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

M.A. Eldon[1], L. Antonian[1], C.M. Staschen[2], T.X. Viegas[3], M. Bentley[3], A. Singhal[1]. *[1]Nektar Therapeutics, R&D, San Carlos, USA; [2]Current Address: Incyte Corporation, R&D, Wilmington, USA; [3]Current Address: Serina Therapeutics, R&D, Huntsville, USA*

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

T. Doi[1], A. Ohtsu[1], K. Nakagawa[2], I. Okamoto[2], K. Kurei[3], K. Kobayashi[3]. *[1]National Cancer Center Hospital East, Digestive Endoscopy/Gastrointestinal Oncology, Kashiwa, Japan; [2]Kinki University School of Medicine, Medical Oncology, Osakasayama, Japan; [3]Novartis Pharma K.K., Oncology Early Clinical Development, Minato, Japan*

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

J. Clarkson-Jones[1], A. Kenyon[1], J. Kemp[1], E. Lenz[1], S. Oliver[1], P. Phillips[1], D. Sandall[1], H. Swaisland[1]. *[1]AstraZeneca, Alderley Park, Macclesfield, United Kingdom*

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

S. Aamdal[1], A. Ahamad[2], J. Evans[3], W. Rasch[4]. *[1]The Norwegian Radium Hospital, Oncology, Oslo, Norway; [2]Institute Jules Bordet, Oncology, Bruxelles, Belgium; [3]Center for Oncology and Applied Pharmacology, Oncology, Glasgow, United Kingdom; [4]Clavis Pharma, Clinical Department, Oslo, Norway*

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

> grade 2 occurs. From this DL, the dose will increase with 66%, 50%, 33% and 25% successively. Standard haematological, biological and clinical dose limiting toxicity (DLT) definitions are used. Activity is assessed at the end of every 2nd cycle (cy). PK is determined at d 1 of cy 1.
Results: 11 pts with solid tumours have been included (4 colorectal, 2 hepatocarcinoma and one each of NSCLC, cholangiocarcinoma, leiomyosarcoma, malignant melanoma, pancreas) with 1 pt/DL from 30 to 240 mg/m^2/d. One grade 2 adverse event (AE), neutropenia, was reported at 480 mg/m^2/d. A total of 4 patients were included at this DL. Accrual is ongoing at 800 mg/m^2/d (DL6). One DLT is reported at 800 mg/m^2/d; d 8 treatment postponed with more than 2 weeks due to reduction in Hb and platelets (CTCAE grade 3) after d 1 treatment. A total of 18 cycles (1 to 4/pt) of treatment have been administered. The main treatment-related AEs have been nausea and vomiting. No significant unexpected AEs occurred. Seven pts have been withdrawn: five due to progressive disease, one due to performance status, and one due to prolonged myelosuppression (DLT). Four pts are ongoing: one with stable disease after 3 cy (at 480 mg/m^2/d).
Conclusions: MTD is not reached. No unexpected AEs have occurred. CP-4126 is well tolerated by pts with solid tumours up to 800 mg/m^2/d in a d1, 8, 15 q4w schedule. Accrual is ongoing. Updated results including PK will be presented.

726 POSTER

Antitumor activity and reversal of multidrug resistance by the newly synthesised oleanolic acid derivative – methyl-3,11-dioxoolean-12-en-28-oate

A. Paszel[1], J. Hofmann[2], L. Zaprutko[3], B. Bednarczyk-Cwynar[3], G. Bock[4], M. Rybczynska[1]. *[1]Poznan University of Medical Sciences, Department of Clinical Chemistry, Poznan, Poland; [2]Innsbruck Medical University, Biocenter Division of Medical Biochemistry, Innsbruck, Austria; [3]Poznan University of Medical Sciences, Department of Organic Chemistry, Poznan, Poland; [4]Innsbruck Medical University, Biocenter Division of General and Experimental Pathology, Innsbruck, Austria*

The aim of this study was to compare the cytotoxic effect of the newly synthesised oleanolic acid-derivative methyl 3,11-dioxoolean-12-en-28-oate (BB.136) in tumor and normal cells with its parent compound oleanolic acid. We also investigated the ability of the compound to reverse multidrug resistance, inhibit P-gp activity, arrest the cell cycle and to induce apoptosis. We used 7 cancer cell lines (MCF7, MCF7/ADR, HL-60, HL-60/AR, CCRF-CEM and CCRF-VCR1000) and one normal cell line (MCF10A). The growth inhibitory activity of BB.136 was assessed using MTT and SRB assays. Cell cycle analysis and induction of apoptosis were determined with propidium iodide.
We observed stronger cytotoxic activity of BB.136 comparing to the control compound oleanolic acid. The antiproliferative efficiency of the tested compound was similar in MCF7 and its resistant subline MCF7/ADR. The IC_{50} values were 4.53 μM and 3.77 μM, respectively (oleanolic acid: 5.38 μM and 37.02 μM). A similar result was obtained in CCRF-CEM and multidrug resistant CCRF-VCR1000 cells. It suggests that MDR1 expressing cells are not resistant to the tested oleanolic acid derivative. The most sensitive of the tumor cell lines to BB.136 were CCRF-CEM and CCRF-VCR1000 (IC_{50} 1.69 μM and 1.56 μM, respectively). MCF10A cells were more resistant (IC_{50} 18.36 μM) to BB.136 than the cancer cells. Additionally the tested compound enhanced the activity of Adriamycin in CCRF-VCR1000 cells, indicating a reversal of resistance. Flow cytometer analysis showed that treatment of HL-60 cells with a 4-fold IC_{50} concentration of the tested compound for 48 hours induced apoptosis in 36.2% of cells.
BB.136 is more potent than the parent compound and is able to induce apoptosis in HL-60 cell. Its lower cytotoxic activity against normal cells and its multidrug resistance reversing ability indicates that it is an interesting compound for further development.

