age was 68 (29−77), 13 (75.5%) were male, 11 (64.7%) were Caucasian, 4 had prior systemic therapy, and 6 pts had prior TACE. Of the 13 pts evaluable for response, 5 SD at 16 wks (38% PFS; 2/5 showed tumor shrinkage <20%), 3 have confirmed PRs, 2 SD at 8 weeks continuing on therapy; 2 pts SD at 8 wks but removed for toxicity; 1 PD. 3 pts not yet evaluable, 1 pt withdrew consent. 8 pts with SD showed radiographic evidence of decreased tumor vascularity (Fig. 1). One pt with 20% tumor shrinkage and improved portal vein involvement was removed from the study and underwent surgical resection. Generally B+E are well tolerated; the most common Gr 1 and 2 toxicities are folliculitis, anorexia, diarrhea, dry skin, and epistaxis. Gr3 toxicities experienced by 4 pts were TA elevation, diarrhea, fatigue, hyperkalemia, hypertension, and proteinuria. No Gr4 toxicities have been encountered.
Conclusions: The trial will continue to full accrual of 40 patients. Based on these early encouraging results and the favorable side effect profile, the combination of B+E warrants further study in HCC.

35 POSTER

A Phase I trial of a combination of the mTOR Inhibitor Everolimus (RAD001) and two schedules of the vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor Vatalanib (PTK787/ZK 222584) in patients (pts) with advanced solid tumors

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Background: Preclinical studies demonstrate synergistic antitumor effects of mTOR inhibitors in combination with anti-angiogenesis agents.
Materials and Methods: A phase I study was performed to define the maximum tolerated dose (MTD), toxicities and clinical activity of escalating single daily doses of vatalanib in combination with RAD001, followed by determination of the MTD of twice daily doses of vatalanib in combination with RAD001 (see table), in pts with advanced cancers. A cycle length was 28 days. Once the optimal dose and schedule of the combination is defined, the study will expand to evaluate pharmacokinetics (PK), and temporal changes in functional imaging and in molecular markers of VEGF inhibition (sVEGFR, VEGF levels) and mTOR inhibition (4EBP, eIF4E, p70S6 kinase activity).
Results: 29 pts received 106 cycles of treatment through 5 dose levels. The most common toxicities were fatigue, hyperlipidemia, transaminitis, nausea, stomatitis and hypertension. NCI CTC grade3+ treatment-related toxicities (cumulative events in all cycles, CTC grade) included transaminitis (3 grade 3 ALT elevation; 1 grade 3 AST elevation), diarrhea (3 grade 3), hypercholesterolemia (1 grade 3), hypertriglyceridemia (2 grade 3), thrombosis (1 grade 3), pancreatitis (1 grade 3), and muscle spasms (1 grade 3). DLTs were grade 3 ALT elevation, muscle spasms and diarrhea. Partial responses were seen in 2 patients (chemo-refractory neuroendocrine pancreatic cancer at dose level 0, treatment-naïve clear cell renal cell cancer at dose level 3). Stable disease (4+ cycles) occurred in 8 pts. Dose level 2 (10 mg RAD001 and 1250 mg vatalanib) is the MTD for the single daily dose schedule. Dose level 4 (10 mg RAD001 and 1000 mg vatalanib) is the MTD for the twice daily dose schedule of vatalanib.

Table 1. Treatment data

Dose level	RAD001 (mg, daily)	Vatalanib (mg)	No. pts (No. replaced)	No. cycles	No. DLTs
0*	5	1000 QD	3 (3)	32	0
1	10	1000 QD	3	14	0
2	10	1250 QD	6	21	1
3	10	750 BID	6 (1)	26	1
4	10	1000 BID	5 (2)	13	1

Conclusions: The combination of RAD001 and vatalanib is effective and well-tolerated. We recommend the twice-daily schedule of vatalanib in combination with RAD001 for future evaluation in phase II studies, based on a higher dose intensity and tolerability. Results of PK and pharmacodynamic studies in the expanded cohort will be presented.

36 POSTER

The combination of a specific endothelin A receptor antagonist ZD4054 and submaximal bisphosphonate pamidronate prevents bone metastasis

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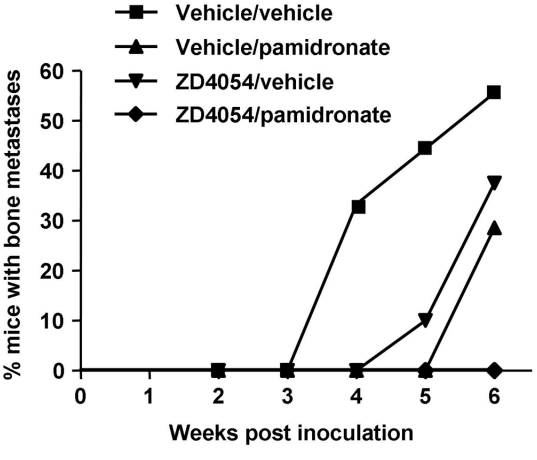
Bone metastases cause significant morbidity for people with cancer due to bone pain, fractures, and nerve compression. Bone metastases are most commonly osteolytic, but some tumour types, most notably prostate cancer, typically form osteoblastic metastases. Nevertheless, many overtly osteolytic metastases have an osteoblastic component, which has been attributed to the ability of bone-synthesising osteoblasts to increase osteoclast function (as osteoblasts are the main regulators of osteoclasts). Tumour secreted endothelin-1 is thought to be a key factor stimulating the osteoblastic phenotype. Clinically approved bisphosphonates prevent bone resorption by osteoclastic mechanisms and reduce the release of bone growth factors, resulting in fewer skeletal-related events.
We have investigated the interaction between the specific endothelin A receptor antagonist ZD4054 and the bisphosphonate pamidronate on the formation of mixed osteoblastic/osteolytic metastases following systemic inoculation of the metastasis-selected B1 subline of the TSU-Pr1 human bladder carcinoma cell line.
Male SCID mice (n = 7–10/group) were randomly allocated to 4 experimental arms: (i) vehicle (oral gavage, daily)/vehicle (s.c., twice weekly), (ii) vehicle/pamidronate (4 mg/kg s.c., twice weekly), (iii) ZD4054 (25 mg/kg, oral gavage, daily)/vehicle, and (iv) ZD4054/pamidronate. Treatment was initiated the day prior to intracardiac inoculation of TSU-Pr1-B1 cells. Mice were X-rayed weekly, and tissues collected for histological analysis and measurement of human DNA at the conclusion of the experiment (6 weeks following inoculation of tumour cells). Treatment with either ZD4054 or pamidronate significantly delayed the formation of bone metastases. In the mice receiving both agents, no bone metastases were detected using high resolution X-ray.
Endothelin A receptors are found both on osteoblasts and on many types of tumour cells, including the majority of invasive bladder carcinomas. Bisphosphonates act on bone cells (predominantly osteoclasts) rather than tumor cells. These data suggest that combined therapy targeting tumour cells and the bone environment by a combination of anti-osteoblastic and anti-osteolytic treatments may provide maximal inhibition of bone metastasis.



37 POSTER

VEGFRs inhibitor E7080 inhibits lymph node metastasis of human breast carcinoma, by preventing murine lymphatic endothelial cells from lymphangiogenesis

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The spread of tumor cells into regional lymph nodes through the lymphatic system correlates with poor prognosis in breast, lung and

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.