stable disease (SD) was noted in several heavily pretreated patients.

Conclusions: This study demonstrated the safety of MGCD265 in patients with advanced malignancies. There are encouraging early signs of efficacy, with prolonged stable disease noted in several heavily pretreated patients. SD was noted in 3 of 5 patients with hepatitis B. SD was noted in 8 of 13 patients with metastatic melanoma. SD was noted in 3 of 7 patients with glioblastoma.

TREATMENT OF CHEMOTHERAPY-INDUCED ORAL MUCOSISIS BY SILMYLAN

T.S. Allani

Pharmacology and Toxicology, Hawler Medical University, Erbil, IRAQ

Background: Oral mucositis is a common and severe complication of head and neck radiation therapy. Silmylan is a polypHENolic flavonoid extracted from the milk thistle exhibits a strong antioxidant activity, and anti-inflammatory effects. The efficacy for the treatment was assessed in comparison with indomethacin.

Methods: A prospective, randomized, double-blind, placebo controlled study was conducted in 65 of chemotherapy-induced oral mucositis patients; indomethacin 25 mg, placebo daily for 14 days, radiation technique and dose were similar. The oral mucositis was assessed weekly according to OMAS and WHO scale, pain related to oral mucositis was scored subjectively by visual analog scale.

Results: Patients’ characteristics showed no significant differences between tested groups. Statistically significant showed in; lower OMAs value at the time of using Silmylan, and lower mean time to healing of oral mucositis in Silmylan treated compared to Indomethacin treated and placebo groups.

Conclusions: Silmylan could interrupt or block the mucositis process at multiple targets that protect the mucosa and promote healing of chemotherapy-induced mucositis by reducing the incidence, blocking the progression, and anti-inflammatory actions. Key words: Silmylan, chemotherapy-induced mucositis, IL-1β, lepin.

Disclosure: All authors have declared no conflicts of interest.
PHASE 1 STUDY OF THE SELECTIVE AKT INHIBITOR MK-2206 IN JAPANESE PATIENTS WITH ADvanced SOLID TUMORS

Y. Tanabe1, T. Doi2, K. Tamura3, K. Yonemori4, M. Kocia5, N. Fuse5, H. Band6, Y. Maeda6, T. Shimamoto6, A. Ohtsu6

1Breast and Medical Oncology Division, National Cancer Center Hospital, Tokyo, JAPAN, 2Gastrointestinal & GI Oncology Department, National Cancer Center Hospital East, Chiba, JAPAN, 3Japan Development, MSD K.K., Tokyo, JAPAN, 4Research Center for Innovative Oncology, National Cancer Center Hospital East, Chiba, JAPAN

Background: The AKT pathway, which mediates cell proliferation, survival, and angiogenesis, is commonly dysregulated in cancer. MK-2206 is an orally active, allosteric AKT 1/2 inhibitor with wide preclinical activity. This open-label, nonrandomized study investigated the safety, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of MK-2206 in Japanese patients with solid tumors who were refractory to standard therapy.

Methods: Patients received once every other day (qod) or once-weekly (qw) doses of MK-2206 in 28-day treatment cycles, with a 1-week holiday following Cycle 1. Dose-limiting toxicities (DLTs) were evaluated during Cycle 1, with cohorts of 3, 6, or 9 patients, depending on the dose studied and adverse events (AEs) experienced by patients. Overall antitumor activity was assessed at designated time points every other treatment cycle after initial screening, following RECIST guidelines.

Results: Treated patients (N = 24; male/female: 10/14; median age: 57 yrs; ECOG PS 0-2) received 1.25 mg qw (n = 12) and 1.2 mg qod (n = 12) and 1.35 mg qw (n = 9). Grade 3 rash was the DLT at both 60 mg qod (1 of 9 patients) and 200 mg qw (3 of 9 patients). Common reversible drug-related toxicities included rash (83.3%), stomatitis (58.3%), pyrexia (58.3%), and hyperglycemia (54.2%). MK-2206 terminal half-life ranged from non-Japanese patients (69-80 h vs 46h), but Cmax, AUC, and Ctrough were generally higher in Japanese patients (1.5–1.7-fold).

Conclusion: Dose-limiting toxicities (DLTs) were evaluated during Cycle 1, with cohorts of 3, 6, or 9 patients, depending on the dose studied and adverse events (AEs) experienced by patients. Overall antitumor activity was assessed at designated time points every other treatment cycle after initial screening, following RECIST guidelines.

Disclosure: All authors have declared no conflicts of interest.

TRASTUZUMAB-INDUCED EARLY CARDIAC DYSFUNCTION ASSESSED BY SPECKLE TRACKING ECHOGRAPHY: CORRELATION WITH CHRONIC INFLAMMATION AND OXIDATIVE STRESS MARKERS

M. Dessi1, G. Mantovani1, C. Mached1, L. Orgiano1, P. Alessandra2, C. Caddeo1, G. Antonini1, R. Serpe1, G. Mercurio1

1Department of Medical Oncology, University of Cagliari, Cagliari, ITALY, 2Department of Cardiovascular Diseases, University of Cagliari, Cagliari, ITALY

Background: Trastuzumab (TZM) was shown to be very effective in patients with breast cancer overexpressing HER-2 in the neoadjuvant, adjuvant and metastatic setting. It has a mild cardiac toxicity which may increase when administered in combination with anthracyclines. The “Speckle Tracking Echocardiography” (STE), able to assess cardiac mechanics (cardiac torsion movements and the global, circumferential, radial and longitudinal Strain (S) and Strain Rate (SR)), and identify at an early stage left ventricular dysfunction, was used for cardiac monitoring. The present study aimed to assess the STE changes induced by TZM and correlate them with changes of chronic inflammation and oxidative stress markers.

Methods: A phase IV, prospective, non-randomized study was designed: planned sample size 60 patients. Inclusion criteria: 18-70 yo women with HER-2 + ve breast cancer receiving TZM, LVEF ≥55%; ECOG PS score 0-2, no history of cardiac disease. The STE parameters (global, circumferential, radial and longitudinal S and SR) and chronic inflammation (IL-6 and TNF-α) oxidative stress (reactive oxygen species and glutathione peroxidase) markers were assessed at baseline, after each three-weekly TZM administration, up to the 8th TZM dose.

Results: At September 2011, 30 patients (mean ± SD age 53 ± 10 y) were enrolled and completed the study. A significant reduction of the peak of radial and circumferential SR (p < 0.01 and p < 0.005) as first sign of systolic dysfunction was observed at the 3rd TZM dose. A significant reduction of the peak of longitudinal SR (p < 0.01) was observed at the 4th TZM dose. As for laboratory parameters, TNF-α increased significantly at the 2nd and 3rd TZM dose, whilst the remaining laboratory parameters did not change significantly.

Conclusions: These preliminary results suggest that TZM treatment induces an early preclinical cardiac systolic dysfunction which correlates with an increase of TNF-α. This study is in progress to reach a planned sample size, monitor patients for an adequate follow-up time and eventually select patients candidates for an effective cardioprotective treatment. This study was Funded by AIRC - project number 8679.

Disclosure: All authors have declared no conflicts of interest.

LIPOSOMAL PRODRUG OF MITOMYCIN C WITH THIOLYTIC ACTIVATION: IMPROVED THERAPEUTIC INDEX OVER MITOMYCIN C IN PRECLINICAL STUDIES

A.A. Gabizon1, Y. Amitay2, H. Shmeida3, S. Zalipsky3

1Oncology, Shaare Zedek Medical Center, Jerusalem, ISRAEL, 2Experimental Oncology, Lipomedix Pharmaceuticals Inc., Jerusalem, ISRAEL, 3Experimental Oncology, Shaare Zedek Medical Center, Jerusalem, ISRAEL

We have developed a formulation of a mitomycin-C lipid-based prodrug (MLP) in pegylated liposomes (PL) in which MLP is activated by thiolic cleavage to mitomycin C (MMC). PL-MLP (PROMITIL™) was previously reported to have reduced toxicity and an improved therapeutic index as compared to MMC in human and mouse tumor models. In the following studies, we examined the pharmacokinetics, toxicity, and therapeutic activity of scaled-up batches of PL-MLP (prepared under the same protocols and clinical batches) in rodent and minipig species. PL-MLP is a liquid suspension of vesicles of ~100 nm diameter with MLP entrapped in the lipid bilayer at 10% molar ratio. Pharmacokinetic studies revealed major (>100-fold) differences in Cmax, AUC, plasma clearance and volume of distribution between MMC (i.v. 3 mg/kg) and PL-MLP (1 mg/kg in MMC-equivalents). While MMC is cleared from blood within minutes and extensively distributed to peripheral tissues, PL-MLP is cleared very slowly with a
mono-exponential half-life of ~15 hours in rats and has a limited volume distribution roughly equivalent to the blood volume. In rat toxicity studies in rats, the MTD of PL-MLP was two to three-fold higher than that of MMC in mg-equivalent doses. Therapeutic studies in BALB/c mice inoculated i.p. with C26 tumor cells show a clear survival advantage for treatment with PL-MLP over free MMC at all dose levels tested, whether treatment was administered by the i.p. or by the i.t. route. In the porcine model, no acute infusion reaction to i.v. administration of PL-MLP was observed. PL-MLP appears to be a stable formulation with minimal prodrg prodrug activation and release of MMC in circulation, yet significant antitumor activity, indicating in vivo prodrg activation in tumors. PL-MLP may represent an effective therapeutic tool in a broad spectrum of malignancies, including multi-drug resistant tumors, with improved safety over free MMC, and is due to be tested in a human phase 1 study in 2012.

