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.

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The effect of food on the pharmacokinetics of GW572016

D. Smith[1], K. Koch[1], D. Lee[1], S. Mangum[1], A. Stead[1], M. Versola[1], T. DeBerardinis[2], H. Burris[3], S. Jones[3], N. Spector[1]. *[1] GlaxoSmithKline, Clinical Pharmacology and Discovery Medicine, Research Triangle Park, NC, USA; [2] GlaxoSmithKline, Clinical Pharmacology and Discovery Medicine, Philadelphia, PA, USA; [3] Sarah Cannon Cancer Center/Tennessee Oncology, Nashville, TN, USA*

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.

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

K. Koch[1], D. Lee[2], S. Jones[3], A. Stead[4], M. Versola[1], H. Burris[3], G. Wilding[5], C. Taylor[6], N. Spector[1], D. Smith[1]. *[1] GlaxoSmithKline, Clinical Pharmacology and Discovery Medicine, Research Triangle Park, NC, USA; [2] GlaxoSmithKline, Drug Metabolism and Pharmacokinetics, Research Triangle Park, NC, USA; [3] Sarah Cannon Cancer Center/Tennessee Oncology, Nashville, TN, USA; [4] GlaxoSmithKline, Biomedical Data Sciences, Research Triangle Park, NC, USA; [5] University of Wisconsin Comprehensive Cancer Center, Madison, WI, USA; [6] Arizona Cancer Center, Tucson AZ, USA*

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)].

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

F. Nolé[1], C. Catania[1], G. Sanna[1], E. Munzone[1], G. Milano[2], B. Laffranchi[3], A. Goldhirsch[1], G. Blanchot[4], C. Puozzo[4]. *[1] European Institute of Oncology, Oncology Clinical Pharmacokinetics Dept., Milano, Italy; [2] Centre Antoine Lacassagne, Nice, France; [3] Institut de Recherche Pierre Fabre, Boulogne, France; [4] Institut de Recherche Pierre Fabre, Oncology Clinical Pharmacokinetics Dept., Castres, France*

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

difference between current study and reference data on VRL blood exposure. Concerning CAP and its metabolites, PK parameters are highly variable. Nevertheless, no statistically significant difference between D1 and D7 is observed for CAP, for the intermediary metabolites 5DFCR and 5DFUR, or for the final active compound 5FU.

Conclusion: From current results based on 12-17 pts, a drug-drug interaction is unlikely to occur when combining VRL and CAP. However, the full study needs to be completed to definitely support this conclusion.

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Clinical results from an ADME (absorption, distribution, metabolism, and excretion) trial of PTK787/ZK 222584 (PTK/ZK): a novel, oral angiogenesis inhibitor in patients with advanced cancer

J. Knoblich[1], P.M. Paldánius[2], H.-P. Gschwind[3], C. Günther[2], A. Henry[4], J. Xia[4], D. Reitsma[4], D. Laurent[2], L. Jost[1]. [1] *Medizinische Universitätsklinik, Kantonsspital Bruderholz/Onkologie, Bruderholz, Switzerland;* [2] *Schering AG, Berlin, Germany;* [3] *Novartis Pharma AG, Preclinical Safety/Europe, Basel, Switzerland;* [4] *Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States of Amercia*

Background: PTK/ZK is a novel, oral, once-daily inhibitor of vascular endothelial growth factor receptor tyrosine kinases, important receptors that contribute to tumor growth and metastases.

Material and Methods: Eight adult patients with advanced cancer and a range of 2 to 8 prior anticancer therapies were enrolled. Eligibility requirements included adequate organ function and World Health Organization performance status 0 to 2. Patients received 1,000 mg PTK/ZK daily for 14 days, and on day 15 received a single dose of 1,000 mg [^{14}C]-labeled PTK/ZK. Pharmacokinetics (PK) was followed up to day 22; thereafter, patients could continue with unlabeled PTK/ZK until disease progression or unacceptable toxicity.

Results: Six patients have completed the 33-day follow-up period. Post-administration of PTK/ZK, no significant changes in clinical parameters were observed. Preliminary PK results for the parent drug demonstrate rapid absorption, and the AUC of unlabeled PTK/ZK is comparable with previously reported results. In 4 patients, almost all radioactivity was completely excreted by day 22. Two patients showed incomplete excretion (67% and 76% of dose), likely due to incomplete sample collection. The mean cumulative excretion of parent drug and metabolites 22 days post-administration was 23% in urine (range, 13% to 28%) and 60% in feces (range, 42% to 74%), indicating mainly biliary/fecal excretion of PTK/ZK and its metabolites. PTK/ZK was well tolerated with no treatment-related SAEs. Adverse events suspected to be treatment related included diarrhea (grade [G]1), headache (G3), hypertension (G1 and 3), nausea (G1 and 2), tremors (G1), vomiting (G1 and 2), and weight loss (G1). Three patients discontinued because of adverse event or abnormal laboratory value 14 to 33 days after study entry. Five patients discontinued because of disease progression; 3 patients discontinued 1 to 2 months after study entry, whereas 2 patients received 7 28-day follow-up cycles of PTK/ZK and had stable disease for 8 months. Of the 2 patients who had stable disease, 1 patient with metastatic colorectal cancer had a significant decrease of tumor marker CEA, and 1 patient with NSCLC showed a minor tumor response on CT scan with significant improvement of clinical symptoms.

Conclusions: PTK/ZK was well tolerated in patients with advanced cancers and showed promising clinical activity. These results confirm previously reported clinical and PK results from other PTK/ZK trials.

