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.

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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.

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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