was tested by reporter assays. For human colon carcinomas, S100A4 expression, beta-catenin genotype, and metachronous metastasis were correlated.
Results: We identified S100A4 as the most regulated gene by gain-of-function beta-catenin using a 10K microarray. Cell lines with mutant beta-catenin expressed up to 60-fold elevated S100A4 levels, and displayed strongly increased cell migration and invasion. Very remarkably, invasion and migration were knocked down by S100A4 siRNA and beta-catenin siRNA. S100A4 cDNA transfection increased migration and invasion. We identified a TCF binding site within the S100A4 promoter and demonstrated the direct binding of heterodimeric beta-catenin/TCF complexes to the S100A4 promoter. Reporter assays confirmed the beta-catenin-induced S100A4 promoter activity. Transfection of dominant negative TCF blocked S100A4 expression. Furthermore, S100A4 mRNA expression was increased in primary colon cancers, which later developed distant metastases, compared to tumors which did not metastasize. Colon tumors heterozygous for gain-of-function beta-catenin showed concomitant nuclear beta-catenin localization, high S100A4 expression and metastases.
Conclusions: S100A4 is a direct beta-catenin/TCF target, which induces cell migration and invasion in cell culture. S100A4 siRNA knocks down beta-catenin-mediated migration and invasion. S100A4 has potential value for prognosis of metastasis formation in colon cancer patients.

96 POSTER

A population pharmacokinetic model for BIBF 1120, a triple angiokinase inhibitor, in cancer patients after single and multiple oral dosing

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Background: BIBF 1120 is a triple angiokinase inhibitor targeting VEGFR, PDGFR, FGFR kinases. The objective of the population pharmacokinetic analysis was to develop a model that describes the pharmacokinetics (PK) of BIBF 1120 in cancer patients and can be used to simulate further dosing schedules.
Methods: PK Data of three Phase I clinical trials were used for analysis, in which BIBF 1120 was orally administered to cancer patients, who received doses ranging from 50 mg to 450 mg once daily (q.d.) and 150 mg to 300 mg twice daily (b.i.d.) for 28 days. 117 patients contributed 1734 plasma concentrations. The population PK model was developed using NONMEM® and S-Plus®. This software was used also for the simulations.
Results: A two-compartmental model with first order absorption and elimination rate adequately described the PK data of BIBF 1120 after single and multiple dose administration. The delayed absorption was accounted for by implementing two transit compartments in the model. Inter individual variability was identified on bioavailability (F), clearance (CL/F) and the first order absorption rate constant (ka). In addition, the random variability in bioavailability within a subject between day 1 and day 28 was described by a parameter for inter occasion variability (IOV). The within subject variability in bioavailability was in the same range as the between subjects variability. No time-dependency (e.g. due to (auto-) induction or inhibition), no study dependency and no dose-dependency of BIBF 1120 PK parameters could be identified. Two separate residual errors were estimated, one for the plasma concentrations in the full PK profile on day 1 and day 28 and one for trough plasma concentrations between day 1 and day 28.
Simulations demonstrated that the b.i.d. dosing schedule results in the expected increase in exposure to BIBF 1120 in cancer patients compared to q.d. dosing. Furthermore, simulations of further dosing regimens for the currently tested Phase II doses of BIBF 1120 (150 mg and 250 mg bid) were performed.
Conclusion: BIBF 1120 plasma concentrations in cancer patients were successfully described by a two-compartmental model with a first order absorption and elimination rate. Two transit compartments accounted for the delayed absorption. No significant study or dose differences or any time-dependency in BIBF 1120 PK parameters could be identified. The model developed serves as a tool to predict further dosing shedules.

