mitotic arrest. Preclinical data suggest that KOS-862 has comparable activity to paclitaxel, but retains efficacy in MDR overexpressing cells (Chou et al, *PNAS* 2001). Previous Phase 1 schedules showed drug-related toxicities recovering within 7 days following an IV infusion. Objective of this protocol was to investigate a more dose intense schedule of KOS-862, administering the drug for 3 out of every 4 weeks to pts with advanced malignancies.

Materials and Methods. Groups of 3 pts were treated at escalating doses of KOS-862. Toxicity was assessed in 4-week cycles. PK sampling occurred after the 1st, 3rd and 4th doses; PD after the 1st and 3rd doses at doses ≥ 100 mg/m^2. Drug concentrations were analyzed using LC/MS/MS (LLQ 2 ng/mL) and analyzed using non-compartmental methods; PD was assessed by percentage tubulin polymerization in PBMCs evaluated by IHC.

Results: (n=21; 5 dose levels: 16-120 mg/m^2). Baseline demographics include median age 58 (38-76); median KPS 80 (70-100); 9 male; diagnoses: 7 ovarian, 5 colorectal, 3 NSCLC; 6 other. Dose limiting toxicity (consisting of one episode each of NVD/dehydration and brief visual hallucination) was observed at the highest dose. The cohort at 100 mg/m^2 is being expanded to 12 patients. Drug-related toxicities (all mild-to-moderate severity) included: fatigue (n=13), sensory neuropathy (n=8) and N/V (n=3). Sensory neurological toxicities were not cumulative but persisted throughout the cycle. Other than the 2 pts with DLT, there were no withdrawals for drug-related toxicities. PK data (n=16 pts; 16-100 mg/m^2; 38 sampling days) showed mean increases in C_{max} (626, 1624, 2215 and 3768 ng/mL) and AUC_{total} (3088, 4610, 7752 and 10812 ng*h/mL) that were linear across the dose levels. At the 100 mg/m^2 dose, there was no significant change in AUC comparing the 3 sampling days (84.3% ± 6.6%) nor accumulation. Compartment independent PK analysis (mean±SD): half-life= 8.5 ± 2.7 hours; Vz = 117 ± 57 L/m^2; CL = 9.9 ± 4.4 L/h/m^2; no dose dependency was observed. Compared to the previous less dose intense schedule, PK on this schedule maintains the systemic exposure with a slightly higher C_{max}; other parameters are similar (although clearance showed a trend towards higher values on this schedule). Data regarding tubulin polymerization in PBMCs (including a comparison between the two schedules) will be presented. Stable disease (≥ 3 months) was seen in renal, ovarian and mesothelioma; tumor marker declines (colorectal, ovarian) were observed.

Conclusions: KOS-862 is a promising new agent; a dose of either 100 or 120mg/m^2 will be the recommended Phase 2 dose, depending on toxicity seen in expanded cohorts. Phase 2 single-agent trials and combination studies using this schedule are planned.

548 POSTER

CERA (Continuous Erythropoiesis Receptor Activator) is an innovative erythropoietic agent with an extended serum half-life: studies of mode of action, pharmacokinetics and erythropoietic activity

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Background: CERA is an innovative erythropoietic agent developed for the treatment of anaemia. Using a combination of *in vivo* and *in vitro* studies, the mode of action, pharmacokinetic properties and erythropoietic activity of CERA were investigated.

Materials and methods: Binding of CERA and epoetin to the erythropoietin (EPO) receptor were compared *in vitro* using a soluble EPO receptor-binding assay. Pharmacokinetic properties of CERA were investigated in dogs and in human volunteers. In dogs, single intravenous (IV) and subcutaneous (SC) doses of CERA (3-10 μg/kg) and epoetin (2.5 μg/kg) were compared. Two randomised, placebo-controlled studies in healthy volunteers were also conducted, where single doses of CERA 0.4-3.2 or 0.1-3.2 μg/kg were administered IV or SC, respectively. Erythropoietic activity of CERA and epoetin were compared *in vivo* using a normocythaemic mouse model and *in vitro* using a UT-7 (human myeloid leukaemia cell line) proliferation assay.

