136 POSTER

Regulation of tumour angiogenesis and cell survival by integrin-linked kinase (ILK): pre-clinical evaluation of novel small molecule inhibitors

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Integrin-linked kinase(ILK) is a PI-3Kinase-dependent focal adhesion serine/threonine protein kinase and couples integrins and growth factor receptors to the actin cytoskeleton and the Akt/PKB signaling pathway. ILK is overexpressed in many types of tumours and its expression is often correlated with disease grade and inversely correlated with patient outcome. ILK activity is also constitutively activated in PTEN-null tumour cells, and inhibition of ILK activity in such cells results in the inhibition of Akt/PKB phosphorylation and induction of apoptosis. We now demonstrate that ILK stimulates the expression of HIF-1alpha and VEGF in a Akt/PKB and mTOR-dependent manner. ILK is also required for VEGF stimulated endothelial cell migration and proliferation. We have identified highly selective small molecule inhibitors of ILK activity. We will provide data with KP-074728, a pre-clinical lead candidate, demonstrating inhibition of Akt/PKB phosphorylation on Serine-473, HIF-1alpha, and VEGF expression in tumour cells. The inhibitor also causes marked inhibition of VEGF stimulated endothelial cell morphogenesis as well as tumor growth and angiogenesis in human prostate and glioblastoma xenograft models in vivo. This compound is also highly effective in inducing apoptosis and growth arrest in several human breast cancer cell lines in vitro and in vivo. ILK is thus an important therapeutic target for the control of tumour angiogenesis and tumour progression.

135 POSTER

A clinical phase I dose escalation, pharmacokinetic (PK) and pharmacodynamic (PD) study of BIBF 1120 in advanced cancer patients

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Background: BIBF 1120 is a potent, orally available triple kinase inhibitor (VEGFRs, PDGFRs, FGFRs) that suppresses tumour growth by inhibition of tumour angiogenesis. A first-in-man study was carried out with a once daily schedule in chemotherapy refractory advanced cancer patients.
Methods: Treatment cycles consisted of 28 days continuous administration of fixed oral BIBF 1120 doses starting at 50 mg/d followed by one week rest. The dose was escalated until dose limiting toxicity (DLT) was observed. Consecutive treatment cycles were allowed in the absence of progressive disease and persistent toxicity. Full PK profiles were obtained at the beginning and at the end of the 1st treatment cycle. Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) measurements were performed at baseline, at day 2, day 28 and after each further cycle. Toxicity was graded according to the Common Toxicity Criteria (CTC). Tumour assessment was done using the RECIST criteria.
Results: 25 pts (10 f, 15 m) were included, 23 received at least one treatment cycle, 3 patients were excluded during the first cycle due to early progression (2) or non compliance (1). The dose was escalated following an accelerated titration scheme from 50 to 450 mg/d: 50 mg (n=2); 100 mg (n=1); 200 mg (n=8); 250 mg (n= 6); 300 mg (n=5); 450 mg (n=3). Predominant drug-related adverse events were nausea, vomiting, diarrhoea, abdominal pain, and elevation of hepatic enzymes (AST, ALT, and GGT). Liver enzyme elevations were dose limiting (=CTC Grade 3) in 1/8 patients at 200 mg/d, in 2/5 patients at 300 mg/d, and in 2/3 patients at 450 mg/d. 13/25 patients were treated for more than 2 cycles. Stable disease (SD) was observed for 2 months (n=1), 3 months (n=5), 4 months (n=2), 5 months (n=1), and 7 months (n=1). 3 patients are still on treatment (+7, +8, +14 months). One patient (renal cancer) treated with 200 mg/d showed a complete regression of pulmonary metastases. In patients with SD or tumour regression DCE-MRI measurements reflected this result by a reduction of permeability and blood flow as judged by $IAUC_{60}$ evaluation. PK evaluations showed that BIBF 1120 exposure (AUC) increased with dose with moderate to high variability. Maximum measured plasma concentrations were reached approximately 3 h after intake. BIBF 1120 was distributed out of the blood and showed a high clearance resulting in a mean terminal half-life of around 13 h. Steady state was reached within 9 days.
Conclusion: BIBF 1120 was well tolerated in this study. Adverse events were mainly of gastrointestinal nature with mild to moderate intensity. Asymptomatic elevations of liver enzymes constituted dose limiting toxicitiy. The dose level of 250 mg/d BIBF 1120 administered once daily is considered the maximum tolerated dose in this study. A significant number of patients reached durable disease stabilization. BIBF 1120 is a promising compound that warrants further clinical evaluation.

