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.

561 POSTER

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

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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)

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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

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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

no shift of pharmacokinetic parameters from week 1 to week 6 rendering dose adjustment under therapy unnecessary.

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564 POSTER

Pharmacokinetics and metabolism of fulvestrant after oral, intravenous and intramuscular administration in healthy volunteers

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Background: Fulvestrant (Faslodex™) is an estrogen receptor (ER) antagonist indicated for the treatment of hormone receptor-positive advanced breast cancer in postmenopausal women progressing on prior anti-estrogen therapy.

Materials and methods: In separate studies, male or postmenopausal female volunteers received [^{14}C]-fulvestrant either as a single oral (po) dose of 400 mg (n=6), a single intravenous (iv) infusion of 10 mg (co-administered with plasma; n=8), or a single intramuscular (im) injection of 18 mg (n=7). The pharmacokinetics of total radioactivity and unchanged drug were assessed for up to14 d. Metabolites in plasma and excreta were investigated.

Results: Following iv infusion of fulvestrant (C_{inf} 121 ng/ml), there was rapid distribution leading to low levels of fulvestrant in plasma at 2 h post-infusion (approx. gmeans, 16.0 and 13.0 ng/ml in male and female volunteers, respectively). The concentration/time profiles of fulvestrant in males and females were very similar up to 24 h after infusion (gmean $AUC_{(0-t)}$, 223.0 and 197.0 ng.h/ml, respectively). After po administration, bioavailability was very low with minimal fulvestrant plasma concentrations (median T_{max} 0.75 h, gmean C_{max}, 9.0 ng/ml). Total exposure to fulvestrant, as determined by gmean $AUC_{(0-t)}$, was 15.2 ng.h/ml. Following im administration, absorption of fulvestrant was slow (T_{max} 8-24 h, gmean C_{max}, 14.6 and 13.3 ng/ml in male and female volunteers, respectively) and prolonged (apparent $t_{1/2}$ λ z 26-30 h) with detectable levels remaining 7 days post dose. Total exposure to fulvestrant, as determined by gmean $AUC_{(0-t)}$, was 555.0 and 646.0 ng.h/ml in male and female volunteers, respectively. Differences between the concentration of fulvestrant in plasma and circulating total radioactivity, particularly after oral administration, suggested rapid metabolism of the parent compound. Total ^{14}C was excreted slowly, almost entirely in the feces. In each case $\geq$ 90% of the dose was recovered, although rate of excretion varied with route of administration in the order po (7-10 d)>iv>im (21 d).

Conclusion: These data suggest that im injection is an appropriate method for administration of fulvestrant.

565 POSTER

Phase I combination study of oral vinorelbine (VRL) and oral cyclophosphamide (CTX) in patients with metastatic breast cancer (MBC)

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Background: VRL and CTX have proven activity in MBC and are orally available. Both have a cytochrome P450-mediated metabolism which justifies the search for drug-drug interaction.

Material and methods: This phase I study is evaluating oral VRL, given on days 1 and 8, and oral CTX from days 2 to 15, every 3 weeks, in patients (pts) failing one line of chemotherapy for MBC. On days 1, 7 and 8 the pharmacokinetics (PK) of both drugs are assessed to explore drug interactions. VRL, deacetylvinorelbine (DVRL), CTX and phosphoramide mustard (PM) are assayed. Dose limiting toxicities (DLTs) are evaluated during the first cycle (cy) and defined as grade (gr) 4 neutropenia for 7 days, gr 3 thrombocytopenia, febrile neutropenia, neutropenic infection, one week toxicity-related delay in starting cy 2, any delay in the administration of VRL or CTX due to toxicity, any gr 3/4 non-haematological toxicity except asthenia and inadequately treated nausea/vomiting.

Results: To date 18 pts have been included at 3 dose levels (DL) of VRL/CTX: DL1 (60/80 mg/m*), DL-1 (50/80 mg/m*) and DL-2 (50/100 mg/m*). Age ranged from 39 to 74 years. Metastatic sites were liver, skin, pulmonary, bone, or local recurrences. Four out of 5 pts at DL1 experienced DLT, consisting in a one-week delay of cy 2 due to neutropenia. At DL-1 none of the 6 enrolled pts developed DLT. Only one gr 3 diarrhoea appeared at DL-2. Main non-haematological toxicities at these 3 DLs during 46 cy were: gr 1-2 nausea (16 pts, 37 cy), vomiting (11 pts, 15 cy), fatigue (6 pts, 19 cy), diarrhoea (11 pts, 18 cy, including gr 3 once in 2 pts), paresthesia in 2 pts for 8 cy with one gr 3 episode once, and gr 1 alopecia in 6 pts for 16 cy.

