differences in disposition between Japanese and Caucasian patients, the pharmacokinetics (PK) of ZD4054 were evaluated in two Phase I studies: one in Japan and one in the UK. Tolerability of ZD4054 was also evaluated.
Patients and Methods: Patients with hormone-refractory prostate cancer were recruited to receive a single oral dose of 5, 10, or 15 mg ZD4054 followed by 3 days washout and then once-daily dosing. PK parameters were evaluated after the first dose, and after 12 consecutive days of dosing. Tolerability outcomes were assessed until data cut off.
Results: Eighteen Japanese and 21 Caucasian patients were recruited into the Japanese and UK studies, respectively. After the first dose, ZD4054 was rapidly absorbed with C_{max} typically being achieved between 1 and 3 hours. Exposure increased with dose and showed a 2–5 fold range within a dose level. Plasma concentrations declined in a monophasic manner with terminal-phase half-life typically between 8 and 13 hours. Total apparent plasma clearance and apparent volume of distribution were low (range 6.9–36.3 ml/min and 7.9–29.1 l, respectively). After 12 days consecutive dosing there was little accumulation of ZD4054, and multiple-dose PK were reasonably predictable from single-dose PK. Overall, ZD4054 PK were similar between Japanese and Caucasian patients, although exposures achieved in some Japanese patients at 15 mg were higher than those achieved in most Caucasian patients. This difference disappeared when data were normalized to a standard patient body weight. ZD4054 was well tolerated in Japanese and Caucasian patients. Adverse events (AEs) were predominantly pharmacologically driven. The most common AE was headache, experienced by 13 Japanese and 12 Caucasian patients. Other AEs included peripheral edema, nausea, nasal congestion, dizziness, and vomiting. All AEs considered related to ZD4054 treatment by the investigators were CTC grade 1–2, except for grade 3 headache in two Caucasian patients and grade 3 aggravation of gastritis in one Japanese patient.
Conclusions: In these studies ZD4054 was well tolerated, and PK profiles were similar between Japanese and Caucasian patients with hormone-refractory prostate cancer.

719 POSTER

Phase I study of AZD2171 in combination with oxaliplatin and infusional 5-FU (mFOLFOX6) in patients (pts) with advanced colorectal cancer (CRC)

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Background: AZD2171 is a potent oral inhibitor of the tyrosine kinase activity of all VEGFR subtypes. Purposes of this study were to determine the recommended phase II dose of AZD2171 in conjunction with standard doses of mFOLFOX6, and the tolerability, safety, pharmacokinetic (PK) profile and anti-tumor activity of this combination in pts with previously untreated advanced CRC.
Methods: Eligibility criteria included: locally advanced or metastatic CRC; PS 0–2; no prior chemotherapy for advanced disease; adequate hematological, liver and renal functions. AZD2171 was administered daily orally starting Day 3 cycle 1 at a starting dose of 30 mg. Modified FOLFOX 6 consisted of oxaliplatin 85 mg/m^2 (2 hour infusion) day 1; leucovorin 400 mg/m2 (2 hour infusion); and 5-FU bolus 400 mg/m^2 day 1 followed by continuous 5-FU infusion at 2400 mg/m^2 over 46 hours. Cycles were repeated every 14 days. Blood sampling for PK were performed during cycles 1 and 2 for oxaliplatin and 5-FU, and cycle 2 only for AZD2171. Response was assessed by RECIST every four cycles.
Results: Sixteen pts (13 males, 3 females), median age 61 years (range: 29−79) received 124 cycles of treatment (median: 6; range: 1−20 cycles). Of 9 pts enrolled at the 30 mg dose level, one pt experienced grade 3 diarrhea and another grade 3 hypertension during cycle 1. No DLTs were observed in 7 pts at the 45 mg dose level, one pt was not able to take week 2 AZD2171 due to toxicities related to mFOLFOX6. Dose intensity was similar at both dose levels. Common grade 3 toxicities related to AZD2171 included hypertension (38%), fatigue (25%), diarrhea (25%), catheter-related venous thrombosis (13%), other venous thrombosis (13%), anorexia (13%), dyspnea (13%), syncope (13%) and elevation of alkaline phosphatase (13%). Hematologic toxicity was similar to that expected with mFOLFOX6 alone. Of 14 pts evaluable for response, there were 1 CR, 6 PR (43.8%, 95% CI: 19.8−70.1%), and 5 SD. Liver metastatic disease became resectable in 2 pts after 20 and 16 cycles of treatment respectively. Modified FOLFOX6 does not appear to affect AZD2171 steady-state PK.
Conclusions: Toxicities of this combination are manageable and consistent with previous studies. Although no DLTs were observed at the 45 mg dose level and dose intensity was similar with both 30 mg and 45 mg, AZD2171 at 30 mg daily appears to be somewhat better tolerated and may be the preferred dose for broader studies in unselected patients. AZD2171 and mFOLFOX6 appear to be active in previously untreated advanced CRC, and this combination warrants further investigation.