727 POSTER

PEGylation governs the disposition and metabolism of irinotecan following administration of a novel PEG–Irinotecan conjugate

L. Antonian[1], K. Burton[2], R. Goodin[3], M. Bentley[4], M.A. Eldon[1]. *[1]Nektar Therapeutics, R&D, San Carlos, USA; [2]Current Address: Brookwood Pharmaceuticals, R&D, Birmingham, USA; [3]Nektar Therapeutics, R&D, Huntsville, USA; [4]Current Address: Serina Therapeutics, R&D, Huntsville, USA*

NKTR-102, a novel PEG-Irinotecan conjugate, is currently in Phase I clinical development. PEGylation dominated the disposition kinetics of NKTR-102 as demonstrated in rat studies where the plasma kinetics of NKTR-102 mimicked that of the 14C-PEG itself used in NKTR-102.
PEGylation of irinotecan enhanced the pharmacokinetic and pharmacodynamic behavior of the active metabolite SN38. Prolonged systemic SN38 exposure resulted in slow disposition and metabolism of NKTR-102. Intravenous administration of 260 mg/kg of 14C-PEG to rats resulted in distribution primarily within the circulatory system. The main route of excretion of the 14C-PEG was via urine where 61.1% of the administered radioactivity was recovered over ten days. Fecal excretion and other elimination routes accounted for 22.7% of the administered radioactivity over the same period.
Intravenous administration of either the 14C-PEG alone or NKTR-102 showed prolonged plasma exposure. At equivalent doses, the plasma clearances of the 14C-PEG alone or NKTR-102 were similarly small, 2.5 mL/hr·kg and 9−30 mL/hr·kg, respectively. In contrast, plasma clearance of irinotecan following irinotecan administration was 2320 mL/hr·kg, 100–300 times greater than that following NKTR-102 administration. Unlike NKTR-102, irinotecan distributed extensively in the tissue compartment and minimally in the plasma compartment.
In the rat, NKTR-102 volume of distribution was comparable to the vascular compartment volume, which contributed to the observed high plasma exposure of NKTR-102. These results, combined with a lower clearance of SN38 derived from NKTR-102, resulted in notably greater exposure to SN38.
In summary, the PEG component of NKTR-102 dominated its disposition kinetics, resulting in greater and sustained systemic exposure to irinotecan and SN38.

728 POSTER

Differential inhibitory effects of epigallocatechin-3-gallate (EGCG) and C75 in cancer fatty acid metabolism

T. Puig[1], J. Relat[2], J.A. Menéndez[1], R. Porta[1], G. Casals[1], P.F. Marrero[2], D. Haro[2], J. Brunet[1], R. Colomer[1]. *[1]Catalan Institute of Oncology, Medical Oncology, Girona, Spain; [2]University of Barcelona (School of Pharmacy), Biochemistry and Molecular Biology, Barcelona, Spain*

Background: Endogenous fatty acid metabolism is crucial to maintain the cancer cell malignant phenotype. Lipogenesis is regulated by the enzyme fatty acid synthase (FASN); and fatty acid oxidation pathway is regulated by carnitine palmitoyltransferase-1 (CPT-1). Inhibition of FASN has been shown to induce apoptosis in a variety of cancer cells, and consequently to be a potential therapeutic target for the treatment of cancer. To date, only a few inhibitors of FASN have been reported (cerulenin, C75, EGCG, orlistat, triclosan), although the degree of specificity of this inhibition has not been addressed.
Material and Methods: We have evaluated the effects of C75 and (−)-epigallocatechin-3-gallate (EGCG) on fatty acid metabolism pathways (FASN and CPT-1 activities), cellular proliferation, induction of apoptosis and cell signalling (HER2, ERK1/2 and AKT cascades) in breast cancer cells and the effect of reduced FASN activity on adipocyte differentiation of 3T3-L1 cells.
Results: C75 and EGCG had comparable effects in blocking FASN activity. Treating cancer cells with C75 or EGCG induced apoptosis and caused a decrease in the active forms of oncoprotein HER2, AKT and ERK1/2 to a similar degree. In addition, C75 and EGCG reduced dramatically visible lipid droplet accumulation during preadypocite differentiation. We observed, in contrast, marked differential effects between C75 and EGCG on fatty acid oxidation pathway. While EGCG had either no effect or a moderate reduction in CPT-1 activity, C75 stimulated CPT-1 activity (up to 129%), even in presence of inhibitory levels of malonyl-CoA, a potent inhibitor of the CPT-1 enzyme.
Conclusions: In cancer cells, pharmacological inhibition of FASN occurs uncoupled from the stimulation of CPT-1 with EGCG but not with C75, suggesting that EGCG might be free of the CPT-I related in vivo weight-loss that has been associated with C75. Our results establish EGCG as a potent and specific natural inhibitor of fatty acid synthesis (FASN), which may hold promise as a target-directed anticaner drug.

729 POSTER

Safety, maximum tolerated dose and pharmacokinetics of a novel micellar formulation of paclitaxel in the treatment of recurrent solid tumours – a phase I/II study

N. Loman[1], O. Borgå[2], S. Lindberg[1], S. Pettersson[3], R. Henriksson[3]. *[1]Lund University Hospital, dept of Oncology, Lund, Sweden; [2]Borgå PK Consulting, Borgå PK Consulting, Malmö, Sweden; [3]Umeå University Hospital, dept of Oncology, Umeå, Sweden*

Background: Paclitaxel (Taxol®) treatment requires extensive premedication, slow infusion (3−24 h) and a close monitoring mainly due to effects caused by the solvent castor oil (Cremophor EL®). Paclitaxel,