402 POSTER

JX-594, a targeted multi-mechanistic oncolytic poxvirus, infects tumor vasculature and causes acute tumor vascular disruption and necrosis in advanced cancer patients

C. Breitbach[1], R. Patt[2], N. De Silva[3], K. Parato[4], M. Daneshmand[4], T. Hickman[5], J.C. Bell[4], D.H. Kirn[5]. *[1]Jennerex Inc, Clinical Research, San Francisco CA, USA; [2]RadMD, Radiology, Doylestown, USA; [3]University of Ottawa, Biochemistry, Ottawa, Canada; [4]Ottawa Hospital Research Institute, Centre for Cancer Therapeutics, Ottawa, Canada; [5]Jennerex Inc, Clinical Research, San Francisco, USA*

Background: JX-594 is a first-in-class targeted oncolytic poxvirus designed to selectively replicate in and destroy cancer cells with cell cycle abnormalities and epidermal growth factor receptor (EGFR)/ras pathway activation. Direct oncolysis plus granulocyte macrophage − colony stimulating factor (GM-CSF) expression also stimulates anti-tumoral immunity.
Material and Methods: JX-594 infection of tumor-associated vasculature in preclinical models (SW620 and HT29 human colon adenocarcinoma) and tumor biopsies from patients with advanced, treatment-refractory solid tumors was evaluated by immunohistochemical analysis. Changes in tumor perfusion were assessed in patients by dynamic contrast-enhanced magnetic resonance imaging (dce-MRI) at baseline and Day 5 after intratumoral JX-594 administration.
Results: JX-594 was capable of infecting tumor-associated endothelial cells after intravenous infusion or intratumoral injection in preclinical tumor models. No infection was observed in vasculature associated with normal tissues, including brain, lung, heart and skeletal muscle. In advanced cancer patients on a Phase 1 dose-escalation trial of intravenous JX-594, biopsy analyses revealed similar infection of tumor-associated vasculature. No clinical evidence of normal vascular infection (including disseminated intravascular coagulation [DIC]) was noted. Acute decreases in tumor perfusion versus baseline were demonstrated 5 days post JX-594 treatment of liver tumors, including hepatocellular carcinoma and colorectal cancer metastases; vascularity was decreased both in treated and untreated lesions. Choi (necrotic) responses at later timepoints (e.g. Week 8) could be observed following acute vascular disruption.
Conclusions: In addition to targeting cancers by direct infection and lysis of tumor cells, JX-594 is capable of directly infecting tumor associated endothelium. By targeting tumor vasculature, JX-594 has the capability of causing rapid destruction of tumors by disrupting the tumor's blood supply. These observations have implications for the treatment of a broad range of tumor types.

403 POSTER

Phase I study on RGB-286638, a novel, multi-targeted protein kinase inhibitor, administered as a 1-hour infusion on five consecutive days every 4 weeks in patients (pts) with recurrent or refractory solid tumors

M. de Jonge[1], R. Mathijssen[1], W. Loos[1], H. Loferer[2], S. Sperka[2], T. Meyer[3], E. Wiemer[1], D. van der Biessen[1], H. Burger[1], J. Verweij[1]. *[1]Erasmus Medical Center, Medical Oncology, Rotterdam, The Netherlands; [2]Agennix AG, Project management, Planegg, Germany; [3]Agennix AG, Pharmacology, Planegg, Germany*

