(n = 1). In cohort 3, one DLT was observed (grade 3 HFSR). Additionally, 2/6 patients discontinued in the first two cycles of full treatment (SOR 400 mg bid + CAP 2100 mg/m^2) due to grade 3 HFSR (n = 1); grade 2 mucositis and grade 3 abdominal pain (n = 1). In cohort 4, treatment is ongoing in 2/12 patients; no DLTs have been observed. The PK of SOR (200 and 400 mg bid) were not affected to a clinically relevant degree by CAP. SOR 200 mg bid had no relevant effect on the PK of CAP. One heavily pretreated patient with breast cancer and skin lymphangitis had tumor regression (cohort 1). Two patients (RCC, n = 1; urothelial cancer, n = 1) had tumor shrinkage.
Conclusions: SOR plus CAP had a safety profile consistent with that of the individual agents. SOR 400 mg bid plus CAP 1700 mg/m^2 per day is the recommended dose for further studies.

99 POSTER

Phase IB trial of PX-12 delivered as a 24-hr infusion in patients with advanced gastrointestinal malignancies

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Introduction: PX-12 is a first small molecule inhibitor of thioredoxin-1 (Trx), a redox regulator involved in tumor cell proliferation, resistance to apoptosis and angiogenesis. High levels of thioredoxin have been detected in many human cancers including colorectal, gastric and pancreatic cancers. PX-12 inhibits Trx resulting in down-regulation of HIF-1α and VEGF and inhibits tumor growth in animal models. In a first phase I trial of PX-12 was delivered as a 1- or 3-hr infusion daily $\times$5 and found to have a good safety profile, lowering circulating Trx levels and producing stable disease in 15 of 37 evaluable patients. It was also observed that prolongation of infusion from 1 to 3 hr resulted in a more pronounced decrease in circulating Trx levels, as a surrogate marcer of activity. Thus, in this Phase I B study we explored a 24-hr infusion of PX-12, administered once every 14 days to determine if this schedule provides additional benefit and tolerability.
Methods: The purpose of this study was to establish safety, assess PK and PD parameters and preliminary clinical activity of PX-12. Patients with advanced, unresectable or metastatic gastrointestinal carcinomas and ECOG PS 0–2 and a good organ function were eligible. Based on the safety data from the phase I trial, PX-12 was delivered at 150 mg/m^2, 200 mg/m^2, 300 mg/m^2 and 450 mg/m^2, as a continuous IV infusion, via portable pump, over 24-hr and repeated every 14 days.
Results: At the time of the abstract submission a total of 8 patients have been enrolled, encompassing dose levels 150–300 mg/m^2. No grade 3 or 4 toxicities were observed. Grade 1–2 toxicities included nausea, cough, taste alteration, fatigue, fever and constipation. PD assessments included plasma Trx and VEGF levels and urine VEGF. In addition, a dynamic contrast enhanced MRI (DCE-MRI) to evaluate PX-12 induced changes in tumor vascularity/permeability was obtained on a limited number of patients.
Conclusion: Initial data indicates that PX-12 can be delivered safely as a 24-hr infusion. Dose escalation continues at the 300 and 450 mg/m^2 dose level and data on clinical activity and PK/PD analyses, including DCE-MRI, will be presented.

100 POSTER

Targeting tie-1 inhibits the growth of tumor xenografts as a monotherapy and has increased activity in combination with a VEGF inhibitor

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The Tie-1 receptor tyrosine kinase plays a critical role in vascular development and Tie1-deficient mice die late in embryonic life with severe edema, hemorrhage and defects in microvessel integrity. Numerous studies have demonstrated Tie-1 induction in the neovasculature of solid tumors. Our lead candidate DX-2240, is a human IgG1 which binds to human and murine Tie-1 with high affinity and inhibits endothelial tube formation *in vitro*. We have demonstrated significant retardation (30−60% TGI) of tumor progression by DX-2240 in colorectal, lung, renal, pancreatic and prostate cancer xenograft models in nude mice. Immunohistochemical analyses of tumors from these mice reveals altered tumor vascular morphology, increased hypoxia and necrosis as well as decreased smooth muscle coverage of the blood vessels. In addition to its effects as a monotherapy in xenograft models, we have demonstrated increased anti-tumor activity of bevacizumab in combination with DX-2240 (~70% TGI). Combining two angiogenesis inhibitors has the potential of increasing the inhibition of tumor growth and decreasing the frequency of tumor resistance in the treatment of human primary and metastatic tumors.

