expression of phosphorylated-PDGR-α was 7-fold higher in the tumor endothelium compared to the tumor cells. However levels of p-PDGFR within each compartment remained the same or were slightly increased after treatment.
Conclusions: GIST tumors that responded to imatinib therapy displayed lower overall levels of phosphorylated-c-Kit (most notably within the tumor endothelium), decreases in blood flow and volume, reductions in MVD, and increased levels of endothelial and tumor cell apoptosis. Imatinib may have anti-vascular effects on GIST tumors and this can be demonstrated at early time-points in therapy. We believe that inhibition of c-Kit activation in the tumor-associated endothelium by imatinib is a novel finding. The significance of these observations will be investigated in this ongoing study.

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A phase I and pharmacokinetic clinical trial of subcutaneous (sc) VEGF Trap in advanced solid tumor patients

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Background: VEGF Trap is a potent angiogenesis inhibitor comprised of portions of the human VEGF receptor VEGFR1 (Flt-1) and VEGFR2 (KDR) extracellular domains fused to the Fc portion of human IgG. VEGF Trap binds VEGF-A 100- to 1000-fold more tightly than monoclonal antibodies (Kd <1 pM) and neutralizes all circulating and tissue VEGF-A isoforms plus placental growth factor.
Methods: In this phase I trial, successive cohorts of pts with relapsed or refractory solid tumors received 1 (or 2) doses of sc VEGF Trap, followed 4 weeks later by 6 weekly (or twice weekly) doses. Pts without disease progression subsequently entered a long-term extension study. Study endpoints included safety, pharmacokinetics, and immunogenicity. Antitumor activity was assessed by CT scan.
Results: A total of 38 pts were treated across 7 dose levels: 0.025, 0.05, 0.1, 0.2, 0.4, and 0.8 mg/kg weekly, and 0.8 mg/kg twice weekly. Potentially drug-related grade 3 or 4 adverse events (AEs) encountered included hypertension (n=2), proteinuria (n=1), afebrile neutropenia (n=1), and pulmonary embolism (n=1). Other than HTN, no dose-related pattern of AEs emerged. The maximum tolerated dose was not reached. No pts have developed anti-VEGF Trap antibodies, including those pts treated for ⩾6 mos. Plasma VEGF Trap levels associated with antitumor activity in animal models were approached in the 0.8 mg/kg once and twice weekly dose groups. Objective partial or complete responses were not achieved, but 17 of 35 evaluable pts, including 8 of 12 pts treated with ⩾0.8 mg/kg/week, maintained stable disease (SD) for at least 10 weeks and entered the extension study.
Conclusions: VEGF Trap has a favorable safety and tolerability profile. Consistent with previous findings with an anti-VEGF antibody, VEGF Trap may be associated with dose-dependent hypertension. Eight of 12 (67%) of evaluable pts treated with 0.8 mg/kg once or twice weekly, compared with 9 of 23 (39%) who received lower doses, maintained SD at the end of the 10-week study. Final results of the study will be presented.

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In vitro and in vivo characterization of exel-7647, a novel spectrum selective receptor tyrosine kinase inhibitior that modulates angiogenesis and tumor cell proliferation