Background: RGB-286638 is a multi-targeted protein kinase inhibitor directed at a selected spectrum of target protein kinases, including the cyclin-dependent kinase (CDK) family, several serine/threonine kinases, and non-receptor as well as receptor tyrosine kinases.
Material and Methods: Objectives of this first in human trial are to determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLTs) and to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profile of RGB-286638. DLTs are defined as grade (G) 4 neutropenia >7 days, febrile neutropenia, G3 thrombocytopenia with bleeding, G4 thrombocytopenia, G $\geqslant$3 non-hematological toxicity except inadequately treated nausea/vomiting or diarrhea, prolongation of QTc >500msec or >60 msec increase from baseline, ocular toxicity, inability to administer $\geqslant$4/5 scheduled treatment days and >2 week delay in starting cycle 2. Sequential cohorts of 3−6 pts are treated per dose level (DL). Blood, urine samples and skin biopsies for full PK and/or PD analysis were collected.
Results: To date 20 pts have been enrolled in 6 DLs (10, 20, 40, 80, 160 and 120 mg/day). Two DLTs were observed in 4 pts enrolled at the 160 mg cohort: transient G3 AST/ALT elevation; paroxysmal G2 SVT with G2 hypotension and transient increase in troponin T to G2. A third pt at 160 mg showed asymptomatic paroxysmal atrial fibrillation. Thus, the MTD was exceeded at 160 mg and the next lower DL of 80 mg/day was expanded to 6 pts. The 120 mg cohort is currently being evaluated. Other G1−2 toxicities observed included nausea/vomiting, diarrhea, fatigue, neutropenia and thrombocytopenia. 6 pts experienced disease stabilization for 4−8+ months. Plasma PK was shown to be linear over the studied doses with mean clearances on Day 1 of 102, 61, 48, 54 and 59 L/h, and mean half-lives on Day 1 of 2.0, 8.4, 9.5, 9.4 and 7.9 h at DLs of 10, 20, 40, 80 and 160 mg, respectively. Interpatient variability in clearance was moderate (7−36%). So far PD analyses did not demonstrate a consistent modulation of mechanism-related biomarkers.
Conclusions: RGB-286638 administered on a D1−5 every 28 day schedule is tolerated at doses up to 80 mg/day. The 120 mg/day DL is currently being evaluated. Prolonged disease stabilization was seen across dose levels.

404 POSTER

Phase I study of MEDI-575, a fully human monoclonal antibody targeting PDGFR-alpha in subjects with advanced solid tumors

R. Lechleider[1], C. Becerra[2], M. Liang[3], R. Narwal[3], L. Shi[1], P. Conkling[4], M. Galsky[5], R. Jotte[6], H. Wu[7], N.J. Vogelzang[5]. *[1]MedImmune, Clinical Development, Gaithersburg, USA; [2]US Oncology Research, Texas Oncology Baylor-Charles A. Sammons Cancer Center, Dallas, USA; [3]MedImmune, Research & Development, Gaithersburg, USA; [4]US Oncology Research, Virginia Oncology Associates, Norfolk, USA; [5]US Oncology Research, Comprehensive Cancer Centers of Nevada, Las Vegas, USA; [6]US Oncology Research, Rocky Mountain Cancer Centers, Denver, USA; [7]US Oncology Research, Central Indiana Cancer Centers, Indianapolis, USA*

Background: MEDI-575 is a fully human monoclonal antibody that selectively binds to platelet-derived growth factor receptor-α (PDGFRα) with high affinity. PDGFRα may drive tumor growth through expression on tumor cells and by activating cancer-associated fibroblasts. MEDI-575 inhibits signaling from PDGFRα but not PDGFRβ.
Methods: We evaluated safety, maximum tolerated dose or optimum biologic dose, pharmacokinetics (PK), and pharmacodynamics (PD) of MEDI-575 in subjects with advanced solid tumors. Subjects were enrolled in a 3 + 3 dose-escalation design and given 3, 6, 9, 12, or 15 mg/kg MEDI-575 once per week (qwk) until toxicity or disease progression. One 0.5 mg/kg lead-in dose was given before the first dose in the 3 mg/kg cohort to determine nonlinear PK. After completion of dose escalation in the qwk cohorts, subjects were enrolled in 2 additional cohorts and treated with 25 or 35 mg/kg once every 3 weeks (q3wk). Enrollment is complete for the qwk cohorts and ongoing for the q3wk cohorts. Subjects with non-small-cell lung cancer (NSCLC), ovarian cancer, glioblastoma multiforme, or synovial sarcoma will be enrolled in a qwk or q3wk expansion cohort. Expansion cohort doses were based on tolerability and determination of likely efficacious serum drug levels.
Results: Twenty-eight subjects with advanced solid tumors for which no standard curative or life-prolonging therapies are available have been treated with MEDI-575 to date (23 qwk; 5 q3wk; median age 65.5 yrs). Half of the tumor histologies were colorectal cancer (n = 9) and NSCLC (n = 5). Preclinical PK/PD modeling accurately predicted observed serum MEDI-575 levels. The median number of drug cycles administered was 2 (range, 1−19). There were 49 adverse events (AEs) at least possibly related to MEDI-575 in 19/28 (67.9%) subjects. Most treatment-related AEs were grade 1/2; those reported in $\geqslant$10% of subjects were fatigue (28.6%); nausea (14.3%); and hypokalemia, anemia, and muscle spasms (10.7% each). No dose-limiting toxicities were reported. The best response of stable disease (SD) for >4 months occurred in 2 subjects (1 subject with chordoma showed SD for 4.4 months; 1 with adenocystic carcinoma ongoing at 11.3 months).
Conclusion: Toxicities observed with MEDI-575 at doses up to 15 mg/kg qwk and 35 mg/kg q3wk support continued development. Most treatment-related AEs were grade 1/2 and reversible. No objective responses were seen, but SD for >4 months was observed in 2 subjects.