Results: Notable differences between CERA and epoetin were observed in both the association and dissociation rates in the soluble EPO receptor-binding assay. The median serum half-life ($t_{1/2}$) for CERA in dogs was 49.0 h versus 6.4 h for epoetin following IV injection, i.e. a 7-fold increase. In humans, mean $t_{1/2}$ for CERA ranged from 70-122 h after IV and from 102-216 h after SC administration, depending on dose. The increase in area under the curve (AUC) and maximum concentration (Cmax) with dose was more than proportional. In the normocythaemic mouse model, *in vivo* comparison of identical amounts of protein across the dose range 60-1000 ng protein/animal revealed that CERA had greater erythropoietic activity than epoetin, with greater bone marrow cell stimulation and reticulocyte counts. However, CERA stimulated less proliferation of UT-7 cells than epoetin in the *in vitro* assay across the dose range 0.003-3 U/ml.

Conclusions: These findings suggest an innovative mechanism of action for CERA. The combination of its different binding characteristics to epoetin, and its extended half-life, may enable an enhanced and sustained stimulation of erythropoiesis with CERA compared with epoetin. This may lead to less frequent dosing and help to optimise patient outcomes.

549 POSTER

Liver toxicity: a predictable and manageable toxicity for kahalalide F (KF)

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Background: KF is a new marine cytotoxic currently under phase II evaluation. Acute (4 to 6 hours after infusion) and reversible grade 4 aminotransferases increase (AI) was the dose limiting toxicity (DLT) in two phase I clinical trials with KF. The following features will be described: a) patients (pts) with grade (g) 3-4 ALT, AST, Bilirubin (Bb), Alkaline phosphatase (AP) and GGT elevation, b) patients with both grade 4 AI and LDH increase, c) duration of aminotransferases increase, d) patients with ALT/AP (times x ULN) ratio >5 (a marker for hepatocellular damage), e) patients with concomitant g3-4 AI and bilirubin or AP elevation, e) patients with encephalopathy, ascites or jaundice, f) dose/toxicity relationship, g) cumulative toxicity: pts treated for more than 4 months (m)

Results: G3/g4 *AST* and *ALT* elevation: 11.7/15% and 11.7/18.3% of pts, respectively. G3 *Bb* elevation: 1.7% of pts (g4, 0%). G3 and g4 *GGT* elevation: 26.7% and 6.7% of pts (6 patients ñout of 20- had normal basal GGT). G3 and g4 *AP* elevation: 11.7 and 1.7% of pts (all these patients had baseline abnormalities).

G4 AI with concomitant LDH elevation: 20% of pts. Only 1 (out of 13) patient with g4 AI showed normal LDH.

Median *time to recovery* from grade 3-4 AI to grade 1 was 6 days [2-10] for AST and 10 d [4-19] for ALT

ALT/AP ratio >5: 25% of patients.

10% of pts had *concomitant g3-4 AI and any Bb deviation*, 38.3% had concomitant g3-4 AI and AP deviation

There were no patients with encephalopathy, jaundice or ascites related to the drug. No significant deviations of prothrombin activity have been reported.

For pts treated with doses lower than 600 μ g/m^2: g4 ALT, AST and GGT was 3.8, 0 and 7.7%, respectively. For pts treated with doses between 600 and 700 μ g/m^2 (recommended dose ñRD-) g4 ALT, AST and GGT was 11.1, 11.1 and 0%. For pts treated with doses higher than 700 μ g/m^2 (above RD) g4 ALT, AST and GGT was 50, 43.8, and 12.5%.

8 pts received KF for more than 4 m. 3 pts showed grade 4 AI and continued to receive treatment without any dose reduction. No evidence of cumulative toxicity was reported and after some cycles, toxicity was even lower.

Conclusions: G4 AI has consistently been DLT for KF administered over one hour. It usually goes with LDH elevation and ALT/AP ratio >5 indicating hepatocellular damage. It is spontaneously reversible and dose-dependent.

Liver toxicity was not clinically significant and features related to cholestasis seemed to be more related to the tumor than to the drug.