720 POSTER

Subcellular distribution and cellular activity of the novel epothilone ZK-EPO

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Background: ZK-EPO is a novel epothilone that has demonstrated highly significant activity in both sensitive and in multidrug-resistant (MDR) tumour models. The work presented here examines the cellular events underlying this promising antitumour activity.
Material and Methods: ZK-EPO activity was determined in a variety of tumour cell lines. The subcellular distribution of radiolabelled ZK-EPO and paclitaxel was determined using cellular fractionation followed by Western blotting. For cell cycle analyses, cell suspensions were stained with propidium iodide prior to FACS analysis. For confocal microscopy cells were fixed and stained with anti-alpha-tubulin antibody and DRAQ5. In vitro tubulin polymerisation was determined using the Cytoskeleton microtubule polymerisation assay.
Results: ZK-EPO demonstrated significant antiproliferative activity in a series of MDR human tumour cells lines, exhibiting a mean IC_{50} ($IC_{50} \leqslant 1$ nM) that was markedly lower than paclitaxel ($IC_{50} > 100$ nM), ixabepilone ($IC_{50} > 100$ nM) and epothilone B ($IC_{50} > 5$ nM). Radiolabelling studies in A549 cells show that ZK-EPO was rapidly taken up into the cells, where it was predominantly localised to the cytoskeletal/nuclear fraction (>80%), unlike paclitaxel which exhibited slower uptake and mainly localised to the cytosolic/membrane fraction (~50%). ZK-EPO showed an accelerated polymerisation of tubulin in vitro compared with paclitaxel and epothilone B. Confocal studies in tumour cell lines showed that ZK-EPO clearly induced tubulin polymerisation, blockage of cell cycle progression and the formation of multiple mitotic spindles and abnormal chromosome alignment. FACS analysis confirmed the confocal studies, showing that ZK-EPO at concentrations of $\geqslant$10 nM blocked cell cycle progression at G2/M and induced apoptosis as detected by TUNEL staining and measurement of caspase activity. Lower concentrations of ZK-EPO induced the formation of a sub-G1 peak indicative of apoptotic fragments, and this was confirmed with TUNEL staining.
Conclusion: The promising preclinical activity of ZK-EPO is underpinned by its rapid localisation to the cytoskeleton and the efficient polymerisation of tubulin, which leads to the disruption of the mitotic spindle, inhibition of cell cycle progression and tumour cell apoptosis. ZK-EPO is currently in Phase II clinical trials.

721 POSTER

Inhibitory effect of Zoledronic acid on endothelial progenitor cells differentiation

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Background and Aim: Zoledronic acid (ZOL), the 3rd generation of bisphosphonate, is clinically available for skeletal complications, such as cancer-induced osteolysis and osteoporosis. It has been shown to exert strong anti-cancer activities against solid tumors, such as breast cancer and prostate cancer, as well as against leukemia. Also the anti-angiogenic activity of ZOL has been suggested by in vitro experiments. Since ZOL is known to accumulate into bone tissue, and endothelial progenitor cells (EPCs) originate form the bone marrow, here we aimed to investigate the effect of ZOL on EPCs.
Methods: EPCs were obtained by culture of peripheral blood mononuclear cells (PBMCs), obtained from venous blood of healthy volunteers', for 7 days in M199 medium supplemented 15%FCS and acid fibroblast growth factor (aFGF) on fibronectin-coated plate. For the experiments, ZOL (gifted by Novartis pharma) was used at 1, 5, 10, 50, and 100 uM. Geranylgeraniol (GGOH) was used at 10uM. The expressions of CD144, VEGFR2, and vWF, the endothelial-specific markers, were measured by flow-cytometry. The ability of EPCs to form tube-like structures was investigated by the tube-like formation assay on Matrigel. The annexin V/PI staining was used to analyze apoptosis.
Results: PBMCs cultured for 7 days on fibronectin differentiated into spindle-shaped cells, which expressed CD144, VEGFR2, and vWF, the endothelial markers, suggestive of EPC differentiation. And these cells had the ability to form tube-like structures on Matrigel. Addition of ZOL from day 2 to day 7 of culture resulted in impaired EPC differentiation, as confirmed by the lack of spindle-shape differentiation, the decreased

