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

M.J. Huang[1], S.F. Lin[2], C.P. Lin[3], C.R. Liu[4], J.M. Chow[5], H.J. Liu[6].
[1] MacKay Memorial Hospital, Medicine, Taipei, Taiwan; [2] Taipei Medical University, Cell and Molecular Biology, Taipei, Taiwan; [3] Taipei Municipal Jen-Ai Hospital, Oncology, Taipei, Taiwan; [4] Taipei Municipal Jen-Ai Hospital, Radiation Oncology, Taipei, Taiwan; [5] Taipei Municipal Wanfang Hospital, Oncology, Taipei, Taiwan; [6] Taipei Medical University, Cell and Molecular Biology, Taipei, Taiwan

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.

C. Delbaldo[1], J.Y. Pierga[2], V. Dieras[2], S. Faivre[1], M. Bonnay[1], J.C. Vedovato[3], M. Mueser[3], A. Nolting[3], A. Kovar[3], E. Raymond[1].
[1] Institut Gustave Roussy, Villejuif, France; [2] Institut Curie, Paris, France; [3] MERCK KGaA, Darmstadt, Germany

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.

M. Airoldi[1], L. Cattel[2], S. Novello[2], R. Passera[2], M. Medail[2], S. Marchionatti[1], O. Bertetto[3], C. Bumma[1]. *[1] S.Giovanni Antica Sede, Medical Oncology Department, Torino, Italy; [2] Turin University, Drug Science Technology Department, Torino, Italy; [3] H.S.Giovanni Battista, Medical Oncology Department, Torino, Italy*

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

altered in VNR-GEM sequence. VNR conc/time curve showed rapid plasma clearance and VNR Cmax values showed some interpatients variability in both sequences. Mean VNR C values were 512.0 vs 728.8ng/ml for GEM-VNR and VNR-GEM respectively while AUC ranged from 203.14 to 304.25ng*h/ml. No other VNR PK parameters showed significant alteration in the two alternate protocols. In conclusion GEM serum levels showed evidence of PK interactions with VNR only in the VNR-GEM sequence, mostly in the elimination phase, while VNR AUC was higher in VNR-GEM than in GEM-VNR protocol. This suggest that GEM-VNR sequence may be safer for patients than inverse protocol, considering the lack of any PK alteration.

554 POSTER

Phase 1 study of CT-2103/cisplatin in patients with solid tumors

K. Skubitz[1], A. Kudelka[2], M.G. Bolton[3]. [1] *University of Minnesota, Minneapolis, USA;* [2] *MD Anderson Cancer Center, Houston, USA;* [3] *Cell Therapeutics, Inc., Seattle, USA*

Background: This 2-center, phase 1 study is designed to determine the maximum tolerated dose of CT-2103 (XYOTAX ") /cisplatin (cis) in patients (pts) with solid tumors. CT-2103 is a tumor-targeted taxane designed to concentrate selectively in tumors, which may result in superior efficacy, safety and symptom control compared with standard taxane therapy.

Materials and methods: Escalating doses of CT-2103/cis 75 mg/m2 are administered to pts with tumors refractory to conventional therapy or for which no conventional therapy exists. CT-2103 is administered as a 10-min IV infusion followed by a 3-hr IV infusion of cis every 21 days. Toxicity and response are assessed according to NCI CTC (v2) and RECIST.

Results: Data are available for 14 pts: ovarian or primary peritoneal (5 pts), thyroid (3), unknown primary peritoneal (1), uterine (1), sarcoma (2), malignant schwannoma (1), or mesothelioma (1). Pts had 0-3 prior chemotherapy regimens (median, 2). Pts have received 1-12 cycles (median, 6) at 175 mg/m2 (3 pts), 210 mg/m2 (6), and 225 mg/m2 (6), and 250 mg/m2 (3) conjugated paclitaxel. 100% ovarian and 85% of other tumors had disease control (partial response [PR] + stable disease [SD]). Five pts have confirmed PR (3 ovarian, 1 mesothelioma, 1 malignant schwannoma) and 6 have SD (2 ovarian, 2 thyroid, 1 uterine, 1 myxoid chondrosarcoma). Response duration in pts with PR ranged from 5-11 months and 3-6 months in pts with SD. CA-125 values in pts with ovarian cancer were normalized in pts with PR and reduced (>70%) in pts with SD. Toxicities reflected the cis toxicity profile; grade 4 regimen-related toxicities are neutropenia (9 pts), anemia (1), and febrile neutropenia (1). One pt had Grade 3 peripheral neuropathy and withdrew after 7 cycles. Neutropenia was responsive to growth factor therapy and did not cause withdrawal.

Conclusions: CT-2103/cis shows manageable toxicity and encouraging efficacy in platinum and taxane resistant ovarian cancer. The MTD has not yet been determined. Based on the results of studies with CT-2103 alone and in combination with platinum agents, the Gynecologic Oncology Group initiated a phase 2 single agent trial in recurrent ovarian cancer pts with <3 prior regimens and is developing a phase 3 front line trial in combination with platinum.

555 POSTER

Phase 1 studies of CT-2103 in patients with non small cell lung cancer and with advanced malignancies

H. Burris[1], D. Shipley[1], A. Greco[1], S. Jones[1], M.G. Bolton[2]. [1] *Sarah Cannon Cancer Center, Nashville, USA;* [2] *Cell Therapeutics, Inc., Seattle, USA*

Background: CT-2103 (XYOTAX™) is a tumor-targeted taxane designed to concentrate selectively in tumors, which may result in superior efficacy, safety, and symptom control compared with standard taxane therapy. Two phase 1 studies were designed to determine the maximum tolerated dose (MTD) of CT-2103 in PS 0/1 patients (pts) with non small cell lung cancer (NSCLC) in one study and advanced malignancies in the other.

