platelets 1.04 [IC 95% (0.47-2.32)], for AST 0.85 [IC 95% (0.61-1.17)], for ALT 0.63 [IC 95% (0.51-0.77)] and for AP 1.57 [IC 95% (0.19-13.2)]. The RR of developing g1-4 nausea was 2.41 [IC 95% (1.61-3.62)], vomiting 1.78 [IC 95% (1.11-2.86)], fatigue 1.81 [IC 95% (1.27-2.60)] and febrile neutropenia 1.45[IC 95% (0.32-6.54)]

Conclusions: The toxicity profile of ET-743 1.3 mg/m^2 over 3 h plus the administration of corticosteroid treatment day -1 to day +2 seems safe, being neutropenia, thrombopenia and reversible and not cumulative aminotransferases increase the principal laboratory toxicities.

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Pharmacokinetics and metabolism of CPT-11 (Campto®) combined with capecitabine (Xeloda®) in patients with advanced colorectal cancer: altered disposition of the metabolites SN-38 and SN-38 glucuronide?

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The plasma concentrations of irinotecan (CPT-11) and its metabolites SN-38 and SN-38gluc were evaluated in 10 patients who were treated with a regimen of Camptoő / Xelodaő against advanced colorectal cancer (paired cross over, Camptoő monotherapy versus Camptoő + Xelodaő schedule). Both cytostatics are prodrugs which have to be bioactivated by liver carboxyesterase to the cytotoxic agents.

Samples were first analysed under acidic conditions to calculate the total amount of **CPT-11** and its metabolites in blood and second under neutral conditions for information of the carboxylate lactone equilibrium of CPT-11 and SN-38. Capecitabine (CCB) did not alter the mean CPT-11 plasma concentrations, only small differences ranging from 4% to + 16% could be found ($p < 0.55$). Noncompartment pharmacokinetic analysis confirmed the results of plasma data: no statistically significant change of cmax, AUC, Vd, Cl and MRT could be observed in the combination schedule.

Contrary to CPT-11 disposition, mean **SN-38** plasma concentrations seemed to be altered in the CCB group of the study. Differences of SN-38 concentrations in the combination treatment (compared to the control arm) were strongly time - dependent: per cent difference increased from -53% at 15 min to + 23% at 300 min after start of infusion ($p < 0.005$, corr = 0.981). For SN-38gluc, a very similar effect was evaluable: from - 39% at 15 min to + 6% at 300 min ($p < 0.027$, corr = 0,959). Analysis of lactone versus carboxylate forms revealed that this effect might base on lower lactone concentrations of SN-38, when CCB was coadministered.

After acidic analytical conditions, PHK parameters of **SN-38gluc** seemed to be unaffected by CCB (noncompartment PHK model). But the apparent formation - rate of SN-38gluc was delayed by CCB significantly: t1/2 appin = 25.0 ± 9.6 min versus 42.3 ± 12.5 min in the CCB group ($p < 0.004$). Accordingly, tmax occurred later: 108.0 ± 32.2 min versus 150.0 ± 31.6 min ($p < 0.016$); cmax was slightly lower (not significant). From our in-vitro results we know that there exists a certain potential of drug-interaction between CPT-11 and CCB. Even small changes in the disposition of SN-38 (activation pathway) and SN-38gluc (detoxification pathway) may have pharmacological consequences in CPT-11 chemo-therapy.

Detailed **in-vivo and in-vitro results** (including drugs of premedication as tropisetrone and dexamethasone) are presented and discussed (studies ongoing).

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Dose finding study of oral vinorelbine (VRL) in combination with capecitabine (CAP) in patients with metastatic breast cancer (MBC)

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Background: VRL and CAP are active in MBC and are often combined with various cytotoxics. Both are orally available, have different mechanisms of action and involve carboxylesterases in their metabolism.