562 POSTER

Dihydropyrimidine dehydrogenase (DPD) activity in peripheral mononuclear cells (PMNC-DPD) during long-term treatment with oral uracil/tegafur (UFT) as postoperative adjuvant chemotherapy for colorectal cancer (CRC)

K. Ishikawa[1], S. Sadahiro[1], T. Suzuki[1], H. Makuuchi[1], C. Murayama[2]. [1] *Tokai University, Surgery, Japan;* [2] *Tokai University, Radiology, Japan*

Background: 48-hour continuous infusion of 5-FU has been reported to reduce PMNC-DPD by 39% in humans. A bolus infusion of 5-FU has been reported to reduce DPD activity in the liver by 50% at 48 hours after infusion in rats. However, there are no reports on variations of PMNC-DPD during long-term administration of 5-FU or oral fluoropyrimidine. UFT consists of tegafur and the DPD inhibitor, uracil, classified as an oral DPD inhibitory fluoropyrimidine (DIF). This study examined the effects of long-term postoperative adjuvant chemotherapy with oral UFT in patients with CRC on PMNC-DPD.

Patients and Methods: UFT was administered for 5 consecutive days at a dose of 400 mg/m^2 /d and not administered on the next 2 days (weekday-on / weekend-off schedule, *Cancer Chemother Pharmacol* 46,180,2000). Treatment was started 2 to 4 weeks after surgery and was continued for at least 6 months. Blood samples were taken constantly at 8 oclock in the morning before taking UFT on the third day of the five drug-on days. PMNC-DPD activities were measured before and 1, 2, 4 and 6 months after starting the UFT treatment.

Results: Seventy patients with CRC who underwent colorectal resection were evaluated. In 11 of 70 patients exclusive of patients who withdrew from the study because of recurrence or death, treatment was suspended within 6 months due to grade 2 or higher adverse reactions. In all patients, there were no significant variations of PMNC-DPD activity during the postoperative administration of UFT for 6 months (pre: 186.9 ±87.4, 1M: 169.6 ±73.7, 2M: 189.3 ±80.3, 4M: 215.6 ±93.3, 6M: 201.1 ±75.1 pmol/min/mg protein). In 11 patients whose treatment was suspended due to adverse reactions, there were no significant variations with time. Thus, it was confirmed that the inhibition of DPD by uracil was reversible, and the DPD activity before treatment was considered to be an individual representing value of 5 time points assayed during the long-term treatment of UFT. The incidence of Grade 2 hematological or non-hematological toxicity increased more significantly in patients with low PMNC-DPD activity than in those with high PMNC-DPD. No grade 3/4 toxicity was observed.

Toxicity	PMNC-DPD Positive	Negative	p-value
High	1	30	0.018
Low	10	29	

*High: PMNC-DPD*186.9 pmol/min/mg protein (mean of pre PMNC-DPD activity), Low: PMNC-DPD<186.9 pmol/min/mg protein>

Conclusions: There were no significant variations of PMNC-DPD activity during the postoperative administration of UFT for 6 months. PMNC-DPD activity before UFT treatment could be a predicting factor for the expression of toxicity.

563 POSTER

Pharmacokinetics of epirubicin and paclitaxel during weekly administration in patients with metastasised breast cancer

R.M. Mader, B. Rizovski, C. Wenzel, R. Bartsch, C.C. Zielinski, G.G. Steger. *University Hospital, Dept. of Medicine I, Vienna, Austria*

Background: In order to reduce the unwanted side effects of highly effective regimens, we administered epirubicin and paclitaxel on a weekly schedule and compared the pharmacokinetics at the begin and at the end of the first therapeutic cycle.

Material and Methods: In a dose escalation study, epirubicin was administered as i.v. infusion over 30 minutes starting at 20 mg/m^2 followed by paclitaxel given as i.v. infusion over 3 hours starting at 70 mg/m^2 with standard premedication. This combination was administered weekly for 6 weeks followed by one week of rest (= 1 cycle) with tumour reassessment after 2 cycles of therapy. Dose escalation in steps of 5 mg epirubicin/m^2 and 5 mg paclitaxel/m^2 was considered, if toxic side effects were not higher than grade 3 according to WHO criteria in 2 of 3 patients per dose level. To evaluate pharmacokinetics, both compounds were monitored at week 1 and 6 in each patient using an on-line HPLC method.

Results: The pharmacokinetics of epirubicin and paclitaxel were similar in week 1 (anthracycline and taxane naive patients) and week 6. In contrast to paclitaxel, there was a good correlation between dose and area under the concentration-time curve (AUC) for epirubicin (r^2=0.73). Nevertheless, the maximum plasma concentration of epirubicin and paclitaxel were closely correlated (r^2=0.69). Considering dose escalation, there was a statistically significant reduction in the total clearance of both agents indicating non-linear pharmacokinetics in the higher dose range (see table for AUC).

	Epirubicin		Paclitaxel	
	dose [mg/m^2]	AUC [nmol.h/l]	dose [mg/m^2]	AUC [nmol.h/l]
dose level 1	20	483 ± 190	70	3405 ±1453
dose level 2	25	874 ± 254	75	8638 ± 4938
dose level 3	30	1654 ± 423	80	9264 ± 2251

Conclusions: Reduced clearance observed after administration of 30 mg epirubicin/m^2 and 80 mg paclitaxel/m^2 may contribute to the dose limiting leukopenia (WHO grade 4 in 2 of 3 patients). Since the dose of 25 mg epirubicin/m^2 and 75 mg paclitaxel/m^2 was well tolerated under a weekly schedule, we recommend this dose as a starting point for future clinical trials. Under repeated administration of epirubicin and paclitaxel, there was