550 POSTER

Antitumour efficacy of MEN4901/T-0128, a new camptothecin derivative-carboxymethyldextran conjugate, in a panel of human gastrointestinal tumours xenografted in nude mice

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Gastrointestinal tumours comprise various histological types including pancreas, oesophageal, stomach, and colon cancers and are among the most unresponsive cancers to the chemotherapy. Recently some camptothecin derivatives like Irinotecan (CPT-11) have been shown to exert a significant antitumour activity against some of these tumour histotypes (colon). How-

ever, the clinical response rates obtained remain modest. MEN4901/T-0128 is a polysaccharide conjugate prodrug composed by the camptothecin derivative T-2513 bound to a carboxymethyldextran moiety via a triglycine spacer, endowed with a remarkable antitumour activity in a large panel of human tumour models of different histotypes. The purpose of the present study is to evaluate, in vivo, the growth-inhibitory effects of MEN4901/T-0128 in comparison with CPT-11, in a panel of human gastrointestinal tumours, i.e. human pancreas (ASPC-1, Capan-1), colorectal (HCT-116), gastric (HGC-27, NCI-N87) and oesophageal (OE-21) carcinoma, xenografted s.c. in nude mice. The two compounds were administered i.v. at the previously established optimal schedule of 60 mg/Kg bi-weekly (q4dx4) for CPT-11, and 80 or 160 mg/Kg as a single dose for MEN4901/T-0128. In all xenografted carcinomas MEN4901/T-0128 exerted a remarkable and significant antitumour activity, always superior to CPT-11, in terms of both tumour volume inhibition (TVI%) and log cell kill (LCK). In particular, MEN4901/T-0128 drastically reduced the growth of tumours fully resistant to CPT-11, like the gastric NCI-N87 (TVI= 98%, LCK=2.3), the pancreas ASPC-1 (TVI=88%, LCK=1.9) and Capan-1 (TVI= 99%, LCK >5), and the oesophageal OE-21 carcinoma (TVI=96%, LCK=1.6). Interestingly, against pancreatic carcinoma Capan-1, the efficacy of MEN4901/T-0128 resulted in a prolonged tumour growth inhibition; the tumours remained undetectable up to 100 days. In conclusion, a single administration of MEN4901/T0128 was active against all the gastrointestinal models evaluated, including naturally CPT-11 resistant tumours. These data further confirm the superior efficacy and the broader spectrum of antitumour activity of MEN 4901/T0128 in comparison with CPT-11.

551 POSTER

Peripheral Blood CD3(+) T cells, independent on their cell-cycle status, are inherently resistant to high concentrations of arsenic trioxide

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Arsenic trioxide (ATO) has been successfully used to treat acute promyelocytic leukemia (APL). The potential of ATO in other cancers are currently under investigation. It is critical to understand the toxicity of ATO to normal peripheral blood cells (PBC). Previously, we have previously demonstrated that ATO sensitivity to leukemic cells was related to cell- cycle status. In this study, we examined the toxicity of ATO in different subsets of PBC. PBC were treated with 0, 0.1, 1, 2, and 5 microM of ATO for 3 and 7 days before phenotypic analysis by flow cytometry. We chose CD15 and CD33 for myeloid cells, CD19 for B cells and CD3 for T cells. Our results showed that the toxicity of ATO to normal PBC, like to leukemic cells, was time- and dose-dependent. We found that ATO toxicity to PBC was not evident at low concentrations (< 1 microM). At high concentration, only CD3+ T cells (95.8%) could survive. Further analysis of the expression of CD4 and CD8 on these ATO-resistant CD3+ cells showed that CD3(+)CD4(+) cells were relatively resistant to ATO compared with CD3(+)CD8(+) cells (62.2% vs 30.5%). But, proliferation kinetics between different subsets of PBC did not differ when estimated by cell-proliferation analysis using CFSE This indicated that the cell cycling did not play a major role in the ATO resistance found in CD3(+) T cells. The expression of MDR1 was not related to the ATO resistance in CD3(+) T cells, when measured by rhodamine-123 efflux. We also found that cells that underwent apoptosis had altered mitochondrial transmembrane potential estimated by differential staining of rhodamine-123 when rhodamine-123 efflux was blocked by MDR1 inhibitor, verapamil, indicating that ATO- mediated apoptosis was most likely mediated by intrinsic mitochondrial pathway. Our results suggested that there could be multiple mechanisms responsible for the sensitivity to ATO, which might play a role in the toxicity observed during the clinical use of ATO. Identification of the mechanisms responsible for these two different types of cells could be useful to ATO- containing regimens for cancers other APL.