Materials and methods: Escalating doses of CT-2103 are administered to pts who have failed prior therapy. CT-2103 is administered as a 10-20 min IV infusion every 21 days. Toxicity is assessed according to NCI CTC (v 2). Blood samples are collected at specified intervals during cycles 1 and 2. Plasma was analyzed for conjugated taxanes (CT-2103) and unconjugated paclitaxel by liquid chromatography and tandem mass spectrometry (LC/MS/MS). Pharmacokinetic (PK) parameter estimates were determined with WinNonlin.

Results: Fifteen pts have been treated. Median number of cycles is 2. Grade 3 (4 pts) and grade 4 (2 pts) neutropenia has been the major toxicity. Grade 3 neurotoxicity has been seen in heavily pretreated patients who received prior neurotoxic agents and had neuropathy at study entry. No other Grade 3/4 drug-related toxicities have been reported to date. An MTD has not been reached in either study (based on toxicities encountered in cycle 1), but 270 mg/m^2 is not a tolerable dose for chronic treatment (> 4 cycles) of heavily pre-treated patients due to neutropenia and neuropathy. In the NSCLC study, 1 pt had a confirmed partial response, 2 pts had stable disease for > 10 weeks as their best response. Response data is not yet available for other pts. Pharmacokinetic data are available for 4 patients receiving 235 mg/m^2 and 8 patients receiving 270 mg/m ^{2}. The concentrations of CT-2103 declined biphasically with a long terminal elimination phase ($T_{1/2}$ >140 hrs.) in both cycles. The clearance for unconjugated paclitaxel was 152 ± 63 mg/min/m^2 and the mean C_{max} was 3.0 ± 2.2 μ mol/L. The mean volume of distribution at steady state (Vss; 4.0 ± 2.5 L) suggests restricted distribution to plasma volume. In cycle 2, there was no evidence of accumulation of either conjugated or unconjugated paclitaxel in these patients. The AUC of unconjugated paclitaxel represented < 6% of the AUC of conjugated paclitaxel. The human PK data support the advantages of polyglutamate technology such as persistence of the molecule in the plasma, restricted tissue distribution over standard taxane therapy, and stability of the polymer conjugate. The NSCLC study has been expanded to obtain additional PK data in chemotherapy-naïve NSCLC pts.

556 POSTER

Clinical pharmacokinetics of erlotinib in healthy subjects

R. Abbas[1], S. Fettner[1], M. Riek[2], S. Davis[3], M. Hamilton[4], P. Frohna[5], A. Rakhit[1]. [1] *Hoffman-La Roche Inc, Department of Clinical Oncology, Nutley, USA;* [2] *Hoffman-La Roche, Basel, Switzerland;* [3] *Hoffman-La Roche, Welwyn Garden City, UK;* [4] *OSI Pharmaceuticals Inc, Boulder, USA;* [5] *Genentech Inc, South San Francisco, USA*

Erlotinib (Tarceva™) is an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor being developed for the treatment of various solid tumors. The objective of this study was to assess multiple-dose pharmacokinetics of erlotinib and to evaluate effect of food on its pharmacokinetics. This was a randomized, open-label, parallel-group study conducted in healthy male volunteers. The subjects were randomly assigned to two treatment groups (A and B) to receive 100 mg erlotinib orally once a day for 8 days. Subjects in group A received erlotinib under fasting condition on days 1-7 and fed condition on Day 8. Subjects in group B received erlotinib under fed condition on days 1-7 and fasting condition on Day 8. Following daily oral administrations of erlotinib under fasting condition, erlotinib was rapidly absorbed and reached peak plasma concentrations at 3-4 hours after a dose. The Cmax and AUC of erlotinib after fasting were 616 ng/mL and 6336 ng.hr/mL on day 1, and 1069 ng/mL and 13739 ng.hr/mL on day 7. Erlotinib concentration reached steady-state on days 4-5, as indicated by steady-state trough concentrations that were maintained at approximately 300 ng/ml. The mean terminal half-life of erlotinib on day 8 was approximately 13 hours in group A and 21 hours in group B. Erlotinib mean AUC was about 33% greater when given with food on day 8 (group A) compared to that on day 7. Following daily dosing of erlotinib with food for 7 days (group B), the mean exposure (AUC and Cmax) on day 7 was about 33% higher than that in fasted subjects (group A). This data indicates that there is an increase in erlotinib exposure after single and multiple dose administrations of erlotinib with a high-fat, high-calorie meal; however, the number of subjects studied was relatively small (8 per group) and the difference in mean exposure between the two groups was not statistically significant (p-value = 0.252).

557 POSTER

BBR 3576: phase I dose escalation study in patients with advanced solid tumors (a study with the participation of CESAR-EWIV)

M.E. Scheulen[1], K. Mross[2], Ch. Peschel[3], C. Unger[2], H. Richly[1], M.G. Camboni[4], P. Barbieri[4], E. Verdi[4], B. Vincenzi[4], A. Bernareggi[4]. [1] *University of Essen Medical School, Department of Internal Medicine (Cancer Research), Essen, Germany;* [2] *Tumor Biology Center, Freiburg, Germany;* [3] *Technical University, III Medical Department, Munich, Germany;* [4] *Novuspharma, Bresso, Italy*

Background: BBR 3576, an innovative DNA intercalating agent and topoisomerase II inhibitor, has demonstrated very promising preclinical