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

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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.

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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

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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.

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

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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.

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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

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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