137 POSTER

A phase I study of an oral vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase inhibitor, CP-547,632, in patients with advanced solid tumors

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VEGF over-expression occurs in a broad spectrum of common tumors, mediates tumor neovascularization, and predicts for a poor clinical prognosis. CP-547,632 is an oral, anti-angiogenic small molecule inhibitor of VEGFR-2 tyrosine kinase activity. It is selective vs EGFR, PDGFR-beta and other related tyrosine kinase receptors. This study examined the feasibility of continuous once-daily oral administration of CP-547,632 in patients with advanced solid tumors and the relationships of CP-547,632 pharmacokinetic parameters with toxicity and biologic activity. Seventy-two patients have received a median of 2 courses (range 1–9) over dose levels ranging from 35 mg po for 14 days to 400 mg po per day continuously. The maximally administered dose was 400mg/d with 2 of 2 patients experiencing dose-limiting headache. Bleeding events, both non-tumor related (eg. epistaxis, gingival bleed, hematuria, hematochezia, melena) and tumor-related have been observed across dose levels. Evaluations of causality have been confounded by progressive bulky disease, prior surgery and concomitant medications such as nonsteroidal anti-inflammatory agents; however, serious non-tumor related events have been limited to doses =300 mg. CTC Gr. 3 hypertension occurred at doses of 300 mg/d in 2 of 6 patients. Other CP-547,632 related adverse events include: mild to moderate diarrhea, fatigue after several cycles of treatment, transient maculopapular or pruritic rash, mild to moderate nausea and anorexia and rare, mild emesis. Of the 62 patients evaluable for tumor response, 12 patients had stable disease for 2 cycles (8 weeks), 1 patient had stable disease for 4 cycles (16 weeks), and 4 patients had stable disease for 6 cycles (24 weeks), 2 of whom had evidence of disease cavitation. One patient had an unconfirmed partial response at cycle 4 (16 weeks). At doses >160 mg QD, the plasma concentrations throughout the dosing interval exceed concentrations associated with anti-angiogenesis in certain preclinical models. The maximally tolerated dose is 250 mg/d for disease directed studies. An encouraging safety profile, evidence of anti-tumor effect and pharmacokinetic parameters that portend angiogenesis inhibition in preclinical models provide further impetus for study in the Phase II setting.

138 POSTER

Enhancement of the action of the antivascular drug 5,6-dimethylxanthenone-4-acetic acid (DMXAA) by co-administration of non-steroidal anti-inflammatory drugs

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Background: DMXAA, a low molecular weight antivascular drug that is currently in clinical trial for the treatment of a variety of cancer types, acts both directly and indirectly to damage tumour vascular endothelial cells and selectively inhibit tumour blood flow. Prostaglandins are often released in response to tissue injury and are likely to increase in response to vascular endothelial injury. Several prostaglandins, particularly PGE1, may have a protective role. We wished to determine whether non-steroidal anti-inflammatory drugs (NSAIDs) modulated the antitumour and antivascular effects of DMXAA in mice. The plasma concentration of serotonin, which is released by platelets in response to a number of antivascular drugs, was used as a surrogate marker for antivascular effects.
Methods: Antitumour effects were measured in Colon 38 murine carcinomas growing in C57Bl mice. Plasma concentrations of DMXAA and of the serotonin metabolite 5-hydroxyindole-3-acetic acid (5-HIAA) were measured by high performance liquid chromatography.
Results: Administration of DMXAA alone as a single sub-optimal dose (25 mg/kg i.p.) provided growth delays of 4 and 6 days in two independent experiments. Administration of diclofenac alone (5 mg/kg) caused no significant growth delay. Co-administration of diclofenac and DMXAA