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Early evidence of tolerability and clinical activity from a phase 1 study of TRC105 (anti-CD105 antibody) in patients with advanced refractory cancer

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Background: TRC105 is a human/murine chimeric IgG1 monoclonal antibody that inhibits angiogenesis and tumor growth. TRC105 binds human CD105, a proliferation-associated and hypoxia-inducible protein found on the surface of proliferating vascular endothelial cells. Preclinical studies have demonstrated the safety and antitumor activity of TRC105 in multiple tumor types as monotherapy and in combination with cytotoxic chemotherapy. An ongoing phase 1 trial is evaluating the safety and tolerability of single-agent TRC105 in patients with solid cancers.
Methods: Study patients were required to have advanced refractory cancer, ECOG $\leqslant$ 1, and adequate organ function. Patients with CNS or central thoracic cancers were excluded. TRC105 was administered by 60 minute IV infusion every 2 weeks until progression. Cohorts of 3−6 patients were planned at doses of 0.01, 0.03, 0.1, 0.3, and 1.0 mg/kg.
Results: A total of 12 patients have been enrolled and treated, 3 each at 0.01 and 0.03 mg/kg and 6 at 0.1 mg/kg. Dose escalation is ongoing. One patient at 0.1 mg/kg experienced Grade 4 hemorrhage from a gastric ulcer within 1 week of the first TRC105 infusion. The hemorrhage was considered possibly related to study treatment and a dose limiting toxicity, and responded to nonsurgical supportive care including red cell transfusions. No other Grade 3 or 4 adverse events have been reported. Possibly related grade 1 or 2 adverse events have included grade 2 fatigue, grade 2 dysgeusia, and grade 1 intermittent vaginal bleeding in a premenopausal woman with locally recurrent ovarian cancer. Two patients at 0.01 mg/kg remain on study without progression at month 5: a man with hormone refractory prostate cancer who had a complete PSA response accompanied by marked improvement in his bone scan, and a woman with metastatic ovarian cancer with radiographically stable disease and a 16% decrease in plasma CA125. Immunogenicity and PK analyses are ongoing and will be presented.
Conclusion: TRC105 is well-tolerated at doses that show evidence of clinical activity in advanced refractory cancer.

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A phase I study of enzastaurin (ENZ), an oral PKC inhibitor, in combination with erlotinib (ERL) administered orally daily to patients with advanced solid malignancies

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Background: ENZ, a serine/threonine kinase inhibitor, targets the PKC and PI3K/AKT pathways to inhibit angiogenesis and tumor cell proliferation and induce apoptosis. This study was conducted to determine the recommended dose (RD) of oral daily (po qd) ENZ in combination with ERL at the standard dose of 150 mg po qd, and to evaluate pharmacokinetics (PK) of the combination in patients (pts) with advanced solid tumors.
Methods: Cohorts of pts received escalating doses of ENZ plus standard ERL. All pts received ERL at 150 mg po qd on an empty stomach. ENZ dose levels of 250 mg (cohort 1) and 500 mg (cohort 2) po qd were studied with Day 1 loading doses of 250 mg bid and 375 mg tid, respectively. ENZ was taken with food. A treatment cycle was 28 days. PK sampling was conducted for all pts.
Results: Sixteen pts were enrolled (age range 46−83 y; 3M/13F; 11 Caucasian, 4 Asian, 1 Hispanic). Pts had NSCLC (n = 10) and 1 each of biliary papillomatosis, sarcoma, GIST, parotid gland tumor, thymoma, hepatocellular carcinoma. Performance status: ECOG 0 (n = 5), ECOG 1 (n = 10), ECOG 2 (n = 1). Pts had received 1 (n = 6), 2 (n = 9) or 3 (n = 1) prior regimens. Eight pts were never-smokers. No DLTs were observed. A pt in cohort 1 expired from rapid disease progression prior to completing 1 cycle and was replaced. The RD was ENZ 500 mg po qd and ERL 150 mg po qd (the established single agent doses of the drugs). Further dose escalation was not attempted. Twelve pts were enrolled in the expanded RD cohort. The majority of pts discontinued due to PD. One pt discontinued due to AEs (diarrhea, nausea/vomiting). One pt discontinued in cycle 1, 11 pts completed 2 cycles (10 with PD, 1 stopped for AEs), 1 pt completed 4+ cycles (ongoing) and 3 pts completed 7+ cycles (2 ongoing). Observed G3 toxicities possibly related to study drug were: diarrhea, deep venous thrombosis, renal insufficiency, hypertension, dizziness, fatigue. The most common AEs included G1/2 rash, diarrhea, and fatigue. Most pts had a red discoloration of urine/feces. One pt had a best response of PR for 11 mo. Three pts had SD for >4 mo including 1 with a 27% reduction in tumor size by RECIST and 1 actively smoking pt with SD for over 10 months. PK analyses are ongoing.
Conclusions: The RD of ENZ in combination with ERL is 500 mg and 150 mg respectively. There were no unexpected toxicities beyond those seen with either drug as a single agent. A phase 2 study of the combination is ongoing in pts with advanced NSCLC.