552 POSTER

Evaluation of the pharmacokinetic (PK) interactions between cetuximab and irinotecan in patients with Epidermal Growth Factor Receptor (EGFR)-expressing advanced solid tumors. Results of a phase I study.

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Background: Cetuximab (Erbitux™) is a chimeric monoclonal antibody, which has shown activity in patients with EGFR-expressing metastatic colorectal cancer (CRC) refractory to prior chemotherapy with irinotecan.

Objectives: This study investigated the impact of cetuximab on PK parameters of irinotecan, and that of irinotecan on PK values of cetuximab in patients with a variety of tumor types.

Methods: Group A received irinotecan from week 1 (350 mg/m^2 q3wks), with cetuximab added in week 2 (400 mg/m^2 1st infusion, then 250 mg/m^2 weekly). Group B received cetuximab weeks 1 to 4 (400 mg/m^2 1st infusion, then 250 mg/m^2 weekly), with irinotecan added in week 4. Patients were treated until progression or impaired tolerance.

Results: 15 patients were enrolled and 13 were evaluable for PK. Patient demographics for group A were median age=56 years and KPS=80, and a 3/3 male/female gender split. The group B demographics were median age=49 years and KPS=80, and a 3/4 male/female ratio. With the exception of a prostate cancer patient in group B, all patients had tumors of gastrointestinal origin. The median treatment duration was 10 weeks. Drug-related adverse events were consistent with the safety profiles of the drugs and consisted of grade 2 fever in two patients in close temporal relationship with the administration of cetuximab and grade 3 diarrhea in two patients in week 4 after irinotecan administration. Minor responses and tumor stabilizations were reported. Concentration-time profiles of cetuximab, when given alone or in combination with irinotecan, were superimposable. The same was true for irinotecan. Derived PK parameters for cetuximab and irinotecan were similar after mono- and combined administration (Table). The calculated ratios for all the irinotecan PK parameters at week 4 over week 1 ranged from 90-112% (group A), showing that the presence of cetuximab did not impact on the single-dose PK of irinotecan. The calculated ratios for all the cetuximab PK parameters at week 4 over week 3 ranged from 87-123% (group B), showing that the presence of irinotecan did not impact on the PK of cetuximab.

Gp	Pts	Treatment	Week	Analyte	AUC_{0-t} (μg/mL*h)	C_{max} (μg/mL)	t_{max} (h)	$t_{1/2}$ (h)
A	6	Irinotecan alone	1	Irinotecan	42.8	8.13	1	10
		Irinotecan+cetuximab	4	Irinotecan	39.1	6.78	1	10
B	7	Cetuximab alone	3	Cetuximab	13039	153	2	119
		Cetuximab+irinotecan	4	Cetuximab	14923	162	2	117

Mean values listed

Conclusion: Results of this study indicate the absence of any appreciable PK interaction between the two compounds.

553 POSTER

Alternate administration sequences of gemcitabine / vinorelbine in advanced solid tumor: a pharmacokinetic study.

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The aim of this study was to investigate a possible pharmacokinetic (PK) interaction between gemcitabina (GEM) and vinorelbine (VNR), when co-administered following the alternate sequence GEM-VNR and VNR-GEM. GEM-VNR sequence: 9 patients with advanced NSCLC or metastatic breast cancer were treated with GEM (60'iv, 1000mg/m^2) followed after 5' by VNR (10'iv, 25mg/m^2) on day 1 and 8 every 3 weeks; VNR-GEM sequence:17 patients received VNR followed by GEM at the same doses and regimen; 5 patients were given only single-agent GEM (60'iv, 1000mg/m^2) as a control group (GEM group). GEM PK profile in both schedules showed biphasic elimination as in monotherapy GEM group; GEM C and AUC values are higher in the GEM group than in GEM-VNR and VNR-GEM sequences (31.62mg/l vs 23.41mg/l and 28.74mg/l for C and 28.17mg*h/l vs 19.37mg*h/l and 23.76mg*h/l for AUC) . GEM Ke and Vss were significantly