So far no responses were noted, but 4 out of 12 evaluable patients showed disease stabilisation. Preliminary PK analysis did not reveal drug-drug interaction between VRL and CTX (DL1/DL-1). The AUCs of VRL on day 1 (without concomitant CTX) and day 8 (with CTX) were not significantly different. DVRL blood concentrations were low and remained within the same range on days 1 and 8. The AUCs of CTX and PM were comparable between days 7 and 8. Exposure to the drugs was similar in all pts, and there was no difference between pts who developed DLTs and the others.

Conclusions: The combination of oral VRL and oral CTX is feasible. No drug-drug interaction between both drugs has been detected up to now. DL-2 has an acceptable toxicity. A 4-week regimen is being studied.

566 POSTER

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

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Background: CT-2103 (XYOTAX™) is a tumor-targeted taxane designed to concentrate selectively in tumors, which potentially may result in superior efficacy, safety and symptom control compared with standard taxane therapy. Conjugation of paclitaxel to poly-L-glutamate enhances aqueous solubility and eliminates the need for Cremophor, resulting in a convenient 10-min infusion. This phase 1 study is designed to determine the maximum tolerated dose (MTD) of CT-2103 in combination with carboplatin (Cb) in patients (pts) with refractory solid tumors.

Materials and methods: CT-2103 is administered in escalating doses per cohort of 3 pts every 21 days as a 10-min IV infusion followed by Cb 30-min IV infusion. Toxicity and response are assessed according to NCI CTC and RECIST. Twenty-two pts have been treated.

Results: Data is available for 17 pts: non small cell lung cancer (4 pts), esophageal adenocarcinoma (1), ovarian cancer (2), breast cancer (1), thyroid (2), squamous cell carcinoma of the head and neck (2), pancreatic (2), colon (1), renal cell (2). Dose levels included: CT-2103 175 mg/m^2 / Cb AUC 5 (3 pts); CT-2103 210 mg/m^2 / Cb AUC 5 (3); and CT-2103 210 mg/m^2/Cb AUC 6 (7); CT-2103 225 mg/m^2/Cb AUC 6 (6); CT-2103 250 mg/m^2/Cb AUC 6 (3). Pts received 1-9 cycles. Disease assessments available for 12 pts. Nine of 12 pts (75%) achieved disease control (partial response [PR], 2 pt + stable disease [SD] for > 10 weeks, 7 pts). Both pts with ovarian cancer had a PR. One of these pts had a 60% reduction in tumor size, completed 9 cycles (discontinued treatment due to grade 3 neuropathy), a decrease in CA-125 from 11,724 to 16 ng/mL. The 2nd ovarian pt has a 75% reduction in tumor size, has completed 6 cycles, and is still on study. Clinically significant drug-related grade 3/4 toxicities were neutropenia (7 pts), thrombocytopenia (6) and febrile neutropenia (1). This toxicity profile is consistent with that of Cb. CT-2103/Cb is well tolerated. The cycle 1 MTD in heavily pretreated patients is 225 mg/m^2/AUC6. The predominant dose-limiting toxicities were neutropenia and neuropathy.

Conclusions: Evidence to date demonstrates anticancer activity. Based on these results and the safety/activity seen in single-agent studies, the Gynecologic Oncology Group is developing a randomized phase 3 trial comparing CT-2103/Cb with paclitaxel/Cb in pts with newly diagnosed, advanced ovarian cancer.

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A phase I and pharmacokinetic study of BMS-247550 in combination with carboplatin in advanced solid malignancies

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Background: BMS-247550 (Epo-B) is a semi-synthetic analogue of epothilone B which has shown antitumour activity in phase I trials. Here we report the final data from a phase I trial of Epo-B and carboplatin in patients with advanced solid malignancies.