101 POSTER

Interleukin-18 regulates vascular endothelial growth factor-mediated angiogenesis in hepatic melanoma metastasis

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Interleukin-18 (IL-18) increases during cancer progression and its seric augmentation has been correlated with poor clinical outcome and shortened survival in some cancer types. Despite its immune-stimulating properties, proinflammatory effects of IL-18 also promote experimental metastasis via cell adhesion molecule and growth factor production. Because IL-18 contributes to angiogenic activity associated to rheumatoid arthritis via motility- and angiogenic-stimulating factor production, the hypothesis has been advanced that tumor-associated IL-18 might also support tumor angiogenesis. In the present work we studied the effect of soluble IL-18 binding protein (IL-18BP) on the endogenous VEGF production and angiogenic activity during the prevascular stage of hepatic micrometastases induced by the intrasplenic injection of murine B16F10 melanoma (B16M) cells. In vitro, IL-18BP was used to study the contribution of VEGF to matrix metalloproteinase (MMP) production and migration of primary cultured hepatic endothelial (HSE) and hepatic stellate (HSC) cells. Mice given one daily intraperitoneal injection of IL-18BP (25 μg/kg) from day 7 to 12 after cancer cell injection decreased metastasis density by 25% and volume by 40%. This treatment schedule also significantly ($p < 0.01$) reduced the augmentation of VEGF in hepatic blood observed since day 8 after intrasplenic injection of B16M cells. Consistent with in vivo data, histological analyses demonstrated that IL-18BP significantly ($p < 0.01$) decreased by 75% both HSC and HSE cell recruitment in hepatic melanoma metastases and by 50% the number of Ki67-positive melanoma cells in metastatic foci. Moreover, in vitro, IL-18BP abrogated VEGF gene transcription and secretion from 3% hypoxic atmosphere-cultured and HSE cell-conditioned medium-treated B16M cells, respectively. IL-18BP also down-regulated MMP-2 and MMP-9 activation in the HSE cell supernatant induced by VEGF and HSC-derived factors. Furthermore, it also inhibited HSE cell and HSC migration induced by either B16M-derived or exogenous recombinant VEGF. These results demonstrate that IL-18 mediates proangiogenic action of VEGF in melanoma hepatic metastasis, and that IL-18 blockade may represent a potentially effective antineoplastic therapy against liver metastasis.

102 POSTER

Pediatric Preclinical Testing Program (PPTP) evaluation of the VEGFR-2 Inhibitor AZD2171

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Background: AZD2171 is an oral, highly potent and selective VEGF signaling inhibitor of all VEGFR tyrosine kinases (VEGFR-1, -2 and -3) and effectively blocks VEGF-induced angiogenesis and neovascular survival. AZD2171 inhibits the growth of a wide range of established adult tumor xenografts in a dose-dependent manner and is in clinical evaluation for adults with cancer.
Methods: The PPTP includes an *in vitro* panel (23 lines) as well as panels of xenografts (n = 61) representing most of the common types of childhood solid tumors and childhood ALL. AZD2171 was tested against the PPTP *in vivo* tumor panels at a dose of 6 mg/kg PO daily for 6 weeks. Three measures of antitumor activity were used: 1) response criteria modeled after the clinical setting [e.g., partial response (PR), complete response (CR), etc.]; 2) treated to control (T/C) tumor volume at day 21; and 3) a time to event measure based on the median EFS of treated and control lines (intermediate activity required EFS T/C > 2, and high activity additionally required a net reduction in median tumor volume at the end of the experiment).
Results: AZD2171 induced significant tumor growth delay in 83% of the solid tumor xenografts tested, with growth delay observed in each of the