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The receptor tyrosine kinases (RTKs) KDR, EGFR and ErbB2 have been implicated in tumor growth and angiogenesis and inhibitors of these RTKs have been validated in the clinic for oncology indications. We have embarked upon a drug discovery program to identify small molecules that simultaneously modulate the activity of the RTKs involved in both tumor growth and vascularization. This effort has identified EXEL-7647, which exhibits potent inhibitory activity *in vitro* against KDR, EGFR and ErbB2 and demonstrates potent anti-proliferative, anti-angiogenic activity and tumor growth inhibition (TGI).
Inhibition of KDR, EGFR and ErbB2 both enzymatically and in cellular assays of receptor phosphorylation by EXEL-7647 translates into potent inhibition of endothelial cell function in response to the key angiogenic factor, VEGF, and broad anti-proliferative activity against tumor cell lines.
In pharmacodynamic studies, oral administration of EXEL-7647 to athymic mice results in a dose dependent and sustained inhibition of KDR, EGFR, and ErbB2 phosphorylation with a single oral dose producing prolonged (>48 h) inhibition of EGFR and ErbB2 phosphorylation. Immunohistochemical analysis of MDA-MB-231 human breast carcinoma xenografts 3–7 days following a single oral dose of EXEL-7647 revealed a rapid and complete loss of microvessels (CD31) in the tumor, a significant decrease in the number of proliferating cells (Ki67) and an increase in tumor necrosis and hypoxia over time. *In vivo* efficacy studies in xenograft-bearing athymic mice demonstrate that EXEL-7647 exhibits broad anti-tumor activity, with a daily oral dose of 100 mg/kg of EXEL-7647 producing inhibition of tumor growth (85% or greater), completely halting growth in some models (A431). In MDA-MB-231 and PC-3 models, EXEL-7647 also induces regression of large established tumors (staged at 500 mg). In all xenograft studies, immunohistochemical analysis of tumors examined at the end of the dosing period, revealed dose dependent increases in tumor necrosis, decreases in tumor vascularity (CD31) and decreases in the number of cells in S-phase (Ki67), thus demonstrating that EXEL-7647 effects both tumor cell proliferation and angiogenesis.
EXEL-7647 is orally bioavailable in rodents and non-rodent species when dosed either as a solution or as a solid. EXEL-7647 exhibits moderate clearance, a half-life >8 h and a large volume of distribution.
In summary, EXEL-7647 is a potent anti-cancer agent that simultaneously modulates three clinically validated targets KDR, EGFR and ErbB2 and has the potential to act as an effective therapy for solid and metastatic tumors.

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A phase II study of oxaliplatin, capecitabine and bevacizumab in the treatment of metastatic colorectal cancer

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Background: Bevacizumab (BV, Avastin™) is a recombinant, humanized monoclonal antibody directed against vascular endothelial growth factor. Phase III results have demonstrated a survival advantage for the addition of BV to bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first line therapy for metastatic colorectal cancer. Recent data, however, suggest that the FOLFOX regimen (biweekly administration of oxaliplatin, leucovorin, and bolus plus continuous infusion of fluorouracil) is superior to bolus IFL with improved response rate, time to progression, and overall survival. The FOLFOX regimen requires the inconvenience of an ambulatory infusion pump which limits its use in many patients. We sought to investigate the combination of capecitabine, oxaliplatin and bevacizumab (XeloxA) as a more convenient and active regimen.
Methods: Patients with previously untreated metastatic colorectal cancer received oxaliplatin 85 mg/m^2 day 1, capecitabine 1000 mg/m^2 days 1–5 and 8–12, and BV 10 mg/kg day 1. Cycles were repeated every 2 weeks. Standard dose reductions for toxicity were permitted.
Results: Twenty patients received XeloxA therapy: 13 men, 7 women, median age 57 (range 24–76), median ECOG performance status 0 (range 0–1). Median follow-up is 5.6 months (range 1.2–7.3). 20 are fully evaluable for toxicity and 15 for efficacy. Therapy was generally well tolerated. Diarrhea was the most prominent adverse effect occurring in 11/20 (55%) patients, although only 7/20 (35%) had grade 3 diarrhea and no patient experienced grade 4 diarrhea. Mild (grade 1) hand-foot syndrome (HFS) was seen in most patients, 13/20 (65%); 9/20 (45%) developed grade 2 HFS, but no patient developed grade 3 HFS Other toxicities were minimal with one patient (5%) developing grade 3 neutropenia, and one patient (5%) developing grade 3 neuropathy. Fifteen patients (75%) required at least one dose reduction of capecitabine, and 6/20 (30%) required 2 dose reductions during treatment, typically for diarrhea and/or HFS. Of the 15 patients evaluable for efficacy, all were restaged every two months while on therapy. Nine patients experienced a partial response and one patient a complete response for an overall response rate of 67%. Responses were typically rapid with 7/10 (70%) responding patients achieving their partial or complete response at the first 2-month restaging. Stable disease as best response was seen in 5 patients (33%) with tumor reductions of 0–29% at follow-ups ranging from 2.7 to 6.2 months.
Conclusions: Preliminary evidence suggests that the XeloxA regimen is highly active. The alternative capecitabine dosing schedule appears to be well tolerated although many patients require an initial dose reduction of capecitabine. Consequently we have modified the current starting dose of capecitabine to 850 mg/m^2. Enrollment will continue to a planned accrual of 50 patients.