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