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