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A phase I dose-escalation study of the safety and pharmacokinetics of a novel spectrum selective kinase inhibitor, XL820, administered orally to patients with solid tumors

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Background: XL820 is an orally available small molecule inhibitor of multiple receptor tyrosine kinases involved in tumor cell growth and angiogenesis. The primary targets of XL820 are wild type and mutationally-activated KIT, VEGFR2/KDR, and PDGFRβ. The purpose of this study is to define the maximum tolerated dose (MTD) and pharmacokinetics (PK) of XL820.
Methods: Patients (pts) with advanced solid malignancies are enrolled in successive cohorts to receive XL820 orally as a single dose on day 1 with pharmacokinetic (PK) sampling, followed on day 4 by 5 consecutive daily doses with additional PK sampling and observation until day 21. In subsequent cycles, pts receive daily dosing for 5 days every 14 days. Tumor response is assessed every 8 weeks by the RECIST.
Results: To date, a total of 17 pts (colon cancer [3], NSCLC [2], mesothelioma [2], GIST [1], testicular cancer [1], ocular melanoma [1], SCLC [1], ampullary cancer [1], thyroid cancer [1], pancreatic cancer [1], renal cancer [1], breast cancer [1], cholangiocarcinoma [1]) have been treated across 6 dose levels: 0.5, 1.0, 2.0, 4.0, 8.0 and 16.0 mg/kg. There has been 1 dose-limiting toxicity of CTCAE grade 3 AST in a pt dosed at 16.0 mg/kg, thus the maximum tolerated dose is not yet defined. Of 15 evaluable pts, 4 have had stable disease (3.5−8+ months). Preliminary PK analysis (0.5−8.0 mg/kg) indicates that systemic drug exposure (area under the plasma concentration-time curve; AUC) and peak plasma levels (Cmax) tend to increase with increasing XL820 dose, but not dose-proportionally with incremental XL820 dose increases. Cohort mean AUC and Cmax values (n = 3 subjects per cohort) were 10,167±4738 ng h/mL and 347±171 ng/mL, respectively, following day 1 dosing at 8.0 mg/kg. Following 5 consecutive daily doses, AUC values were generally <2-fold higher than following a single XL820 dose, suggesting minimal drug accumulation with repeat dosing. Terminal half-life values were approximately 20 hours, and appeared to be unaffected by dose level or duration of treatment.
Conclusions: XL820 is well tolerated up to the 8.0 mg/kg dose. Accrual to the 16 mg/kg cohort is ongoing.

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A Phase I study of sorafenib in combination with capecitabine in patients with advanced, solid tumors

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Background: This single-center, dose-escalation study investigated the safety and pharmacokinetics (PK) of the oral multi-kinase inhibitor sorafenib (Nexavar®) (SOR) in combination with capecitabine (CAP).
Materials and Methods: SOR was given twice daily (bid) on Day 8–21 in Cycle 1, and continuously thereafter. CAP was given orally bid from Day 1 in a 2 weeks on/1 week off schedule. Four cohorts were investigated: SOR 200 mg bid + CAP 2100 mg/m^2 (cohort 1); SOR 400 mg bid + CAP 2100 mg/m^2 (cohort 2); SOR 200 mg bid for the first two cycles, then 400 mg bid thereafter + CAP 2100 mg/m^2 (cohort 3); SOR 400 mg bid + CAP 1700 mg/m^2 (cohort 4). PK were investigated on Day 21 of Cycle 1 and Day 7 of Cycle 2 for SOR, and on Day 7 of Cycles 1 and 2 for CAP. Safety was determined based on the first two cycles in each cohort.
Results: Thirty-five patients were treated (cohorts 1–4; n = 13, 4, 6, and 12, respectively). Common tumors were colorectal cancer (CRC; n = 12) and renal cell carcinoma (RCC; n = 11). Median treatment duration was 133, 110, >225, and >157 days in cohorts 1–4, respectively. In cohort 1, one RCC patient had 932 days of treatment and one CRC patient had 496 days. Median duration on treatment (n = 35) for SOR was 147 days (range 2–925) and 131 days (range 9–903) for CAP. Frequent drug-related toxicities (all grades) over all cycles were hand–foot skin reaction (HFSR; 89%), diarrhea (71%), and fatigue (69%). In cohort 1, two patients had grade 3 dose-limiting toxicities (DLTs): HFSR (n = 1) and diarrhea/HFSR (n = 1). In cohort 2, all four discontinued after Cycle 1 or 2, due to grade 3 fatigue (n = 1); grade 2 HFSR and grade 3 mucositis (n = 1); grade 1 HFSR, grade 1 epigastric pain, and grade 1 nausea (n = 1); and grade 1 thrombopenia

(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.

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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.

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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.

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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