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

A. Haselbeck[1], B. Reigner[2], P. Jordan[2], A. Pannier[2], J. Glaspy[3]. [1] *F. Hoffmann-La Roche, Penzberg, Germany;* [2] *F. Hoffmann-La Roche, Basel, Switzerland;* [3] *UCLA Medical School, Los Angeles, CA, USA*

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)

J.H.M. Schellens[1], L. Paz-Ares[2], J.M. Trigo[3], B. Pardo[4], A. Ruiz-Casado[5], E. Ciruelos[2], M. García[3], J. Beijnen[1], M.A. Izquierdo[5]. [1] *The Netherlands Cancer Institute, Medical Oncology, Amsterdam, The Netherlands;* [2] *Doce de Octubre, Medical Oncology, Madrid, Spain;* [3] *Vall d Hebron, Medical Oncology, Barcelona, Spain;* [4] *Institut Catalá d Oncologia, Medical Oncology, Barcelona, Spain;* [5] *PharmaMAr, Medical Oncology, Madrid, Spain*

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

M. Bigioni[1], F. Animati[1], M. Kakushima[2], T. Kawaguchi[2], C.A. Maggi[1], S. Manzini[1], C. Goso[1]. [1] *Menarini Ricerche S.p.A., Pomezia (Rome), Italy;* [2] *Tanabe Seiyaku Co., Ltd., Discovery Research Laboratories, Saitama, Japan*

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-