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

P. Stopfer[1], R. Kaiser[2], N. Snelder[3], B. Ploeger[3], A. Staab[1]. *[1]Boehringer Ingelheim GmbH&Co KG, Department of Drug Metabolism and Pharmacokinetics, Biberach (Riss), Germany; [2]Boehringer Ingelheim GmbH&CO KG, Department of Clinical Research, Biberach (Riss), Germany; [3]LAP&P Consultants, Leiden, The Netherlands*

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.

97 POSTER

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

K. Papadopoulos[1], J. Rodon[1], A. Mita[1], P. O'Rourke[1], A. Patnaik[1], E. Rubin[2], A. Tolcher[1], M. Stein[2]. *[1]Institute for Drug Development, Cancer Therapy and Research Center, San Antonio, Texas, USA; [2]Cancer Institute of New Jersey, Robert Wood Johnson University Hospital, New Brunswick, NJ, USA*

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.

98 POSTER

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

A. Awada[1], T. Gil[1], K. Burk[2], J. Vanhamme[1], I. Mancini[1], T. Besse[1], E. Brendel[3], A. Matthys[4], M. Piccart[1], A. Hendlisz[1]. *[1]Jules Bordet Institute, Brussels, Belgium; [2]Bayer Pharmaceuticals Corporation, West Haven, CT, USA; [3]Bayer HealthCare AG, Wuppertal, Germany; [4]Bayer SA-NV, Brussels, Belgium*

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