(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-1$\alpha$ 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 $\mu$g/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