Disclosure: A.A. Gabizon: I am the founder and Chief Scientist of Lipomedix Inc., a company with a vested interest in the product discussed in this presentation. Y. Amitay: Paid employee of Lipomedix, a product of which is discussed here. All other authors have declared no conflicts of interest.

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PHASE I SAFETY AND TOLERABILITY OF ONCE DAILY ORAL AFINITABIN (A) (BIBW 2992) IN COMBINATION WITH GEMCITABINE (G) IN PATIENTS (PTS) WITH ADVANCED SOLID TUMOURS

S. Zanetta1, J. Bennouna2, N. Isambert3, H. De Mont-Serrat4, I. Tschoepe4, P. Squiban5, J. Delord5

1Oncology Department, Centre Georges François Leclerc, Dijon, FRANCE
2Oncology/Pneumology, Institut de Cancérologie de l’Ouest-site René Gauducheau, Nantes, FRANCE
3Medical Oncology, Centre Georges François Leclerc, Dijon, FRANCE
4Medical Affairs, Boehringer Ingelheim, Reims, FRANCE
5Clinical Research Unit, Institut Claudius Regaud, Toulouse Cedex, FRANCE

Background: A is an orally bioavailable, irreversible, ErBB Family Blocker. This open label, Phase I, dose escalation trial investigated the safety, tolerability and pharmacokinetics of A in two parallel dose cohort expansion parts, in combination with either G (Part A) or docetaxel (Part B) in pts with relapsed or refractory solid tumours. Preliminary results from Part A are presented here.

Methods: Eligible pts (confirmed diagnosis of advanced solid tumours, Eastern Cooperative Oncology Group Performance Status 0–1) received once-daily, oral dosing of A in combination with G, given intravenously at Day 1 and at Day 8 of every 3 week cycle. Dosing of A started on Day 2 of Cycle 1. The primary objective was to establish the maximum tolerated dose (MTD) based on the occurrence of dose limiting toxicities (DLTs) observed in Cycle 1. Dose escalation was performed with cohorts of 3–6 pts using a 3+3 design. Initial starting dose level was 30 mg/day and G 1000 mg/m², escalating up to 50 mg/day and G 1250 mg/m², until the MTD was reached, and followed by a pharmacokinetic expansion cohort of 12 pts at the MTD level.

Results: Nineteen pts were treated in the escalation part of the study with the following baseline characteristics: mean age (53.7 years), female (63.2%) and number of prior chemotherapies (following baseline characteristics: mean age (53.7 years), female (63.2%) and number one pt out of six receiving A 30 mg and G 1250 mg/m², and in two pts at a dose level of A 40 mg/day and G 1000 mg/m², escalating up to A 50 mg/day and G 1250 mg/m², until the MTD was reached, and followed by a pharmacokinetic expansion cohort of 12 pts at the MTD level. Dosing of A started on Day 2 of Cycle 1. Dose escalation was performed with cohorts of 3–6 pts using a 3+3 design. Initial starting dose level was 30 mg/day and G 1000 mg/m², escalating up to 50 mg/day and G 1250 mg/m², until the MTD was reached, and followed by a pharmacokinetic expansion cohort of 12 pts at the MTD level.

Results: Nineteen pts were treated in the escalation part of the study with the following baseline characteristics: mean age (53.7 years), female (63.2%) and number of prior chemotherapies (≤2–36%); ≥74.7%. In Cycle 1, DLTs were experienced by one pt out of six receiving A 30 mg and G 1250 mg/m², and in two pts at a dose level of A 40 mg/day and G 1250 mg/m². Adverse events (AEs) observed in most pts were diarrhea (89.5%) and rash (63.2%). MTD was exceeded at a dose level of A 40 mg/day and G 1250 mg/m². An intermediate dose level of A 40 mg/day and G 1000 mg/m² is currently under evaluation with two pts enrolled to date.

Conclusions: In pts with relapsed or refractory advanced solid tumours, the combination of A with G is well tolerated, with manageable AEs. Dose finding is considered to ensure generalisability of results and equality of access.

Disclosure: All authors have declared no conflicts of interest.

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SINGLE INSTITUTION PHASE I TRIAL OF THE NOVEL COMPOUND FIRST-IN-CLASS PDM08 IN REFRACTORY SOLID TUMOURS (NCT01380249)

J. Barruso1, I. Soria2, V. Moreno1, M. Coronado1, I. Galicia1, M.A. Figueroedo1, J. Fraser3, J. Feliu4, A. Carcass4, J.L. Subiza5

1Oncology Phase I Unit, La Paz University Hospital, Madrid, SPAIN
2Immunology Department, San Carlos Hospital, Madrid, SPAIN
3Nuclear Medicine, La Paz University Hospital, Madrid, SPAIN
4UCIC, La Paz University Hospital, Madrid, SPAIN
5Pharmaceutical, La Paz University Hospital, Madrid, SPAIN
6Medical Oncology, La Paz University Hospital, Madrid, SPAIN

Background: PDM08 is a synthetic derivative of the pyrroglutamic acid with anti tumor effect in different murine cancer models. The absence of direct effect on tumour cells and the antitumor activity found in immunocompetent models indicates an immune response mediated mechanism. The aim was to assess the tolerability and safety profile of PDM08.

Methods: PDM08 was administered twice a week for four-week cycles. An accelerated dose escalation phase was chosen with cohorts of 2 pts (pts) that had the possibility of escalating to the next dose level if no grade ≥2 toxicity and no progressive disease were observed. An expansion cohort was planned at the MTD or the optimal biological dose (OBD). Extensive pharmacokinetic and pharmacodynamic (PD) data were collected. Preliminary efficacy was evaluated by PET-CT.

Results: Since July 2011, 17 patients (pts) were recruited into 8 different dose levels (4pts were escalated) ranged from 0.560 mg to 56 mg. Pt characteristics were: males 52.9%, Median age: 68 (28–76), ECOG 0: 64.7%. Median of previous treatments was 3 ranged 2 to 5. 3 pts presented G1 headache. No DLTs were found. The best outcome was stable disease (SD) for 5 pts (4 colonicar and 1 endometrial), one being stable for 12 weeks, 14 weeks and remains stable until 21 weeks. 12.9% of the patients evaluated using PET-CT showed a reduction in the maximum Standard Uptake Value (SUV) of 18-FDG. A pooled analysis of PD data from patients with the best response showed a statistically significant increase in serum levels of IL-17A, IL-13, IL-4, IL-5, TNFα, IL-22 and IL-1p (p < 0.05) from baseline.

Conclusions: We show for the first time that social deprivation affects referral to an early phase cancer trials unit. The least deprived patients are almost twice as likely to be referred to the trial unit compared with the most deprived. This may be because patients in the higher deprivation quintiles are less suitable for a trial, for example due to comorbidities, or because of inequalities that could be addressed with patient or referrer education.

Disclosure: All authors have declared no conflicts of interest.

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THE IMPACT OF PATIENT SOCIO-ECONOMIC STATUS ON ACCESS TO EARLY PHASE CANCER TRIALS

A. Mohd Noor1, S. Vizor2, B. McLennan2, D. Sarker2, H. Moller1, J. Spicer1, S. Zanetta1, J. Bennouna2, N. Isambert3, H. De Mont-Serrat4

1School of Medicine, Cancer Research Division, King’s College London, London, UNITED KINGDOM
2Medical Oncology, Guy’s and St Thomas NHS Foundation Trust, London, UNITED KINGDOM

Background: Little is known about the influence of sociodemographic factors on patient’s access to early phase cancer trials. The toxicity and efficacy of cancer drugs can vary according to sociodemographic factors, and these differences should be considered to ensure generalisability of results and equality of access.

Method: We conducted a review of patients referred to the early phase trials unit at our centre in the five years to 2012. Electronic records were studied for demographic and cancer-specific data. Socio-economic status was defined by the Index of Multiple Deprivation (IMD 1 - least deprived, 5 - most deprived) recorded for the regional Cancer Registry population according to postal code. Multivariate analysis (adjusting for gender, age and tumour type) was performed comparing 10,784 incident cancer cases in south east London with the patients referred to our unit, and with those enrolled in a trial.