405 POSTER

A mass balance study to investigate the metabolism, excretion and pharmacokinetics of [14C]-olaparib (AZD2281) in patients with advanced solid tumours refractory to standard treatments

J.E. Ang[1], J.A. Clarkson-Jones[2], H. Swaisland[2], A.T. Brunetto[1], R. Lal[1], A.P. Farnsworth[2], L.R. Molife[1], S.B. Kaye[1], J. Carmichael[2], J.S. de Bono[1]. *[1]The Centre for Cancer Therapeutics, The Institute of Cancer Research, Cotswold Road, Sutton, Surrey, UK; [2]AstraZeneca, Alderley Park, Macclesfield, United Kingdom*

Background: Olaparib (AZD2281) is an oral poly(ADP-ribose) polymerase (PARP) inhibitor with minimal toxicity in patients with solid tumours and single-agent activity in patients with *BRCA1- or BRCA2*-deficient ovarian or breast cancers.
Material and methods: This was an open-label, single centre study that involved the oral administration of a single 100 mg dose of [^{14}C]-olaparib (120 μCi, 4.44 MBq) comprising 50 mg [^{14}C]-labelled and 50 mg

non-radiolabelled olaparib capsules to six patients. The primary aim was to investigate the metabolism, excretion and pharmacokinetics (PK) of olaparib in patients with advanced solid tumours.
Results: Six female patients (aged 34−72 years) were included. Data from one patient were excluded for PK analysis as she had received only half the total dose of olaparib with the planned dose of radioactivity (120 μCi). Absorption of olaparib was rapid, with maximum plasma concentrations (geometric mean 3556 ng/mL) observed at 1.5−2 hours (h) post dose. Following this, plasma concentrations declined polyphasically, and were below the limit of quantification by 16 to 24 h post dose. The geometric mean AUC was 19856 ng.h/mL, oral clearance was 4 to 14 L/h, apparent volume of distribution was 20 to 50 L, and the terminal half-life was between 2.4 and 4.7 h. Total plasma radioactivity concentrations were mostly higher than those of the parent compound, and these values declined in parallel. In addition, the mean ratio of the concentration of radioactivity in blood to plasma was 0.8, suggesting some association of olaparib-related material with cellular components of the blood. Mean total recovery (over 144 or 168 h) of the radioactive dose from all patients was 86%; 44% in the urine (15% as the parent compound) and 42% in the faeces. In most patients, the majority of the excreted radioactivity was recovered within 72 h of dosing.
Conclusions: After a single dose of olaparib 100 mg (50 mg contained [^{14}C]), absorption was rapid and elimination occurred relatively quickly, mainly via the urine and faeces. Furthermore, these data indicate the presence of circulating metabolites and suggest association of olaparib and/or metabolites with the cellular components of blood.

