gastrointestinal tract tumors. Vascular endothelial growth factor (VEGF)-C/D-VEGF receptor-3(VEGFR3) is a key signaling in this process. VEGF-C and D bind to and activate VEGFR3, which is primarily expressed on lymphatic endothelium, and also bind to VEGFR2 (only after those ligands are fully processed).
In cell free and cell based kinase assays with IC_{50} of sub-nanomolar concentrations, E7080, a multi-kinase inhibitor, potently inhibits VEGFR1–3, particularly VEGFR2 and -3. In this presentation, we report the potency of E7080 as an anti-metastatic agent through inhibition of lymphangiogenesis. MDA-MB-231 is a breast tumor cell line over-expressing both VEGF-A and -C. The administration of E7080 at 100 mg/kg clearly decreased tumor growth of orthotopically transplanted MDA-MB-231, and also inhibited lymph node and lung metastases. On the other hand, the administration of Bevacizumab (Avastin, a recombinant humanized monoclonal antibody directed against VEGF-A which is a ligand for VEGFR1 and VEGFR2) at 800g/head immunohistochemical analysis of tumor specimen, E7080 diminished both tumor angiogenesis and lymphangiogenesis being measured by CD31 staining and LYVE-1 staining, respectively. In comparison, Bevacizumab diminished only tumor angiogenesis but was ineffective for lymphangiogenesis. We also evaluated the effect of E7080 against lymph node metastases after surgical resection of primary tumor tissues, which may refer to adjuvant therapy after surgical resection in breast carcinoma patients. E7080 showed anti-tumor regression against lymph node metastases and disappearance of lymph node metastases in 2/4 mice.
These results clearly showed that the blockage of VEGFR3 is a promising therapeutic strategy against lymph nodes metastases and E7080, an inhibitor of all three VEGFRs, is useful for anti-angiogenic and anti-metastatic therapy.

38 POSTER

Phase I and pharmacological study of KRN951, a potent VEGFR tyrosine kinase inhibitor given in a 4 week on, 2 week off schedule in patients with advanced solid tumors

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Background: KRN951 inhibits VEGF induced phosphorylation of VEGFR2 and 1 (IC_{50} of 0.16 and 0.21 nM) and phosphorylation of c-Kit and Platelet Derived Growth Factor Receptor (PDGFR), (IC_{50} of 1.63 and 1.72 nM).
Methods: The principal objectives of this first in man study were (1) to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of KRN951 administered orally once daily (OD) for 28 days followed by 14 days off treatment, (2) to characterize safety and tolerability, (3) to characterize single and multiple dose pharmacokinetics, (4) to explore inhibitory effects on tumor blood flow, and (5) to look for evidence of antitumor activity.
Results: 14 male and 6 female patients, median age 59 yrs (28−72) have been enrolled at dose levels of 1 mg (n = 6), 2 mg (n = 8), and 1.5 mg (n = 6). The total number of courses given is 77 (1−19 per patient). At the initial dose of 2 mg DLT (grade 3 asymptomatic proteinuria, grade 3 ataxia and grade 4 intracranial hemorrhage) was seen in three consecutive patients. As in the next-lower dose level of 1 mg only one DLT (grade 3 fatigue) was seen, an intermediate dose level of 1.5 mg was studied. One DLT (uncontrollable hypertension) was seen, and therefore this dose level is considered as Recommended Phase 2 Dose (RPTD). Hypertension occurred in 15/19 patients but could be medically controlled, other frequently occurring mild side effects were hoarseness, anorexia, nausea, diarrhea and fatigue.
Pharmacokinetic analysis revealed dose dependent drug exposure and peak plasma concentrations. Plasma levels of VEGF tended to increase, whereas sVEGFR2 levels decreased following exposure to KRN951. Exploratory analysis by means of Dynamic Contrast Enhanced MRI analysis indicated a decrease in tumorperfusion in selected patients. One confirmed partial response lasting more than 100 weeks in a patient with renal cell carcinoma was seen, and stable disease lasting more than 2 courses of treatment was seen in 8 patients.
Conclusion: Once daily KRN951 can be administered safely in doses up to 1.5 mg when given for 28 days followed by 14 days off treatment. This dose constitutes the RPTD. In order to obtain more safety data, we are currently expanding the RPTD with 10 additional patients.