Results: 410 patients (195 female) were referred for consideration of an early phase trial, with a median age of 62 years (range: 22-86). Ethnicity was 74% white. Univariate analysis of ethnicity suggested the non-white population was less likely to be recruited (OR 0.48; 95% CI 0.26-0.88), but this relationship was lost with adjustment for age, gender, cancer type and IMD. Multivariate analysis showed that referral was less likely for patients in the more deprived quintiles (IMD 5: OR 0.53; 95% CI 0.38-0.74). However, once referred to the unit, enrollment in a trial was not affected by IMD (IMD 5: OR 0.81; 95% CI 0.40-1.63).

Conclusion: We show for the first time that social deprivation affects referral to an early phase cancer trials unit. The least deprived patients are almost twice as likely to be referred to the trial unit compared with the most deprived. This may be because patients in the higher deprivation quintiles are less suitable for a trial, for example due to comorbidities, or because of inequalities that could be addressed with patient or referrer education.

Disclosure: All authors have declared no conflicts of interest.

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TESETAXEL: ANALYSIS OF TWO DOSING SCHEDULES (ONCE WEEKLY VS. EVERY 3 WEEKS) USING A NOVEL ORAL TAXANE

M. Beeram1, K. Papadopoulos1, A.W. Tolcher1, D. Rasco1, T. Cousin2, L. Itri2, L. Amanat1

1Developmental Therapeutics, The START Center for Cancer Care, San Antonio, TX, UNITED STATES OF AMERICA
2Developmental Therapeutics, Genta Incorporated, Berkeley Heights, NJ, UNITED STATES OF AMERICA

Background: Tesetaxel (TST) is a novel oral taxane that is active in taxane-resistant models, is not a substrate for p-glycoprotein, and has limited preclinical neuropathy.

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TST is active in breast and gastric cancers when administered orally once every 3 weeks (Q3W). Taxanes may have schedule-related activity and adverse reactions. We conducted a dose-ranging study comparing the safety, efficacy, and pharmacokinetics (PK) using two schedules.

Methods: Patients (pts) had solid tumors, ECOG PS ≤ 2, and adequate organ function. In Schedule 1, TST was given once every 3 weeks from 18 to 27 mg/m², escalated in increments of 3 mg/m² to determine the MTD. In Schedule 2, TST was given once weekly for 3 weeks every 28 days, beginning at a total flat dose of 25 mg/m² cycle with increases up to 75 mg/m². Dosing was then converted to a weight-based regimen at weekly doses of 12.5, 15, and 17.5 mg/m² (i.e. total per cycle dose up to 52.5 mg/m²). 3 pts were treated at each dose level until the MTD.

Results: 27 pts were treated on Schedule 1. The MTD was 27 mg/m² and neutropenia was dose-limiting. One pt with nasopharyngeal carcinoma had a PR and 11 pts had stable disease, including several with taxane-resistant breast cancer. Cmax and AUC increased with increasing dose; however, the differences across the dose range examined were modest. No dose-related differences were apparent for other PK parameters. On schedule 2, 26 pts were treated in 8 dose cohorts. The MTD was 15 mg/m² (total cycle dose, 45 mg/m²). Constitutional symptoms (fatigue and anorexia) proved dose-limiting at 17.5 mg/m²/ wk. Only 1 pt had Grade 3 neutropenia. One pt with MBC (who had progressed after 2 prior taxane regimens) had a PR; 1 pt with prostate cancer had prolonged PSA reduction. PK analyses showed low but progressive increases in trough TST concentrations (0.4-4.6 nmol/L) 7 days after each succeeding dose, consistent with the prolonged T1/2 of this drug (~180 hrs). There was no substantial drug accumulation over multiple cycles.

Conclusions: Tsetexel administered once every 3 weeks is active in pts with advanced gastric, breast and other solid tumors, including pts who have received prior taxanes. The weekly regimen is currently being evaluated in Phase 2.

Disclosure: A.W. Tolcher: Corporate sponsored research. T. Cousin: Employee of Genta Inc. L. Itri: Employee of Genta Inc. All other authors have declared no conflicts of interest.

PHASE 1 STUDY OF BPR 21510 (UBIDECARANO) IN ADVANCED SOLID TUMORS: UPDATED ANALYSIS OF A NOVEL TREATMENT WITH PROMISING ACTIVITY

S.P. Chawla1, A. Hendler1, V.S. Chua2, D. Quon3, V. Narasimhan4, V. Lavinski5, J. McCook2, R. Sarangarajan3, P. Songi6, N. Narain3
1Clinical Research, Sarcoma Oncology Center, Los Angeles, CA, UNITED STATES OF AMERICA, 2Research, MutualHealth LLC, Newport Beach, CA, UNITED STATES OF AMERICA, 3Clinical Research, Berg Pharma, Natick, MA, UNITED STATES OF AMERICA

Background: BPM is a novel small molecule that targets aerobic glycolytic pathway, re-capitulates BCL-2 mediated apoptosis and disrupts tumor angiogenesis.

Methods: A standard 3 + 3, dose-escalation study was designed with primary objectives of dose finding (MTD), toxicity and pharmacokinetic correlates (PK). Secondary objectives included response, response duration and clinical benefit.

Results: 42 patients with advanced solid tumors (refractory to standard therapy) were enrolled in 8 dose cohorts (5.6 mg/kg to 104.3 mg/kg). The trial is still ongoing as the MTD has yet to be reached. 31 (74%) patients completed at least one cycle and are evaluable for efficacy and clinical benefit. Median number of treatment cycles administered were 2 (range, 1-7) with median duration of 14 weeks (4-52 weeks). Of the 31 evaluable patients, 23 had grade I and 14 patients grade II elevation of INR without any significant clinical bleeding. Normalization of INR was observed in all the patients with vitamin K supplementation. Nine patients (29.0%) experienced mild headache during the first week of therapy, relieved with acetaminophen. There was no grade 3/4 treatment related toxicity. The pharmacokinetics of BPM was noted to be linear. The values for t1/2 ranged from 2.18 to 13.3 hr, with little or no dependence of 11/2 on dose. Objective tumor responses were noted at the dose of 58.6mg/kg with 1 complete response (myxoid liposarcoma) and 1 minor response (fibrosarcoma). With a median follow up of 14 weeks (4-52 weeks) clinical stabilization was observed in 61% of the patients.

Conclusions: Interim data from this phase 1 study indicate that BPM is well tolerated with no dose limiting toxicity to date. There was no grade III/IV toxicity. Grade I/II toxicity included elevation of INR (without significant clinical bleeding) and mild headache. One patient had partial and one patient had minor response with stabilization of the disease in the majority. The current trial is in progress and there is strong rationale for further development of this unique compound which lacks the toxicity associated with chemotherapy.

Disclosure: S.P. Chawla: I am an adviser to Berg Pharma LLC, Natick, MA; USA. A. Hendler: I am an adviser to Berg Pharma LLC, Natick, MA; USA. V.S. Chua: I am an adviser to Berg Pharma LLC, Natick, MA; USA. D. Quon: I am an adviser to Berg Pharma LLC, Natick, MA; USA. Y. Lavinski: I am an employee of Berg Pharma LLC, Natick, MA; USA. J. McCook: I am a member of Berg Pharma LLC, Natick, MA; USA. R. Sarangarajan: I am an employee of Berg Pharma LLC, Natick, MA; USA. P. Songi: I am an employee of Berg Pharma LLC, Natick, MA; USA. N. Narain: I am an employee of Berg Pharma LLC, Natick, MA; USA. All other authors have declared no conflicts of interest.

LURBIEXECITEDIN (PM01183) IN COMBINATION WITH GEMCITABINE (GEM), PRELIMINARY RESULTS OF AN ONGOING PHASE IB STUDY

E. Calvo1, L. Are2, M. Foster3, I. López Calderer0, A. Cubillo4, A. Velasco5, V. Borí6, D. Wikins7, A. Soto-Matos8, S. Slyzdergeman9
1Oncoology, Hospital Sanchinarro/START, Madrid, SPAIN, 2Oncoology Service, Hospital Virgen del Rocío, Seville, SPAIN, 3Oncoology, University College of London Hospital, London, UNITED KINGDOM, 4Clinical Operations, PharmaMar, Colmenar Viejo, Madrid, SPAIN, 5Clinical, PharmaMar, Colmenar Viejo, Madrid, SPAIN

Background: PM01183 is a new anticancer agent. It exerts a wide anti-tumour activity through minor groove DNA-binding. Pre-clinical evidence of synergism has been observed in combination with GEM. Single agent PM01183 has clinical activity in pancreatic and platinum-resistant ovarian cancer. Reversible neutropenia and high emetogenic potential are the main single agent toxicity.