solid tumor panels. Using a time to event measure of efficacy, AZD2171 had intermediate and high levels of activity against 10 and 1 of 26 solid tumor xenografts evaluable for this measure, respectively. Intermediate activity was observed in 4 of 5 rhabdomyosarcoma, 3 of 3 Ewing sarcoma, and 2 of 3 Wilms tumor (WT) xenografts, with high level activity observed in 1 of 2 evaluable rhabdoid tumor (RT) xenografts. AZD2171 induced CR against 1 of 3 osteosarcoma (OS), 1 of 3 RT, and 1 of 3 WT xenografts, but had no effect on *in vivo* growth of any ALL xenografts. Kasumi-1, the only PPTP *in vitro* panel cell line with an $EC_{50} < 1\,\mu M$ (EC_{50} 0.175 μM) is known to have a gain-of-function $KIT^{Asn822Lys}$ mutation.
Conclusions: AZD2171 demonstrated broad activity against the PPTP's solid tumor panel. Antitumor activity was manifested primarily as tumor growth delay, although tumor regressions were observed in the OS, RT, and WT panels. Further preclinical evaluation of AZD2171 is warranted and will include studies of AZD2171 in combination with clinically relevant agents for selected xenografts in which activity was observed. The Pediatric Brain Tumor Consortium is planning clinical evaluations of AZD2171 in children.
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103 POSTER

A phase II study of enzastaurin as second- or third-line treatment of non-small cell lung cancer (NSCLC)

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Background: Enzastaurin, an oral serine/threonine kinase inhibitor, targets the PKC and PI3K/AKT pathways to inhibit tumor cell survival and proliferation and tumor-induced angiogenesis. PKC isoforms and PI3K/AKT are over-expressed and active in NSCLC and are associated with poor prognosis and treatment resistance. Based on preclinical and phase I trial data, this multicenter phase II trial was conducted to evaluate enzastaurin as second- and third-line treatment of NSCLC. The primary objective was to determine the rate of progression-free survival (PFS) at 6 months. Secondary objectives included safety, antitumor activity, and the rate of survival at 12 months.
Methods: Patients with advanced (stage IIIB) or metastatic (stage IV) NSCLC, who had failed at least 1 prior therapy, received 500 mg of oral enzastaurin (tablets), once daily after breakfast, every 28 days until disease progression or unacceptable toxicity occurred. All patients had to have failed prior platinum-based chemotherapy and had to be considered eligible for second- or third-line treatment.
Results: Fifty-three patients (55% male, 45% female; ECOG $\leqslant 2$), were enrolled. All patients had prior chemotherapy, including 28% with EGFR inhibitor treatment. At the time of interim analysis, 34 (64%) patients were alive. The median PFS time was 1.84 months (95% limits: 1.68–1.87 months) and the rate of PFS at 6 months was 10.4% (95% limits: 8.4%-10.9%). Eighteen patients (34%) had a best response of stable disease, while no patients had a partial or complete response. Of the 53 patients, 10 (19%) received therapy for $\geqslant 6$ cycles, 3 of whom are currently receiving enzastaurin beyond 9 cycles of treatment. The most common toxicity was fatigue (n = 21), noted within 1 week of starting treatment, but was not reported in patients with disease stabilization.
Conclusion: Although no objective tumor responses were observed in this study, 10.4% of the patients were progression-free at 6 months. Additional evaluations are ongoing to better understand the use of enzastaurin in the treatment of NSCLC, including studies to determine how to best combine enzastaurin with other agents active in NSCLC.

104 POSTER

Simultaneous blockade of VEGF and HGF receptors results in potent anti-angiogenic and anti-tumor effects