expression of endothelial markers, and the loss of tube-like formation ability. These effects were observed even with low dose of ZOL (1uM), but could be restored by co-treatment with GGOH. On the other hand, treatment of putative EPCs with ZOL at higher doses (>10uM) resulted apoptosis induction, as confirmed by annexinV/PI staining.
Conclusion: ZOL inhibited the differentiation of EPCs from PBMC, in a dose-dependent manner, the effect being observed even at low levels. Treatment with higher doses of ZOL resulted in apoptotic death of putative EPCs. Since GGOH could restore the inhibitory effect of ZOL on EPC differentiation, the effect of ZOL was speculated to be dependent on the inhibition of prenylation of small-G-proteins. From the present findings, we concluded that ZOL should be a potential anti-cancer agent, by inhibiting important steps of the angiogenic process.

722 POSTER

Antitumor activity and pharmacokinetics of a novel PEGylated irinotecan in irinotecan-resistant colorectal tumours implanted in mice

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NKTR-102, a novel PEG-Irinotecan conjugate, is currently in Phase I clinical development. Nonclinical studies examined the antitumor activity and pharmacokinetics in a mouse HT29 colorectal tumor model, which is moderately resistant to irinotecan treatment.
Intravenous administration of NKTR-102 at 40, 60 or 90 mg/kg (irinotecan equivalent dose) on days 1, 4 and 8 to tumor-bearing mice caused marked, statistically significant dose-related decreases in HT29 tumor growth (relative to saline control) that persisted until termination on day 60. Intravenous irinotecan at the same doses resulted in only modest suppression of tumor growth that was short lived and not statistically different from saline control. Tumor growth delay after NKTR-102 was significantly longer than that after irinotecan at all 3 dose levels ($p < 0.001$). Tumor regression was observed after NKTR-102 at 90 mg/kg, but not after irinotecan at any dose level.
A 40 mg/kg IV administration of NKTR-102 on days 1, 4 and 8 resulted in prolonged plasma and tumor exposure to active metabolites irinotecan and SN38 that correlated with marked suppression of tumor growth. Mean Tumor SN38 Cmax of 1100 ng/g occurred on day 15, and tumor SN38 concentration was maintained above 100 ng/g observed at termination on day 60. Apparent t1/2 values for SN38 in plasma and tumor after the first dose of NKTR-102 were 17 and 15 days, respectively, whereas, SN38 t1/2 values after 40 mg/kg irinotecan were in the expected range of 2−4 hr. SN38 AUC values in plasma and tumor after the first dose of NKTR-102 were 531- and 366-fold greater, respectively, than those after irinotecan dosing. Subsequent doses of NKTR-102 on days 4 and 8 resulted in even greater SN38 exposure relative to irinotecan dosing, resulting from accumulation in both plasma and tumor.
In summary, NKTR-102 resulted in marked, prolonged growth suppression of HT-29 tumor, which is otherwise modestly resistant to irinotecan. Pharmacokinetic results indicate that this suppression results from prolonged systemic and tumor SN38 exposure resulting from slow disposition and metabolism of NKTR-102.

723 POSTER

A phase I dose-escalation study of RAD001 administered daily to Japanese patients with advanced solid tumors