Methods: Informed and consented adult patients (pts) were included. The starting dose was PM01183 2.5 mg + GEM 800 mg/m2 on Days 1 and 8 q3wk. The dose was escalated in cohorts of 3-6 pts aiming to define the maximum tolerated dose (MTD). The highest dose reached with less than 1/3 of at least 9 pts having dose-limiting toxicities (DLTs) in Cycle 1 will be the recommended dose (RD). Age was restricted up to 75 years, PS-ECOG 0-1, have adequate major organ function and no more than 2 prior chemotherapy lines. Prior adjuvant GEM was allowed if relapse occurred >6 months.

Results: As of May 2012, 23 pts were treated across 4 dose levels (DL), 8 (35%) patients, median age was 60 (37-72). NSCLC (n = 12; 52%), pancreatic/biliary tract (n = 5; 22%) and gynaecological (n = 4; 17%) were the most frequent tumour types. Dose escalation proceeded until the MTD was reached: DL 4 PM01183 3.5 mg + GEM 1000 mg/m2. Three pts experienced DLTs: Day 8 omission (neutropenia), febrile neutropenia, neutropenic infection/sepsis and grade 4 thrombocytopenia. One fatal sepsis occurred at the MTD. DL 3 (PM01183 3.5 mg + GEM 800 mg/m2) expansion as possible RD is ongoing. PM01183/GEM seems well tolerated at doses below the MTD. Other toxicities in addition to reversible myelosuppression were: mild nausea/vomiting, asymptomatic LFTs increases, pneumonia, anaemia or fatigue.

Evidence of activity includes: 2/12 partial (PR) + 1/12 complete response (CR) in NSCLC (2 pts are ongoing after 13+ and 10+ cycles) and 1/4 PR in gynecological. No pharmacokinetic interaction was observed.
Conclusions: The combination of PM01183 and GEM seems feasible with an acceptable safety profile below the MTD: PM01183 3.5 mg·GEM 1000 mg/m². RD cohort expansion is currently ongoing. The combination is showing promising anti-tumour activity. Updated results will be presented in the meeting.


E. Raymond

Methods:

Limiting. We conducted a phase I intersubject dose-escalation study to evaluate safety and PK in Japanese pts.

Disclosure:

All authors have declared no conflicts of interest.

IX152 doi:10.1093/annonc/mds395

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Results: Twelve pts (9 men, 3 women; age 39-74 yr) were enrolled (3 each in the 24 and 31 mg/m² cohorts and 6 in the 27 mg/m² cohort). Most pts were heavily pretreated; the median number of prior chemotherapy regimens was 4. Neutropenia grade 2 or grade 3 occurred in 1 pt in the 24 mg/m² and 27 mg/m² cohorts and 2 pts in the 31 mg/m² cohort. DLT (lefe neutropenia) was observed in 1 pt at the 31 mg/m² dose. Mean PK data (see table) were similar in Western and Japanese pts, with an expected dose-dependent increase in exposure.

Dose level 

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Cmax (µg/L)</th>
<th>Tmax (h)</th>
<th>AUC(0-168 h) (µg·h/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 mg/m²</td>
<td>Western (11)</td>
<td>29.7 ± 2.5</td>
<td>594 ± 101</td>
</tr>
<tr>
<td></td>
<td>Japanese (3)</td>
<td>29.0 ± 2.7</td>
<td>658 ± 101</td>
</tr>
<tr>
<td>27 mg/m²</td>
<td>Western (7)</td>
<td>31.2 ± 2.1</td>
<td>869 ± 101</td>
</tr>
<tr>
<td></td>
<td>Japanese (3)</td>
<td>46.6 ± 4.7</td>
<td>818 ± 101</td>
</tr>
<tr>
<td>31 mg/m²</td>
<td>Japanese (3)</td>
<td>57.0 ± 2.0</td>
<td>1036 ± 101</td>
</tr>
</tbody>
</table>

† Results of PK analyses for last 3 pts enrolled not yet available * Dose not studied in Western pts

Conclusion: This study indicates that tolerability and PK of tesetaxel is similar in Western and Japanese pts. Final data will be presented.

Disclosure: T. Cousin: I am an employee of Genta Incorporated, the company that is developing tesetaxel. All other authors have declared no conflicts of interest.
Treatment-induced shedding of circulating sTNF-R1 or R2 may block drug effects. The impact of this counterregulatory mechanism on NGR−hTNF activity was assessed in two phase I trials.

Methods: Sixty patients (pts) with refractory solid tumors (median age, 60 years; M/F 44/16; PS 0/1-2/3/5; median prior treatment lines, 3) received NGR−hTNF every 3 weeks (q3w) given at low doses (0.2 to 1.6 µg/m² n = 14) or high doses (60 to 325 µg/m² n = 46). Tumor assessment by RECIST was done q4w until progressive disease (PD). We assessed the associations between baseline normalized plasma levels of sTNF-R2 after 1st treatment cycle and clinical outcomes in terms of disease control rate (DCR, rate of pts without PD after 6 weeks) and progression-free survival (PFS).

Results: The levels of sTNF-R2 peaked significantly higher than sTNF-R1 (p < 0.001) and increased dose proportionally (p = 0.003), with a median distribution value of 8.6 ng/mL (interquartile range 4.5-10.7). Using the 25th percentile as cut-off values for the sTNF-R2 levels were dichotomized in low (<4.5 ng/mL n = 15) or high (>4.5 ng/mL n = 45). Mean number of cycles was 5.5 (range 1-9) and 2.5 (1-6) in pts with low or high levels, respectively. By univariate analyses, low sTNF-R2 levels were significantly associated with increased DCR (odds ratio, OR 3.8 p = 0.04) and improved PFS (hazard ratio, HR 0.29 p = 0.002). DCR was 58% (95% CI 32-81) and 26% (16-41) in pts with low or high levels, respectively. Six-month PFS rates were 29% in pts with low levels and 0% in pts with high levels (log-rank p = 0.0008).

Conclusions: Early treatment-induced changes in sTNF-R2 shedding may identify pts who have a greater likelihood of benefit from NGR−hTNF.

Disclosure: A. Lambiase: Employment - MolMed. C. Bordignon: Employment - MolMed. All other authors have declared no conflicts of interest.

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FOOD EFFECT STUDY OF THE INVESTIGATIONAL AURORA A KINASE (AAK) INHIBITOR MLN8237 (ALISERTIB) IN PATIENTS WITH ADVANCED SOLID TUMORS

G.S. Falchook1, X. Zhou2, L.S. Rosen3, K. Venkatakrishnan4, R. Kurzrock1, D. Mahalingam1, J. Goldman1, J. Jung1, C. Michy5, J. Sarantopoulos1

1Investigational Cancer Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, TX, UNITED STATES OF AMERICA, 2Clinical Pharmacology, Millennium Pharmaceuticals, Inc., Cambridge, MA, UNITED STATES OF AMERICA, 3Oncology, Premiere Oncology, Santa Monica, CA, UNITED STATES OF AMERICA, 4Oncology, Institute for Drug Development, Cancer Therapy and Research Center at University of Texas Health Science Center San Antonio, San Antonio, TX, UNITED STATES OF AMERICA, 5Department of Biostatistics and Epidemiology, Institut Gustave Roussy, Villejuif, FRANCE

Background: MLN8237 (alisertib) is an investigational, orally available, selective AAK inhibitor currently in clinical development for multiple oncology indications. The recommended phase 2 dose is 50 mg twice daily for 7 d in a 21-d cycle. This study was conducted to characterize the effects of food on single-dose pharmacokinetics (PK) of MLN8237 in pts with advanced solid tumors.

Methods: Eligible pts were aged ≥18 y and had ECOG PS 0-1. Following overnight fasting for at least 10 h, pts received a single 50 mg dose of MLN8237 (enteric-coated tablet) under either fasted or fed conditions with a standard high-fat meal using a 2-cycle, 2-way crossover design. PK samples were collected in Cycles 1 and 2 pre-dose and following Day 1 dosing up to 48 h post-Day 1 dose. Ratio of geometric mean Cmax and AUC0-last under fed conditions in reference to those under fasted conditions was calculated and the associated 90% CI were estimated using analysis of variances. Additional endpoints were safety and response.

Results: 24 pts were enrolled: 33% male, 96% white, median age 58 y, and mean weight 64 kg. 14 pts were PK-evaluable (10 pts not PK-evaluable due to insufficient data). Following a single oral dose of MLN8237, median Tmax was 6 and 3 h for fed and fasted treatment, respectively. The geometric mean of AUC0-last following dose under fed conditions was 106% of that under fasted conditions (90% CI 82%, 137%). The geometric mean of Cmax under fed conditions was 83% of that under fasted conditions (90% CI 66%, 106%). Following multiple dose administration, 23 (96%) pts had a drug-related adverse event (AE). Most common drug-related grade 3/4 AEs were neutropenia (50%), leukopenia (38%), and thrombocytopenia (21%). 3 pts had drug-related serious AEs. One pt died (non-drug-related respiratory arrest). Stable disease was achieved in 12 pts, including 1 pt with melanoma who received 11 cycles.