39 POSTER

A heparan sulfate mimetic compound KI-105 inhibits the invasion and migration of HT1080 cells

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Background: Heparan sulfate glycosaminoglycans (HSGAGs) on cell surface regulate signal transduction from the outside to the inside of tumor cells due to the interaction of HSGAGs with various growth factors such as bFGF and VEGF. On the other hand, HSGAGs in the ECM act as a physical barrier against tumor metastasis, and they also function as storage sheds for various proteins. The enormous structural diversity of HSGAGs makes it possible for them to interact with a wide variety of proteins. Such interactions make crucial contributions to the regulation of normal and pathological processes. In order to dissect a variety of the pathological roles of HSGAGs and develop novel antitumor agents, we designed novel HSGAG-mimetic compounds (KI compounds).
Materials and Methods: Design And Computer Calculations: A HS disaccharide unit of HexUA-GlcNAc(6S) was used as a template structure. Focusing on carboxylic acid and sulfate groups, a partial structure search was carried out using the ISIS/Base in combination with a 2D structure database containing 50,000 compounds (i.e., both original and commercial compounds).
Results: We developed novel functional regulators of HSGAGs that do not have a saccharide-based structure. We selected 2-(3-nitrobenzoyl)benzoic acid by database searches with regard to Lipinski's "Rule of Five" and the ease of organic synthesis; molecular dynamics calculations were also carried out as part of the selection process. A novel invasion/migration inhibitor, KI-105, was identified among the 2-(3-nitrobenzoyl)benzoic acid derivatives (KI compounds), using cell-based assays (i.e., invasion, migration, adhesion, and growth assays). The amount of cell-surface HSGAGs and focal adhesions were also increased by KI-105 treatment. Moreover, KI-105 (50 mg/kg) was administered p.o. in mice received B16ML6 melanoma cells intravenously. After 15 days, about 40% of the number of B16BL6 metastases in their lungs were suppressed.
Conclusions: It is the first report of a rationally designed and experimentally identified low molecular weight HSGAG-mimetic compound demonstrating potent inhibition of the various functions involved in malignant phenotypes.

40 POSTER

Update on survival in a phase Ib/II study of DMXAA combined with carboplatin and paclitaxel in non-small cell lung cancer (NSCLC)

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Background: DMXAA (AS1404) is a small-molecule vascular disrupting agent in trials for treatment of various solid tumours. This integrated phase Ib/II trial evaluated DMXAA in combination with carboplatin (C) and paclitaxel (P) in NSCLC. The phase Ib component confirmed 1200 mg/m^2 as the principal dose of DMXAA for the phase II part of the trial.
Methods: Patients had histologically confirmed stage IIIb or IV NSCLC previously untreated with chemotherapy. In the phase II component of the trial, patients were randomly assigned to receive up to 6 cycles of C (AUC 6 mg/ml*min) + P (175 mg/m^2) with or without 1200 mg/m^2 DMXAA. Safety assessments included ECG, adverse events, laboratory screens, pharmacokinetics and ophthalmic exams. Efficacy endpoints were objective response rates, time to progression, duration of response and stable disease, and median and 1-year survival.
Results: 37 patients were randomised to DMXAA 1200 mg/m^2 with C and P (34 eligible for efficacy analysis) and 36 to C and P alone (all eligible for efficacy analysis). Overall safety profiles in the two groups were similar (24 treatment-emergent SAEs with DMXAA and 23 with chemotherapy alone). Addition of DMXAA to C and P did not exacerbate chemotherapy-related adverse events. Patients assigned to the DMXAA arm showed a higher RECIST response rate (31.2% vs 22.2%), longer time to tumour progression (132 vs 115 days; based on uncensored analysis) and enhanced projected survival (26 week rates of 82.0% vs 54.8% and projected median survival of 12.0 vs 7.6 months after 21 deaths) than patients receiving C and P alone.
Conclusion: Addition of 1200 mg/m^2 DMXAA to standard doses of C and P was well tolerated and associated with a 4.4 month increase in projected median survival after 21 deaths. Updated survival findings including one-year survival rates will be presented.