406 POSTER

Phase 2 study of XL184 in a cohort of patients (pts) with castration resistant prostate cancer (CRPC) and measurable soft tissue disease

D.C. Smith[1], A. Spira[2], J. De Grève[3], L. Hart[4], S. Holbrechts[5], C.C. Lin[6], M. Hussain[1], S. Herrick[7], K. Houggy[7], N. Vogelzang[8]. *[1]University of Michigan, Department of Medicine, Ann Arbor, USA; [2]Fairfax Northern Virginia Hematology-Oncology PC, NA, Fairfax, USA; [3]Universitair Ziekenhuis Brussel, Department of Medical Oncology, Brussels, Belgium; [4]Florida Cancer Specialists, NA, Fort Myers, USA; [5]Center Hospitalier Universitaire Ambroise Paré, NA, Henegouwen, Belgium; [6]National Taiwan University Hospital, Department of Oncology, Taipei, Taiwan; [7]Exelixis Inc, NA, South San Francisco, USA; [8]Comprehensive Cancer Centers of Nevada, NA, Las Vegas, USA*

Background: XL184 is an oral potent inhibitor of MET, VEGFR2 and RET. Activation of the MET pathway promotes tumor growth, invasion, and metastasis. Overexpression of MET and/or its ligand HGF have been shown to correlate with prostate cancer metastasis to lymph nodes and bones, and disease recurrence. In addition, androgen ablation has been shown to upregulate MET signaling in preclinical studies. Targeting the MET pathway with XL184 may therefore be a promising treatment strategy. Preliminary data from the open label Lead-in Stage of a Phase 2 randomized discontinuation trial are presented showing the effects of XL184 in pts with CRPC.
Methods: Eligible pts have CRPC with measurable disease and have progressed on up to 1 prior non-hormonal systemic treatment after antiandrogen withdrawal. XL184 is administered open label at 100 mg free base equivalent (125 mg XL184-malate-salt) qd for 12 weeks (wks) (Lead-in Stage). Tumor response is assessed radiologically every 6 wks. Pts with partial or complete response (PR or CR) at wk 12 continue to receive XL184; pts with progressive disease (PD) discontinue XL184. Pts with SD at wk 12 are randomized 1:1 to receive XL184 or placebo. Cross-over from placebo to XL184 is allowed upon PD. Primary endpoints are objective response rate at wk 12 and progression free survival in the Randomized Stage. PSA levels will be correlated with clinical outcomes.
Results: A total of 16 pts have been enrolled with a median age of 69 years. The median number of prior non-hormonal systemic treatments was 1, with 7 pts receiving docetaxel. Of 9 pts who were evaluable (minimum 12 wks follow up) to date, 1 pt achieved a PR and 5 pts achieved SD for an overall disease control rate of 67% at wk 12. Two pts achieved a near complete resolution of tracer uptake on bone scan with one pt previously treated with docetaxel who attained a 41% reduction in measurable disease and a reduction of PSA > 50% at wk 12. Most frequently observed adverse events regardless of causality with CTCAE Grade ⩾3 in the Lead-in Stage were fatigue and asthenia (each n = 2).
Conclusions: Preliminary results suggest that XL184 is active in CRPC pts who failed prior treatment. XL184 was generally well tolerated. Updated efficacy and safety results will be presented.

407 POSTER

Phase 2 study of XL184 in a cohort of ovarian cancer patients (pts) with measurable soft tissue disease

I. Vergote[1], A. Sella[2], C. Bedell[3], L. Ramondetta[4], G.I. Shapiro[5], K. Balic[6], E. Prokopczuk[6], L. Sauer[6], L. Tseng[6], R. Berger[7]. *[1]University Hospital Leuven, Gynecological Oncology, Leuven, Belgium; [2]Assaf Harofeh Medical Centre, Department of Oncology, Zerifin, Israel; [3]Mary Crowley Medical Research Center, Dallas, USA; [4]MD Anderson Cancer Center, Gynecologic Oncology, Houston, USA; [5]Dana Farber Cancer Institute, Department of Medical Oncology, Boston, USA; [6]Exelixis Inc., South San Francisco, USA; [7]Chaim Sheba Medical Center, Institute of Oncology&Radiotherapy, Tel Hashomer, Israel*