Conclusions: Systemic exposures achieved following a single 50 mg dose of MLN8237 administered following a high-fat meal are similar to those observed in the fasted state. These data support the conclusion that MLN8237 may be administered without regard for the timing of meals in future clinical studies.


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CLINICAL EVALUATION OF DENDRITIC CELL BASED VACCINES PULSED WITH WT1 AND/OR MUC1 FOR PATIENTS WITH ADVANCED OR RECURRENT CANCERS

S. Tautjani1, M. Tani2, Y. Yonemitsu3

1Department of Translational Medicine, National Center for Global Health and Medicine, Tokyo, JAPAN, 2Department of Medical Oncology, Fukuoka Imam Clinic, Fukuoka, JAPAN, 3R&D Laboratory for Innovative Biotherapeutics, Kyushu University, Fukuoka, JAPAN

Background: Dendritic cell (DC)-based vaccines have been expected as one of new therapeutic approaches to treat cancer patients; however, their clinical outcome is not fully elucidated. We here report a single center retrospective analysis studying the survival of patients with various cancers.

Patients and methods: DC-based vaccines pulsed with WT1 and/or MUC1 peptides has been carried out in 180 patients with advanced or recurrent cancers between September 2009 and September 2011. Previous standard chemotherapy was done in most patients and another chemotherapy was given with DC-based therapy. Intradermal injection of 1 x 107 mature DCs was repeated biweekly. After 1 course of treatment (7 times of injection), clinical efficacy was evaluated with RECIST criteria or tumor markers.

Results: In 180 patients, 119 patients completed 1 course treatment. Patient with 0-1 levels of performance status occupied 93% of 119 patients. One-year survival rate of the 119 patients was 57.6% and did not reach to MST. One-year survival rates were 54% in lung cancer (n = 14), 35% in pancreas cancer (n = 14), 100% in colon cancer (n = 9), 50% in ovarian cancer (n = 9), 83% in breast cancer (n = 7) and 86% in gastric cancer (n = 5). In 20 patients with more than 1-year follow-up period and definite assessment of clinical response, 4 (20%) CR, 4 (20%) PR, 9 (45%) SD and 3 (15%) PD were obtained. One-year survival rates were 100% in CR cases, 100% in PR, 67% in SD and 33% in PD.

Conclusions: In patients with 1 course DC-based therapy, survival more than 1 year may be expected, particularly in those with definitive disease control after treatment. DC-based therapy may be suitable to patients with better performance status.

Disclosure: All authors have declared no conflicts of interest.

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BODY COMPOSITION IS LINKED TO TOXICITY AND OUTCOME IN PATIENTS (PTS) INCLUDED IN PHASE I TRIALS

S. Cousin1, A. Hollebecque1, S. Koscielný2, A. Vargal3, V. Baracó3, J. Soria1, A. Antoni1

1Department of Medicine, Institut Gustave Roussy, Villejuif, FRANCE, 2Department of Biostatistics and Epidemiology, Instituto Gustave Roussy, Villejuif, FRANCE, 3Department of Oncology, University of Alberta, Edmonton, AB, CANADA, 4Emergency Department, Institut Gustave Roussy, Villejuif, FRANCE

Background: Phase I clinical trials are dose- and toxicity–finding studies designed to identify the recommended phase II dose of new drugs. Thus, it appears crucial to distinguish toxicity directly related to the tested drug or to pts characteristics. Because previous studies have shown that sarcopenia could be linked to drug toxicity, we have evaluated the effects of body composition parameters on the toxicities incidence among phase I included pts.

Methods: We have carried out a prospective single institution study which included all pts consecutively treated from January 2011 to July 2011 in our phase I unit, irrespective of the tumor type and/or drug nature. Clinical and biological nutritional parameters were recorded. Analysis of the computed tomography (CT) images realized within 30 days before inclusion was used to evaluate cross-sectional areas (cm²) of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and muscle tissue (MT). The 3rd lumbar vertebra (L3) was chosen as a landmark since L3 and whole-body measurements are linearly related. Images were analyzed using SimpleDW-Matic software V4.3 (Tomovision). Tissue cross-sectional areas were computed. Analysis was stratified on sex. Comparisons used Chi 2 test, Kruskal-Wallis test and log rank test.

Results: The study population consisted in 64 men and 49 women. The median age was 57.3 years. Drug interruption due to toxicity (DIT) occurred in 15% of the pts. The only factor associated with DIT was WT1 dose low MT 117 cm² versus 138 cm² (p = 0.039). Pts who did not experiment DIT were more likely to have MT median (56% versus 15%, p = 0.007). None of the following parameters were found to be associated with DIT: weight change <5%, >10%, Albumin <35 g/L, lactate dehydrogenase >250 IU/L, transferrin <0.21mg/dL, C reactive protein >6mg/L. Additionally, VAT <
Background: MGCD265, a multitasking inhibitor with nM IC50 against Met, VEGFR 1, 2 and 3, Tie-2 and Ron, has been shown in preclinical models to possess broad antitumor effects. A phase 1 study was undertaken to assess therapy with MGCD265 and docetaxel or erlotinib for treatment of solid tumors.

Methods: Patients (pts) with advanced solid tumors were enrolled in an open-label, dose-escalation study using the standard 3+3 design. All pts received 3-wk cycles of MGCD265 (p.o. QD or BID) with docetaxel or erlotinib per standard of care, as defined by investigators. Endpoints were safety, pharmacodynamics, pharmacokinetics, and tumor activity of the combination therapy.

Results: Of 89 pts enrolled, there were 12 cases of NSCLC (docetaxel group) and 9 cases of gastroesophageal (GE) cancer (erlotinib group). Of 10 response-evaluable NSCLC pts, all met criteria for stable disease (SD) for ≥2 cycles (including 2 pts with partial response). Five pts achieved SD for 5-16 mos, with four exceeding time on prior therapy. Two pts have not reached first evaluation. Treatment continues in 3 pts. Four of nine GE pts achieved SD. Three remained stable for 10-18 mos, exceeding time on prior therapy. Treatment continues in 1 pt. A plasma-based assay of Met phosphorylation showed up to 30% inhibition at doses to date. PK analysis is pending. Dose escalation continues. Toxicities were mostly mild to moderate. Nonhematologic adverse events (AEs) ≥grade 3 were reported in 20% of pts in each treatment arm, and were primarily GI-related. Expected docetaxel-associated hematologic AEs were also observed.

Conclusions: Preliminary findings from a phase 1 study suggest that MGCD265 and docetaxel or erlotinib may hold promise for treatment of NSCLC and GE tumors. For the fed condition, subjects received a standard meal 30 mins before drug administration. Blood samplings for the pharmacokinetic (PK) evaluation were done from pre-dose up to 96 hrs post-dose. Safety was evaluated through the assessment of adverse events (AEs), laboratory tests, vital signs, and 12-lead ECG.

Results: Fourteen subjects were recruited [M:F 8:6; median age: 51 years old (range 41-65); median BMI: 25 kg/m2 (range 19-29)]. One female subject discontinued early due to a fall (unrelated to MGCD265). Using nominal timepoints, on average, the fed condition was associated with an ~3 fold increase in Cmax, AU(0-t), and AU(0-inf). The half-life of MGCD265 was found to be ~34 hrs. Tmax was calculated to be 7 hrs and 10 hrs under fasting and fed conditions, respectively. MGCD265-related AEs were mostly mild and included dry mouth in 3 subjects, somnolence in 1 subject and moderate diarrhea in 1 subject. There were no clinically significant changes in vital signs, ECG or laboratory values.

Conclusions: Exposure of MGCD265 increased significantly in the presence of a meal, with no added toxicity. The prolonged sampling time used in this study provided a more accurate estimation of MGCD265 half-life (~34 hrs) compared to the estimate found in patients with advanced malignancies (~23 hrs).


PHARMACOKINETIC PROFILE OF MGCD265, AN ORAL TYROSINE KINASE INHIBITOR, WITH OR WITHOUT FOOD IN HEALTHY VOLUNTEERS

E. Scard1, M. Juretic2, M. Drouin3, G. Reid4, J. Wang5, W. Hunt4, C. Maroun4, J. Besterman5

1Clinical Research, Algorithm Pharma, Laval, QB, CANADA 2Clinical Affairs, Methylgene, Inc, Montreal, QB, CANADA

Background: MGCD265 is a novel targeted cancer therapeutic, currently in phase I/II clinical trials, that inhibits Met and VEGF receptor tyrosine kinases. The abnormal activation of Met is involved in tumor development and metastasis, and VEGF kinase is responsible for inappropriate angiogenesis that nourishes the tumor. DLTs were observed at 40 mg/day A + 75 mg/m2 D, the decision was made to evaluate further the A 30 mg/day + D 75 mg/m2 dose regimen in an additional cohort of 12 pts. Additional safety data and preliminary evidence of outcome in phase I pts.