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Vascular endothelial growth factor (VEGF) and its tyrosine kinase receptors, VEGFR1 and VEGFR2, are expressed on the surface of vascular endothelial cells and play a central role in the promotion of tumor angiogenesis. Hepatocyte growth factor (HGF) and its tyrosine kinase receptor Met are overexpressed or activated in a wide variety of tumor types, promoting tumor growth. Additionally, HGF and VEGF interact synergistically to promote endothelial cell proliferation, tubule formation, and growth of new vessels in vivo. EXEL-7184 (XL184) is a small molecule tyrosine kinase inhibitor that targets the VEGF and HGF receptor tyrosine kinases.
In enzymatic assays, EXEL-7184 is a potent inhibitor of VEGFR2 and Met tyrosine kinase activities, with IC_{50} values in the sub-nanomolar and single digit nanomolar range, respectively. EXEL-7184 also exhibits potent activity in cell based assays, inhibiting VEGF-induced activation of ERK in endothelial cells, and HGF-induced activation of Met in tumor cells. EXEL-7184 also inhibits endothelial tubule formation stimulated by VEGF or by conditioned media derived from tumor cell lines, and HGF induced responses in tumor cells (e.g. invasion, chemotaxis). In pharmacodynamic assays, oral administration of EXEL-7184 resulted in dose-dependent and reversible inhibition of VEGFR2 in mouse lung, and of Met in xenograft tumors and in mouse liver. Following acute administration to xenograft tumor-bearing mice, EXEL-7184 caused rapid disruption of the tumor vasculature, and apoptosis of both tumor and endothelial cells. Administration of EXEL-7184 using both once-daily and less frequent oral dosing schedules resulted in significant efficacy in a range of solid tumor models, with substantial regression of large tumors. Immunohistochemical analysis at the end of efficacy studies demonstrated potent inhibitory effects on the tumor vasculature, and strong induction of tumor cell death.
In summary, EXEL-7184 is a potent inhibitor of VEGFR2 and Met, and exhibits potent anti-tumor and anti-angiogenic activity in preclinical models. A phase I clinical trial for EXEL-7184 is in progress.

105 POSTER

A prospective study of the cutaneous side effects of sorafenib, a novel multi-kinase inhibitor

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Background: This study investigated the incidence, severity and management of cutaneous reactions to the oral multi-kinase inhibitor sorafenib (Nexavar®) (SOR) in advanced renal cell carcinoma (RCC) patients. Additional objectives were to determine the effect of SOR on nevi and on ERK phosphorylation in normal skin.
Materials and Methods: During a 16 month period from Nov. 2003 to Feb. 2005, all consecutive patients included in our center in the Phase III TARGETs RCC trial were enrolled in this dermatologic sub-study. Patients were randomized to receive either SOR 400 mg twice daily (bid) or placebo. Dermatologic examination was performed before treatment, every 3 weeks during the first four cycles, and every 4 weeks thereafter.
Results: Ninety-six patients with unresectable or metastatic RCC and failure of one systemic therapy were enrolled, and 85 received either SOR (n = 43) or placebo (n = 42). Thirty-nine patients (90.7%) on SOR, and three (7.1%) on placebo, had $\geqslant$ one cutaneous adverse event. Most cutaneous adverse events were mild or moderate; only two SOR patients had grade 3 toxicity (hand–foot skin reaction [HFSR]). No patient discontinued due to cutaneous side effects. HFSR was typically less severe and more localized than the form associated with traditional chemotherapies. HFSR (grade 3) led to dose reductions in two patients (50%), but resolved in 3–4 weeks without sequelae. After restoration of full-dose treatment, HFSR recurred in only one of these patients. SOR-induced nevi modification was not observed and no clear difference in ERK phosphorylation was reported between treated and non-treated patients. Dermatologic symptoms were easily managed with topical treatments.
Conclusions: Despite a high frequency of SOR-induced cutaneous toxicities, most were mild to moderate in severity and easily manageable. The majority of SOR-induced grade 2 HFSR can be treated symptomatically without dose decrease or interruption. For grade 3 HFSR, dose reduction (by 50%) or interruption for 5–7 days, plus symptomatic treatment, usually leads to rapid symptom relief. In this study, treatment discontinuation for HFSR was not necessary. Further experience at our center shows that even when discontinuation is necessary for severe HFSR, reinitiation at the same dose is often possible without reoccurrence of this grade of toxicity. Final clinical and pharmacodynamic results, including correlation of cutaneous events with patient response, will be reported.

106 POSTER

Methylnaltrexone inhibits S1P, VEGF and PDGF-induced angiogenesis: role of receptor transactivation

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Background: The role of opioids in angiogenesis is largely unknown. The peripheral mu opioid antagonist, methylnaltrexone (MNTX), allows exploration of the role of opioids in angiogenesis. We have shown in human dermal microvascular endothelial cells (EC) that clinically relevant concentrations of morphine sulfate (MS) cause EC migration, inhibited by pretreatment with MNTX at therapeutically relevant levels (0.1 μM). To confirm the angiogenic effect of opioids and determine its mechanism, we examined MNTX in agonist-induced human pulmonary microvascular EC (HPMVEC) proliferation (P) and migration (M), two key elements in angiogenesis.