Background: XL184 is an oral, potent inhibitor of MET, VEGFR2 and RET. MET overexpression has been observed in advanced ovarian cancer (OC). Anti-VEGF pathway agents have shown clinical benefit in pts with OC. Co-targeting of the MET and VEGF signaling pathways using XL184 may therefore be a promising treatment strategy. Preliminary data from the open label Lead-in Stage of a Phase 2 randomized discontinuation trial are presented showing the effects of XL184 in pts with OC.
Methods: Eligible pts have advanced epithelial OC, primary peritoneal, or fallopian tube cancer with measurable disease. Up to 3 prior regimens are allowed for platinum-resistant (disease recurrence within 6 months after last platinum based chemotherapy [PBC]) and refractory pts, and up to 4 for platinum-sensitive (disease recurrence >6 months after last PBC) pts. XL184 is administered open label at 100 mg free base equivalent (125 mg XL184-malate-salt) qd for 12 weeks (wks) (Lead-in Stage). Tumor response is assessed radiologically every 6 wks. Pts with partial or complete response (PR or CR) at week (wk) 12 continue to receive XL184; pts with progressive disease (PD) discontinue XL184. Pts with stable disease (SD) at wk 12 are randomized 1:1 to receive XL184 or placebo (P). Cross-over from P to XL184 is allowed upon PD. Primary endpoints are objective response rate at wk 12 and progression free survival in the Randomized Stage. CA125 levels will be correlated with clinical outcomes.
Results: A total of 21 pts have been enrolled to date with a median age of 60 years. The median number of prior systemic treatments was 2. Of the 7 pts who were evaluable (minimum 12 wk follow up) to date, 3 pts achieved an unconfirmed PR and 4 pts achieved SD. One pt with platinum-sensitive serous adenocarcinoma (SAC) achieved a 34% tumor reduction at wk 12. One pt with platinum-resistant SAC experienced a CA125 response per GCIG criteria and a 24% tumor decrease at wk 12. A second pt with platinum-resistant SAC achieved re-stabilization of PD after cross-over from P to XL184. Most frequently observed adverse events regardless of causality with CTCAE Grade ⩾3 in the Lead-in Stage include rash, palmar-plantar erythrodysesthesia syndrome, pruritus, pulmonary embolism, staphylococcal infection (each n = 1).
Conclusions: Preliminary results suggest that XL184 is active in pts with advanced OC who failed prior treatment. XL184 was generally well tolerated. Updated efficacy and safety results will be presented.

408 POSTER

Phase 2 study of XL184 (BMS-907351) in a cohort of patients (pts) with hepatocellular carcinoma (HCC)

E. Van Cutsem[1], W.C. Su[2], J. Davis[3], N. Haas[4], T.A. Samuel[5], C.J. Tsao[6], T.S. Yang[7], H. Brandy[8], G. Mann[8], A. Cohn[9]. *[1]University Hospitals Leuven, Department of Digestive Oncology, Leuven, Belgium; [2]National Chen Kung University Hospital, Department of Internal Medicine, Tainan, Taiwan; [3]Kansas City Cancer Center, Lee's Summit, USA; [4]University of Pennsylvania, Abramson Cancer Center, Philadelphia, USA; [5]Medical College of Georgia, Department of Medicine, Augusta, USA; [6]Chi Mei Hospital, Tainan, Taiwan; [7]Chang Gung Memorial Hospital, Tao-Yuan, Taiwan; [8]Exelixis Inc, South San Francisco, USA; [9]Rocky Mountain Cancer Center, Division of Medical Oncology, Denver, USA*

Background: XL184 is an oral, potent inhibitor of MET, VEGFR2 and RET. MET overexpression has been found to correlate with an increased incidence of intrahepatic metastasis and inversely correlated with survival of HCC patients. In addition, HCC is a hypervascular malignancy. Thus co-targeting of the MET and VEGF signaling pathways by XL184 may be a promising treatment strategy. Preliminary data from the open label Lead-in Stage of a Phase 2 randomized discontinuation trial are presented showing the effects of XL184 in pts with HCC.
Methods: HCC pts with a Child–Pugh score of A who failed up to 1 prior treatment regimen are eligible. XL184 is administered open label at 100 mg free base equivalent (125 mg XL184-malate-salt) qd for 12 weeks (wks) (Lead-in Stage). Tumor response per mRECIST is assessed every 6 wks. Pts with partial or complete response (PR or CR) at week (wk) 12 continue to receive XL184; pts with progressive disease (PD) discontinue XL184.