Methods: Eligible pts (advanced solid tumours, Eastern Cooperative Oncology Group Performance Status 0–1) received once daily, oral dosing of A with D, given intravenously on Day 1 of every 3 week cycle. Primary objective was to establish the maximum tolerated dose (MTD) based on the occurrence of dose limiting toxicities (DLT) observed in Cycle 1. Dose escalation was performed with cohorts of 3–6 pts using a 3 + 3 design. Initial starting dose level was A 30 mg/day and D 60 mg/m2, escalating up to A 50 mg/day and D 75 mg/m2 until the MTD was reached, and followed by a PK expansion cohort of 12 pts at the MTD level.

Results: To date, 27 pts have been treated in Part B, 18 pts in the escalation phase with A (30–50 mg/day) and D (60–75 mg/m2), and 9 pts in the expansion phase with A 40 mg/day and D 75 mg/m2. Baseline characteristics were mean age (56.4 years), female (44.4%), and number of prior chemotherapies (< 2: 48%; >2: 52%). Adverse events (AEs) were manageable and the MTD was not exceeded in the tested dose range up to A 50 mg/day and D 75 mg/m2. AEs were diarrhoea (92.6%) and asthenia (77.8%). Selected dose level for the expansion cohort (A 40 mg/d with D 75 mg/m2) was based on the potential for diarrhoea and rash during later cycles. At this dose, events qualifying for DLT such as febrile neutropenia (2), diarrhoea Grade 3, hypokalaemia Grade 3, hyponatraemia Grade 3, increase of creatininaemia Grade 2 and oral mucositis, were observed in 7 pts.

Conclusions: Based on the rate of DLTs observed at 40 mg/day A + 75 mg/m2 D, the decision was made to evaluate further the A 30 mg/day + D 75 mg/m2 dose regimen in an additional cohort of 12 pts. Additional safety data and preliminary evidence of activity are anticipated to be available at the time of presentation.

Disclosure: J. Bennouna: I have received honoraria from roche, boehringer, amgen for advisory board. It is for myself. H. De Mont-Serrat: Employee of Boehringer Ingelheim. P. Squiban: Employee of Boehringer Ingelheim. I. Tschoepe: Employee of Boehringer Ingelheim. All other authors have declared no conflicts of interest.

CONTRIBUTION OF IMMUNOCOMMUNIC CELL DEATH (ICD) TO THE ANTI-TUMOR ACTIVITY OF CATUMAXOMAB (ANTI-EP-CAM X ANTI-CD3)

D. Godec, C. Flamant, N. Chaput-Gras, L. Zitougal

Surgical Oncology, Institut Gustave Roussy, Villejuif, FRANCE

Background: The trifunctional antibody catumaxomab (anti-EP-CAM x anti-CD3) is approved (EU) for the intraperitoneal treatment of malignant ascites. Catumaxomab is a trifunctional antibody targeting EpCAM on tumor cells, CD3 on T lymphocytes and binding to FcγR positive accessory cells thereby leading to the elimination of FcγR+ tumor cells by different immune mediated mechanisms. It has been reported that tumor cell death triggered by some immunogenic compounds or drugs used in the oncological armamentarium participates in the long term protection of patients treated with chemotherapy. The present nonclinical study investigated whether catumaxomab promotes immunogenic cell death (ICD) mechanisms which may contribute to its mode of action and its pharmacological activity in vivo.
Methods: Either co-cultures of peripheral blood mononuclear cells from healthy volunteers and EpCAM+ tumor cells (allogeneic system) or ascites cells from patients with malignant ascites (autologous system) were incubated in the presence of catumaxomab for 24-48 hours. Analysis of T, NK, DC, or monocyte cell activation and measurement of cytokine release in cell culture supernatants was performed. Subsequent analyses included investigation of cell death of EpCAM+ tumor cells and evaluation of ICD parameters (calreticulin, HMGB1, ATP).

Results: The trivalent antibody catumaxomab, in the presence of EpCAM+ tumor cells, induces activation of T lymphocytes, both CD4, CD8, with induction of Th1 and Th17 polarization accompanied by a bystander NK cell triggering. In the absence of ICD chemotherapy (oxaliplatin, doxorubicin), no ICD markers (calreticulin, HMGB1, ATP) can be detected on EpCAM+ tumor cells. However, following a pre-sensitization by suboptimal doses of oxaliplatin, catumaxomab could promote enhanced exposure of calreticulin, HMGB1 and ATP release from EpCAM+ tumor cells (allogeneic system).

Conclusions: Activation of T cells and induction of inflammatory lymphocytes mainly contribute to the catumaxomab mediated elimination of EpCAM+ tumor target cells. ICD mechanisms including release of HMGB1 and ATP, exposure of calreticulin by targeted tumor cells may further promote the anti-tumor activity of catumaxomab.

Disclosure: All authors have declared no conflicts of interest.

496P A PHASE 1 STUDY OF MM-111: A BISPECIFIC HER2/HER3 ANTIODYN FUSION PROTEIN, COMBINED WITH MULTIPLE TREATMENT REGIMENS IN PATIENTS WITH ADVANCED HER2 POSITIVE SOLID TUMORS

D. Richards1, F. Brateh1, S. Anthony1, W. Edenfield1, B. Hellerstedt1, R. Raju2, D. Connelly8, C. McDonagh6, S. Frye9, V. Moyo9

1Research, US Oncology, The Woodlands, TX, UNITED STATES OF AMERICA, 2Research, Alliance Oncology Research, Kettering, OH, UNITED STATES OF AMERICA, 3Clinical Development, Merrimack Pharmaceuticals, Cambridge, MA, UNITED STATES OF AMERICA, 4Medical Oncology, Karmanos Cancer Institute / Wayne State University, Detroit, MI, UNITED STATES OF AMERICA, 5Clinical Research, FV-Clinical subcontractor for Merrimack, Paris, FRANCE, 6Biostatistics, Sanofi, Bridgewater, NJ, UNITED STATES OF AMERICA, 7Research and Development, Sanofi, Montpellier, FRANCE, 8Clinical Research, Sanofi, Bridgewater, NJ, UNITED STATES OF AMERICA, 9Medical Oncology Department, Fox Chase Cancer Center, Philadelphia, PA, UNITED STATES OF AMERICA

Background: Ligand-activated HER3 forms a potent signaling heterodimer with HER2 and is emerging as key tumorigenic node and mediator of drug resistance. MM-111 (111) is a novel molecule that inhibits ligand activated HER3 signaling in HER2+ tumors. Preclinically, MM-111 potentiates the anti-tumor activity of and mitigates resistance to trastuzumab, lapatinib and chemotherapies. This study evaluates the safety of MM-111 combined with standard of care (SOC) HER2-targeting regimens (Rx), namely; cetuximab (X), cisplatin (C), and trastuzumab (T) (Arm 1); lapatinib (L) +/- trastuzumab (Arm 2); and pacitaxel (P) with trastuzumab (Arm 3).

Methods: This was a multi-arm Phase 1, dose escalation study of MM-111 in combination with SOC regimens to evaluate safety, pharmacokinetics (PK), and anti-tumor activity. Patients were required to have documented advanced HER2+ cancer, with adequate organ function. Each arm was designed to run as a separate Phase 1 study to address safety and tolerability and each arm utilized a “3 + 3” design with standard dosing of the SOC regimen. MM-111 was dosed weekly at 10mg/kg and escalated up to 20mg/kg where possible.

Results: As of 30 March 2012, thirty patients had been enrolled across three arms. Dose-limiting toxicities (DLTs) included myelosuppression, infection, vomiting, diarrhea, neutropenia, thrombocytopenia, and sepsis. All DLTs were febrile neutropenia (FN) (4 pts), Grade (Gr) 4 neutropenia (2 pts), Gr 4 thrombocytopenia (2 pts). Pts experienced a DLT, regardless of administration sequence. DLTs were febrile neutropenia (FN) (4 pts), Grade (Gr) 4 neutropenia (2 pts), Gr 4 thrombocytopenia (2 pts). Pts and Gr 3 AST increase (1 pt). No MTD was established and part 2 was not performed. All pts experienced at least 1 treatment-emergent AE (TEAEs); the most frequent all grade non-haematological TEAEs were fatigue 66.7%, decreased appetite 50.0%, diarrhea 44.4%, nausea 38.9% and weight decrease 33.3%. Gr 3-4 haematological toxicities included neutropenia 66.7%, thrombocytopenia 33.3% and FN 22.2%. Nine pts continued study treatment and received 6-22 cycles; 3 pts had a partial (melanoma, prostate small cell and appendicular tumours), while 8 pts experienced stable disease, PK analysis did not reveal a drug-drug interaction between Cbz and Gem.

Conclusion: The MTD of Cbz + Gem could not be established due to DLTs. Anti-tumour activity was observed and drug administration sequence did not affect the toxicity profile. Further investigation of alternative dosing regimens is warranted in an effort to establish a tolerable combination.