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A phase I study of gemcitabine, capecitabine and vandetanib in patients with advanced solid tumors with an expanded cohort in biliary and pancreatic malignancies

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Background: Vandetanib (V) is a multi-tyrosine kinase inhibitor with the ability to inhibit three key pathways involved in tumor growth: VEGF, EGF, and RET. Both VEGF and EGF pathways are overexpressed in biliary and pancreatic cancers. The objectives of this phase I study are to evaluate the safety profile of V in combination with standard doses of gemcitabine (G) and capecitabine (C); and to determine the maximum tolerated dose (MTD). In the expanded cohort, additional patients with biliary or pancreatic malignancies will be enrolled to further evaluate the safety of the combination and to assess the antitumor activity in this subset of patients.
Methods: Escalating doses of V (200 mg and 300 mg) administered orally for 28 days in combination with G 1000 mg/m^2 intravenously on days 1, 8, 15 and C 1660 mg/m^2/d given orally in divided doses on days 1−21. A cycle (cy) is 28 days. Inclusion criteria: ECOG PS 0−1; adequate hematologic, hepatic, and renal function. Exclusion criteria: infection, use of immunosuppressive agents, prolongation of QTc, and uncontrolled intercurrent illness. Dose Limiting Toxicites (DLT) was defined as >grade 3 (gr) non-hematologic toxicity or >gr 4 hematologic toxicity = 5 days. Response is assessed by RECIST criteria every second cy. Correlative studies: Plasma concentrations of VEGF and soluble VEGFR2 are being evaluated as potential biomarkers in the expanded cohort.
Results: To date, 9 patients have been enrolled in the dose escalation cohort. The median age is 55 (range 35−73); PS 1. All patients were evaluable for toxicity and had received a total of 30 cy (median 3 cy). There was one DLT (grade 4 neutropenia), which occurred in the 200 mg V cohort. Adverse events of gr 2 or above occurring in = 10% of the cy (n = 30) were neutropenia (gr 2 – 1 cy; gr 3 – 7 cy and gr 4 – 1 cy) and diarrhea (gr 2−3 cy). Considering antitumor effects (n = 9), 1 patient had a confirmed PR (metastatic cholangiocarcinoma with 80% tumor reduction, 5+ cy administered) and 5 had stable disease (endometrial, 6 cy; ovarian, 5+ cy; colon, 3+ cy; thymic, 3 cy; and cervical cancer, 3+ cy). Four patients are still on study.
Conclusions: V at 300 mg given orally for 28 days in conjunction with standard doses of G and C was well tolerated. No MTD was identified. Accrual of an expanded cohort of untreated systemic biliary and pancreatic cancer patients has commenced and an update of these patients will be presented at the meeting.

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Clinical responses in highly refractory solid tumor patients with oral MP-470, a multi-targeted tyrosine kinase inhibitor, in combination with standard of care chemotherapy regimens: preliminary report from a multi-institutional phase-1b clinical trial

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Background: MP-470 (MP) is an orally bioavailable multi-targeted tyrosine kinase inhibitor which hits a number of validated tumor targets. MP also sensitizes cancer cells to DNA damaging agents and to radiation therapy, presumably through the suppression of Rad51, a key component to the cellular repair machinery in response to DNA double-strand breaks. Preliminary phase-1 data on MP as a single agent have been presented previously. Results presented here are from a phase-1b trial of MP combined with five standard-of-care (SOC) anticancer therapies.