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

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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

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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

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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)

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

activity in various human tumor xenografts and only minimal delayed cardiotoxicity.

Patients and Treatment: A three-center phase I study was performed in patients (pts) with advanced solid tumors without established systemic treatment options. Primary objectives: maximum tolerated dose (MTD) and dose-limiting toxicity (DLT). Secondary objectives: recommended dose (RD), toxicity profile, pharmacokinetics (PK) and antitumor activity. BBR 3576 was given as a 1-hour infusion up to 2 cycles, q28d. Dose was increased from 1 up to 150 mg/m2 in 10 steps according to an accelerated dose escalation scheme. Safety was evaluated by vital signs, clinical laboratory parameters, ECGs, echocardiography and adverse events.

Results: 27 pts (12 females/15 males) were enrolled, age was between 32 and 74 years (median: 60 years), 12 pts had colorectal cancer, 3 ovarian cancer, 3 lung cancer and 9 other solid tumors. The main toxicity after cycle 1 was haematological, with neutropenia nadir occurring after 2 weeks and a recovery time of 1 week; neutropenia first occurred as Grade 3 at the 90 mg/m2 dose level (1/4 pts). Of the 6 pts treated with the highest dose (150 mg/m2) one pt had DLT (stomatitis Grade 3), 2 pts had a Grade 3 and 1 pt a Grade 4 neutropenia. The PK of BBR 3576 was linear over the whole dose range investigated. The compound has a large volume of distribution (Vz= 88.3 L/kg), a high systemic clearance (CL= 1.86 L/h/Kg), and a long elimination half-life (t1/2,z= 41.8 h). The renal excretion represents a minor elimination route: < 5% of the dose is excreted unchanged in 3 days.

Conclusions: BBR 3576 was well tolerated up to a dose level of 150 mg/m2. Doses higher than 150 mg/m2 were not evaluated and the RD for phase II was set to be 150 mg/m2.

558 POSTER

The effect of food on the pharmacokinetics of GW572016

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GW572016 is an orally active dual EGFR/ErbB2 kinase inhibitor that blocks signal transduction pathways implicated in cancer growth. GW572016 has been administered to both healthy subjects and cancer patients. The effects of high-fat and low-fat meals on the pharmacokinetics of GW572016 were investigated in separate studies. In one study, 19 healthy subjects received a single 100 mg dose of GW572016 following either an overnight fast or a high-fat breakfast in a randomized crossover manner. The high-fat breakfast consisted of eggs, bacon, toast, butter, hash-browned potatoes, and whole milk (1000 calories, 50% fat). In another study, 6 Phase I cancer patients received a single 1250 mg dose of GW572016 following either an overnight fast or a low-fat breakfast in a randomized crossover manner. The low-fat breakfast consisted of cereal (Special *K* or Corn Flakes), toast, jam, juice (apple or grape), 2% milk, and tea or coffee. Doses of GW572016 were separated by at least 7 days in both studies.

Results: following administration of GW572016 with a high-fat breakfast in the healthy subjects, there was an increase of approximately 60% in area under the serum concentration curve (AUC) and maximum serum concentration (Cmax) of GW572016. Geometric mean AUC increased from 1136 h*ng/mL to 1867 h*ng/mL, while geometric mean Cmax increased from 92 ng/mL to 151 ng/mL. Median time to achieve peak concentration (4 h) and geometric mean half-life (10 h) did not differ between the fasted and fed states in these healthy subjects. The results of the second study, examining the effect of a low-fat breakfast on the pharmacokinetics of GW572016 are currently being evaluated. GW572016 was well tolerated by both healthy subjects and Phase I cancer patients in these studies.

559 POSTER

Pharmacokinetics of GW572016 in an ascending dose tolerability study of phase I cancer patients

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GW572016 is an orally active dual EGFR/ErbB2 kinase inhibitor that blocks signal transduction pathways. This study was the first administration of GW572016 to cancer patients. Patients within a cohort received the same assigned dose of GW572016 for 14 days. Doses, examined in ascending order, were 175, 375, 675, 900, 1200, 1600, and 1800 mg QD, and 900 mg BID. Cohorts receiving the next higher dose were initiated after the previous cohort completed 14 days of dosing. Blood samples for pharmacokinetic analysis were obtained over 24 h on Days 1 and 14 with sampling times appropriate for QD or BID dosing. Patients continued treatment with GW572016 past Day 14 until the occurrence of unacceptable toxicity, disease progression, or patient/physician request. Thirty-nine patients were examined over all doses: 175 mg (n=3), 375mg (n=3), 675 mg (n=4), 900 mg (n=4), 1200 (n=6), 1600 mg (n=4), 1800 mg (n=9), and 900 mg BID (n=6). Serum concentrations (AUC and Cmax) of GW572016 increased in proportion with increasing dose over the range of doses examined. Moderate accumulation (approx. 60%) in serum concentration (AUC) was observed over the 14 days of continuous dosing. A short lag time in absorption was apparent, and the time to achieve peak concentration was 4 h post-dose. The pharmacokinetics of GW572016 with twice-daily dosing were consistent with those after once-daily dosing. The pharmacokinetics of GW572016 in Phase I cancer patients were consistent with previous observations in healthy subjects at lower doses following a shorter duration of continuous dosing [Proc Amer Soc Clin Oncol 2002, 21: 94a (374)].

560 POSTER

Search for drug-drug interaction between oral vinorelbine (VRL) and capecitabine (CAP) in metastatic breast cancer (MBC) during a dose finding study

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Background: Oral VRL and CAP are active in MBC through distinct mechanisms of action. Combining these drugs is therefore an attractive option which advantageously allows fully oral regimens. Both are administered orally, and furthermore involve carboxylesterases in their metabolism pathway. As a consequence, drug-drug interaction might theoretically occur when combining these 2 drugs and has to be assessed to guarantee the further safe use of this combined treatment.

Material and methods: The study objectives were to determine the recommended dose (RD) of the combination and to investigate during the 1st cycle of treatment the putative pharmacokinetic (PK) interaction. Oral VRL was given on days (D)1 and 8, and weekly once reached a RD, and CAP twice daily from D1 to D14, both every 3 weeks. For oral VRL, PK was evaluated on D1, when co-administered with CAP, using limited sampling strategy (LSS) over the first 24 hours post-dosing. This LSS was developed and validated from VRL PK model developed on NONMEM software and Bayesian PK parameters were calculated. These parameters were compared to reference data from a population PK database constituted of Phase I patients having received oral VRL alone. For CAP, PK of parent compound and metabolites 5DFCR, 5DFUR and 5FU were evaluated on D1(CAP+VRL) and on D7(CAP alone) through full blood sampling. PK parameters were calculated by model-independent approach. Data between D1 and D7 were compared through variance analysis.

Results: The study is still ongoing. The first 5 dose levels are completed and PK data of 17 and 12 pts for VRL and CAP respectively, are available at the moment. These patients received VRL from 60 to 80 mg/m2 and CAP from 1650 to 2500 mg/m2/D according to dose level. PK parameters of VRL (Cmax/dose, AUC/dose, T1/2z) are similar whatever the dose level of co-administered CAP. Furthermore, there is no statistically significant