Disclosure: P.M. LoRusso: Has received research funding from Sanofi. J. Yin: Is a Sanofi employee and owns Sanofi stocks and shares. S. Douroumis: Is a Sanofi employee (pharmacokineticist) and owns Sanofi stocks and shares. X. Zhi: Is a Sanofi employee (statistician) and owns Sanofi stocks and shares. A.J. Olszanski: Research funding - Sanofi supplies support for the conduct of the study. All other authors have declared no conflicts of interest.

498P FIRST-IN-HUMAN PHASE I ADMINISTRATION OF YS110, A HUMANIZED MONOCLONAL ANTIBODY DIRECTED AGAINST THE CD26 MOLECULE IN CANCER PATIENTS


1Step, Institut Gustave Roussy, Villejuif, FRANCE, 2Service d’Oncologie Médicale, Hopital Lyon Sud, Pierre Béralde, FRANCE, 3Unite De Phase I, Centre Georges Fracqes Leclerc, Dijon, FRANCE, 4Service d’Oncologie Médicale, Hôpital Cochin, paris, FRANCE, 5Clinical Research, PV-Clinical subcontractor for Harrison Clinical Research, Pontoise, FRANCE, 6Oncology Department, Y’s Therapeutics, Redwood City, CA, UNITED STATES OF AMERICA, 7Clinical Development, Kisspeptides Pharmaceuticals, Tokyo, JAPAN, 8Department of Pathology, Keio university School of Medicine, Tokyo, JAPAN, 9Clinical Development, Y’s, AC, Tokyo, JAPAN, 10Division of Clinical Immunology, University of Tokyo, Tokyo, JAPAN

Background: YS110 is a recombinant humanized IgG1 monoclonal antibody that selectively binds with high affinity to the extracellular domain of the CD26 antigen. CD26, a widely distributed 110-kDa transmembrane glycoprotein with intrinsic DPPIV activity and its truncated soluble form (sCD26/DPPIV) also present in serum...
INCIDENCE AND RELEVANCE OF PROTEINURIA IN BEVACIZUMAB (BV)-TREATED PATIENTS (PTS): POOLED ANALYSIS FROM RANDOMIZED CONTROLLED TRIALS (RCTs)

R. Lafayette1, B. McCaII, N.F. Li1, L. Chu2, P. Werner4, A. Das6, R.J. Glasscock2

1Nephrology, Stanford Glomerular Disease Center, Stanford, CA, UNITED STATES OF AMERICA, 2Product Development, Oncology, Genentech, Inc., South San Francisco, CA, UNITED STATES OF AMERICA, 3Biostatistics, Genentech, Inc., South San Francisco, CA, UNITED STATES OF AMERICA, 4Global Product Development Biometrics, Genentech, Inc., South San Francisco, CA, UNITED STATES OF AMERICA, 5Statistical Programming and Analysis (spa), F. Hoffmann-La Roche AG, Basel, SWITZERLAND, 6PDCO, Genentech, Inc., South San Francisco, CA, UNITED STATES OF AMERICA, 7The David Geffen School of Medicine, UCLA, Laguna Niguel, CA, UNITED STATES OF AMERICA

Background: Proteinuria (PU) is a recognized adverse event with BV treatment (tx); however it is not known if BV-related PU is associated with clinical outcomes. This analysis was undertaken to define the relationship between PU with BV tx and sequelae, including changes in kidney function.

Methods: A pooled safety database, comprising 22 phase 2/3 RCTs of BV across tumor types, was used to characterize PU events. Analysis pools were created based on data availability in individual studies. Raw and time-adjusted PU rates and data on the association between PU and arterial thromboembolic events (TEs), venous TEs, and infection were derived from Pool 1 (17 RCTs; n = 14,548). Data from Pool 2 (8 RCTs; n = 9,158) were used to estimate the association between lab-reported PU and changes in kidney function based on serum creatinine (sCr) levels. Severity of kidney function change was categorized using the RIFLE classification for acute kidney injury (AKI). Potential predictors of PU were also assessed.

Results: In Pool 1, the incidence rate of any-grade (gr) PU was 8.2% (733/8917) and changes in kidney function based on serum creatinine (sCr) levels. Severity of kidney function change was categorized using the RIFLE classification for acute kidney injury (AKI). Potential predictors of PU were also assessed.

Conclusions: The use of laboratory events and pooled data confirm a modest increase in PU with BV tx. The development of PU in BV-treated pts was associated with the most modest increase in the risk of infection, but not TEs, and a trend toward a decrease in kidney function. Whether these associations are causal cannot be determined by this analysis.

THE LEEDS FORMULA: A NEW, MORE ACCURATE AND WIDELY APPLICABLE FORMULA FOR ESTIMATING RENAL FUNCTION, ACCOUNTING FOR VARIABILITY IN CREATININE ASSAY MEASUREMENT

F. Collisson1, W. Gregory4, C. Twelves2, C. Handforth3, M. Bosomworth4, G. Hall5

1Clinical Trials Research Unit, University of Leeds, Leeds, UNITED KINGDOM, 2Oncology Research, Genentech, Inc., South San Francisco, CA, UNITED STATES OF AMERICA, 3Statistical Programming and Analysis (spa), F. Hoffmann-La Roche AG, Basel, SWITZERLAND, 4PDCO, Genentech, Inc., South San Francisco, CA, UNITED STATES OF AMERICA, 5The David Geffen School of Medicine, UCLA, Laguna Niguel, CA, UNITED STATES OF AMERICA

Introduction: Many formulae are used to estimate renal function, but none account for the significant variation in creatinine (Cr) measurement between the 26 assays currently used in the UK. The UK National External Quality Assessment Service has published assay-specific Cr adjustors, but the calculated standardised Cr (sCr) dangerously overestimates GFR when used in formulae such as Cockcroft and Gault (C&G) and Wright (W). We aimed to develop a simple formula to accurately estimate GFR in oncology patients, using easily available patient characteristics and the sCr, hence accounting for inter-assay variation.

Methods: Isotopic GFR (iGFR) was measured using Tc-99mDTPA clearance. Serum Cr was measured using the O’Leary radio assay and from this SG derived. Clinical parameters (age, sex, height, weight, sCr, serum urea and albumin) were used in regression modelling (STATA) to investigate the relationship of individual parameters with iGFR. From this a novel formula was derived to estimate iGFR (the Leeds formula). This formula was then prospectively validated on a second cohort of patients.

Results: In the discovery set 423 oncology patients were included with a range of malignancies, a median age of 49 (range 18–91) years and serum Cr between 50–130 µmol/l who underwent iGFR measurement between 1/4/09 and 31/3/11. A model incorporating SG, age, sex, height, weight, Cr and albumin predicted iGFR (median calculated C&G 92 ml/min, range 25–217; r2 = 0.74) more accurately than alternative established GFR formulae e.g. C&G and W formula (r2 = 0.45–0.6). Prospective validation on a separate cohort of oncology patients (496 patients between 1/4/09 and 31/3/11) validated the Leeds formula with an r2 of 0.71 for correlation with iGFR.

Conclusions: The Leeds formula uses readily available clinical information to estimate GFR more precisely than existing formulae and has the advantage of being directly comparable to Cr results from any laboratory provided the assay type is known. Many oncologists do not appreciate the resultant effect of inter-Cr assay variability on estimated renal function (GFR) and hence chemotherapy dosing.

Disclosure: All authors have declared no conflicts of interest.
Background: SRC, a non-receptor tyrosine kinase, has been shown to be involved in anti-VEGF drug resistance. Anti-VEGF drugs provide standard of care in renal cell carcinoma (RCC) and therefore we investigated the potential of the SRC inhibitor saracatinib for clinical trials of RCC.

Methods and results: In vitro MTS assays were performed on a panel of RCC cell lines which demonstrated saracatinib significantly reduced cell viability in all RCC cell lines tested in a dose-dependent manner. Follow-up experiments performed using two separate isogenic cell lines confirmed that mutation of the VHL gene impaired saracatinib’s ability to reduce cell viability. In vitro migration assays confirmed saracatinib’s ability to reduce motility and migration and this effect did not correlate with VHL status. Using the VHL-null 786-O xenograft model we investigated the impact of saracatinib in vivo. Saracatinib (25 mg/kg) significantly slowed tumour growth compared to vehicle-treated tumours. Furthermore, when combined with the anti-VEGF drug cediranib, combination therapy (25 mg/kg + 3 mg/kg) significantly slowed tumour growth when compared to cediranib monotherapy (3 mg/kg). Combination therapy significantly reduced vessel density (as measured by CD31 immunohistochemistry [IHC]) and increased the percentage of apoptotic cells (cleaved-caspase 3 IHC) compared to vehicle-treated tumours. Moreover, combination therapy increased the percentage of apoptotic cells compared to cediranib monotherapy but this result did not reach statistical significance. IHC analysis showed that saracatinib (25 mg/kg) significantly reduced tumour phospho-STAT3 levels.