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Background: RAD001 (everolimus) is an oral rapamycin derivative targeting mTOR (mammalian target of rapamycin), a key downstream serine-threonine kinase in the PI3K/AKT/mTOR pathway regulating protein synthesis and ultimately cell growth, proliferation, and survival. 10 mg is considered safe and tolerable in Western pts; this is the first study conducted in Japan.
Methods: Pts with relapsed/refractory advanced solid tumors were treated at doses of 2.5, 5.0, and 10.0 mg qd. The primary objective was to confirm the tolerability of and assess the safety profile of single agent RAD001 in Japanese pts. Secondary objectives were to assess pharmacokinetics, inhibition of tumor p70 ^{S6K} activity, and preliminary anti-tumor activity.
Results: 9 (4M and 5F) pts with a median age of 64 y (range: 49−74) were treated, 3 at each dose level. No DLT has been observed and the drug has been generally well tolerated. The most frequently observed adverse events (in $\geqslant$2 pts) were thrombocytopenia, anorexia, rash, weight decrease, abdominal pain, diarrhea, fatigue, leucopenia, mucosal inflammation, nasopharyngitis, nausea, stomatitis. One pt developed grade 2 interstitial pulmonary disease. One PR was observed in a pt with esophageal CA (10 mg); this pt's response involved rapid regression of disease surrounding the major subclavicular vessels, which ultimately caused hemorrhage and death. Another pt with gastric CA (10 mg) having a response of PR at one assessment before progression of disease; One pt with colon CA (5 mg) had SD for $\geqslant$4 months by RECIST. Dose-exposure relationship in Japanese pts were similar to Western pts. Inhibition of p-S6K and p-Akt was achieved at the initial dose of 2.5 mg. A dose of 10 mg was selected for further development.
Conclusions: 10 mg qd of RAD001 is safe and generally well tolerated in Japanese pts with advanced solid tumors. RAD001 demonstrated pharmacodynamic and preliminary clinical activity. Further development is ongoing.

724 POSTER

Metabolism of [^{14}C]-ZD4054 in healthy volunteers

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Background: ZD4054 is a specific endothelin A receptor antagonist being developed for the treatment of cancer.
Patients and Methods: The metabolism, excretion, and pharmacokinetics of ZD4054 were studied following administration of a single oral dose of [^{14}C]-ZD4054 (15 mg, 90 μCi) to six healthy volunteers (three female; three male) aged 52–65 years.
Results: The total recovery of radioactivity over 5 days was high (mean 93.4$\pm$7.3%; range 80.6–99.0%), with 78% recovered within 24 hours. Most of the dose was eliminated in the urine (71–94%), in which the main component was unchanged ZD4054 (35–77% of the dose; mean 58%). Several metabolites were identified in the urine. Excretion into the feces accounted for 5–19% of the dose, and comprised a number of minor metabolites with little unchanged ZD4054. The concentrations of radioactivity in whole blood were generally lower than those in plasma (geometric mean blood:plasma ratio ranged from 0.67 at 2 hours after dosing to 0.75 at 24 hours), suggesting limited association of drug-related material with blood cells. Concentrations of ZD4054 and radioactivity in plasma were similar up to 12 hours post dose, indicating the absence of circulating metabolites, and diverged thereafter as radiolabeled metabolites appeared in the plasma. ZD4054 was the major radiolabeled plasma component over 24 hours (75–86% of plasma radioactivity), with one detectable metabolite accounting for 4% of plasma radioactivity. No other metabolites were detected in plasma over 24 hours. Results were similar for male and female subjects. The single oral dose of [^{14}C]-ZD4054 was well tolerated in these healthy volunteers aged >50 years; no adverse events (AEs) were serious or greater than CTC grade 2. Headache (five subjects) and nausea (two subjects) were the only AEs that occurred in more than one subject.
Conclusions: These results show that ZD4054 is predominantly eliminated unchanged in the urine and that concentrations of circulating metabolites are low.

725 POSTER

A multicenter phase I study of a novel nucleoside analogue, CP-4126, in patients with advanced solid tumours – preliminary results

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Background: CP-4126 (gemcitabine 5′-elaidic acid ester) is a novel optimized nucleoside analogue with a broad spectrum of preclinical antitumour activity. The intracellular uptake of CP-4126 is independent of nucleoside transporters and its antitumour activity is less affected by multidrug resistance than gemcitabine. The study aims to determine the maximum tolerated dose (MTD) and the recommended dose of CP-4126, to establish its safety profile and pharmacokinetic parameters (PK) characteristics, and to preliminary assess the antitumour activity.
Materials & Methods: 15 to 25 patients (pts) with confirmed solid tumour diagnosis are to be accrued in this dose escalation study [1 to 6 pts per dose level (DL)]. CP-4126 is administered on days (d) 1, 8 and 15 every 4 week (q4w) by a 30-min infusion. Dosing started at 30 mg/m^2/d and the dose is to increase with a 100% escalation factor until CTCAE toxicity