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.

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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