Conclusions: These data demonstrate saracatinib’s potential to reduce RCC cell viability and motility in vitro and slow tumour growth in vivo both as monotherapy and in combination with an anti-VEGF agent. A randomised phase II trial is ongoing to investigate the potential of combining saracatinib and cediranib in VEGF TKI refractory RCC.

Disclosure: K. Sharpe: Kevin Sharpe receives an MRC CASE stipend which AstraZeneca contributes towards. T. Powles: Thomas Powles has participated in advisory boards for Pfizer and GSK and has received research funding from these institutions. All other authors have declared no conflicts of interest.
clinical studies from Fresenius Biotech GmbH. P. Rosenberg: financial support for clinical studies from Fresenius Biotech GmbH. J. Sehouli: consultant for Fresenius Biotech GmbH and financial support for clinical studies. All other authors have declared no conflicts of interest.

Methods: An exploratory retrospective analysis of 4 randomized clinical trials (linifanib or other treatments: ABT-510 [thrombospondin mimetic], pemetrexed +/- ABT-751) in relapsed NSCLC was conducted. Evaluable baseline plasma samples were obtained from 116 pts who received linifanib and 125 pts on other treatments. A signature combining established tumor markers (carcinoembryonic antigen [CEA] and fragments of cytokeratin 19 [CYFRA 21-1]) was derived using a sequential BATTING approach. The signature was then tested across a randomized trial of CP + placebo, linifanib 7.5 mg, or linifanib 12.5 mg in first-line advanced, non-squamous NSCLC.

Results: In 2/3 NLSCC, the signature was associated with improvement in survival on linifanib monotherapy (HR = 0.51 vs. signature negative; P = 0.0017), but no improvement in survival on other treatments (P = 0.72). In the first-line setting with CP + linifanib (HR = 0.83 [9.2, NR] vs. signature negative; P = 0.03), but no improvement in survival on other treatments (P = 0.72). In the first-line setting with CP, the signature was associated with significant PFS improvement with linifanib and improvement in survival on other treatments (P = 0.72). In the first-line setting with CP, the signature was associated with significant PFS improvement with linifanib and improvement in survival on other treatments (P = 0.72).

Conclusion: A baseline plasma biomarker signature is associated with improved survival in unselected advanced NSCLC patients on linifanib. Incorporation of this signature should be considered in any further investigation of linifanib in NSCLC.


Background: Linifanib (ABT-869) is a novel, orally active and selective inhibitor of VEGF and PDGF family of receptor tyrosine kinases that has shown antitumor activity in multiple types of solid tumors. This study was conducted to evaluate the potential effects of linifanib on QTc prolongation in patients (pts) with advanced solid tumors.

Methods: Enrolled pts (N = 24; ≥18 years) had measurable disease refractory to standard therapies, ECOG PS 0-1, and adequate organ function. Pts received 2 sequences of regimens of 0.25 mg/kg orally administered linifanib up to a maximum dose of 17.5 mg. Pts received a morning dose on Days 1 and 7 under fasting and fed conditions in a crossover fashion. Serial triplicate ECG recordings were obtained on Day –1, and over 24 hours on Day 1 and 7; single recordings were obtained at screening and study completion or discontinuation. Plasma samples were collected for 72 hours on Day 1 and 7 for pharmacokinetic analysis. Effects of linifanib on cardiac repolarization were analyzed using a linear mixed effects model on time-matched baseline adjusted QTcF intervals. The primary end point was the time-matched difference for on-treatment QTcF from baseline (ΔQTcF). An intersection-union test was performed within the framework of the corresponding linear mixed effects model. The relationship between ΔQTcF and plasma linifanib concentration was explored using a linear mixed effects model.

Results: In the 24 pts evaluated, baseline QTcF ranged from 360.9 ms to 468.6 ms. After linifanib administration, the mean ΔQTcF ranged from –4.04 ms to 0.73 ms for the fasting regimen, and from –5.94 ms to –1.37 ms for the fed regimen. The upper 95% confidence bound of 7.2 ms. No pt had QTcF >500 ms or change of >30 ms from baseline.

Conclusion: At the maximum tolerated dose of 0.25 mg/kg, linifanib had no effect on cardiac repolarization in pts with advanced solid tumors.


Background: Pazopanib is a potent multi-targeted tyrosine kinase inhibitor which is approved for the treatment of advanced RCC patients. While exploring the therapeutic index of TKIs, oncology investigators are confronted with drug adverse effects such as cardiac toxicities. QT prolongation has taken attention because of the risk of serious cardiac arrhythmias such as torsade de pointes (TDP) and sudden cardiac death. In several studies QTc prolongation was observed with TKIs such as sunitinib, vandetanib, dabatinib, cirzotinib. However there are no data showing QTc prolongation with pazopanib treatment. In this study, we aimed to demonstrate the pazopanib induced proarrhythmic electrophysiological effects and investigate the possible protective effects of metoprolol and diltiazem to ECG changes in an experimental model.

Method: In this study 24 Sprague-Dawley adult male rats were used. Rats were randomly assigned to 4 groups (n = 6). To the first group (normal group), intraperitoneal injection of 6 mg/kg of saline were given and to the other groups 100 mg/kg pazopanib were given via orogastric tubes. 3 hours after oral administration of pazopanib, to the second group (control group) saline, to the third group 1 mg/kg metoprolol and to the fourth group 1 mg/kg diltiazem were applied intraperitoneally. 1 hours after application of these drugs, under anaesthesia, QTc was calculated by taking ECG in derivation I.

Results: The mean QTc interval was 126.2 ± 2.99 s in group 1, 159.66 ± 6.20 s in group 2, 106.66 ± 2.64 s in group 3 and 123.33 ± 1.72 s in group 4. Groups 3 and 4 had significantly shorter QTc intervals compared to group 2 (p < 0.001).

Conclusion: This is the first experimental study evaluating the use of prophylactic therapy with metoprolol and diltiazem in pazopanib induced QT prolongation. In this present experimental study we demonstrated the beneficial prophylactic effects of metoprolol and diltiazem in pazopanib induced QT prolongation. More evidence is needed to evaluate the effectiveness and safety of these drugs. Future prospective and randomized studies will be needed to confirm recommendations for high risk patients.

Disclosure: All authors have declared no conflicts of interest.
Background: Patients with advanced squamous cell carcinoma (SCC) of the lung have limited treatment options. Although treatment with the EGFR tyrosine kinase inhibitor erlotinib is indicated in the second- or third-line or maintenance setting, the benefit is limited. Afatinib is a novel, selectively, orally bioavailable, ErbB family blocker, irreversibly blocking EGF (ErB1), HER2 (ErB2) and HER4 (ErB4). Based on its promising preclinical profile and clinical activity in trials of SCC of the head and neck and gastrointestinal adenocarcinoma, Afatinib has become a well-tolerated, irreversible inhibitor of the ErbB family translates into clinical benefit for patients with SCC of the lung.

Methods: This trial will compare the efficacy of afatinib versus erlotinib as second-line treatment for patients with SCC of the lung, as measured by progression-free survival. Key patient eligibility criteria include: advanced NSCLC squamous or mixed histology, completion of at least 4 cycles of platinum doublet chemotherapy, eligibility to receive EGRF-directed therapy as second-line treatment, ECOG PS 0–1, adequate organ function, availability of archived tumour tissue for correlative studies and no prior EGRF-directed therapy. Secondary endpoints are comparison of overall survival, objective response rate, disease control rate, tumour shrinkage, assessment of health-related quality of life and safety in both treatment groups. Eligible patients will be randomized (1:1) to receive either afatinib or erlotinib and stratified based on race (Asian vs. other). Eight hundred patients are planned to be stratified globally, with randomization to the primary endpoint will be completed at a treatment-blinded manner. An independent data monitoring committee will monitor safety and efficacy of the trial.

Disclosure: G. Goss: Consultant or advisory relationship to Boehringer Ingelheim, compensated prior to conduct of the study. S. Lu: Consultant or advisory relationship, compensated. A. Arzadun: Other remuneration: GSK DSMC PRAIME Study. V. Georgoulas: Consultant or advisory relationship, uncompensated for GSK, Novartis, Sanofi, Janssen-Cilag, Amgen. Honoria and research funding from GSK, Novartis, Sanofi, Janssen-Cilag, Amgen. S. Gadgeel: Consultant or advisory relationship. Independent Clinical Research Investigator. V. Chand: Employee of Boehringer Ingelheim Pharmaceuticals, Inc. Y. Gu: Employee of Boehringer Ingelheim Pharmaceuticals, Inc. Y.S. Olive: Employee of Boehringer Ingelheim Pharmaceuticals, Inc. J. Soria: Honoria from Boehringer Ingelheim and Roche. All other authors have declared no conflicts of interest.