Material and methods: We aimed at determining the maximum tolerated dose (MTD) and the recommended dose (RD) of oral VRL given on days (D) 1 and 8 at 60 or 80 mg/m^2 and CAP from D1 to D14 at doses ranging from 1650 to 2500 mg/m^2/d every 3 weeks. At the RD, a weekly schedule of oral VRL is to be evaluated. Pharmacokinetics of VRL, CAP and metabolites are determined on D1 and 7 of cycle 1 to study putative mutual interaction. Dose limiting toxicities (DLTs) are defined during the first cycle as grade (gr) 4 neutropenia for 7 days, gr 3 thrombocytopenia, febrile neutropenia, neutropenic infection, one week-delay in starting cycle 2 due to toxicity, gr 3/4 non-haematological toxicity except asthenia, inadequately treated nausea/vomiting or diarrhoea. Cohorts of 3 to 6 patients are treated per dose level (DL). DLT in 2 pts in any DL determines the MTD.

Results: To date 24 pts were included in 5 DLs. Age ranged from 31 to 66 years. Main metastatic sites were visceral (83%) and bone (38%). Fourteen pts had 2 or more organ involved. DL1 (60 VRL + 2000 CAP) was well tolerated without gr 3/4 event in 3 pts and 13 cycles. MTD was reached at DL3 (60 VRL + 2500 CAP) and DL4 (80 VRL + 1650 CAP): DLTs consisted in persisting neutropenia which resulted in delay in starting cycle 2 for 5 pts (gr 2, gr 3 and gr 4 neutropenia each in 1 pt at DL3, and, at DL4, gr 2 neutropenia in 2 pts) and febrile neutropenia in 1 pt. DL2 (60 VRL + 2250 CAP) was a RD. As per protocol a weekly schedule of 60 VRL + 2250 CAP was tested and MTD (gr 2 neutropenia on D21 in 1 pt, gr 3 thrombocytopenia concomitant with gr 3 neutropenia in another pt) was reached.

Gr 3/4 toxicities among 31 cycles at DL2 were one episode of gr 3 diarrhoea (2 pts) and, in 1 pt each, gr 4 bilirubin, gr 3 nausea and gr 3 wound infection while haematological events consisted in gr 4 neutropenia (2 pts, 2 cycles) and gr 3 leucopenia once in 1 pt. To date, 1 CR and 3 PRs are confirmed in the study population. Drug-drug interaction has not been suspected up to now.

Conclusions: Oral VRL 60 mg/m^2 on D1 and 8 and CAP 2250 mg/m^2 from D1 to D14 every 3 weeks is currently the RD. The weekly administration of oral VRL 60 mg/m^2 and CAP 2000 mg/m^2 every 3 weeks and a 4-week regimen are now being investigated.

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Phase I dose-finding study of the combination of alimta (pemetrexed) and paclitaxel in patients with solid tumors

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Background: Pemetrexed, a novel multitargeted antifolate, has activity in mesothelioma, NSCLC, breast and colon cancers. Paclitaxel exerts its anti-neoplastic effect via disruption of microtubule assembly and also has activity in a variety of solid tumors. This reports on one schedule of 3 different sequences evaluated in a phase I study of pemetrexed in combination with paclitaxel in patients with advanced malignancies.

Patients and methods: The primary study objective was to determine the maximum tolerated dose (MTD) of the combination; secondary objectives included determination of dose-limiting toxicity (DLT) and recommended doses for phase II study. DLT was defined as the occurrence of * 1 of the following during cycle 1: Grade (G) 4 neutropenia lasting * 5 days (d), febrile neutropenia, G4 thrombocytopenia, or G3 non-hematologic toxicity (except G3 nausea, vomiting, and transaminase elevation). Paclitaxel was infused over 3 hours on d1 and d8 of a 21d cycle; standard taxane premedications were also administered. P emetrexed was infused over 10 minutes on d8 prior to paclitaxel; oral folic acid and parenteral vitamin B_{12} were also administered to reduce pemetrexed toxicity.

Results: Twenty-one patients (15 men, 6 women) with a median age of 59 (range, 34-77) and a WHO performance status 0/1 (90%) were enrolled and treated as described below. Tumor types represented in this study include: pancreas (4), esophagus (3), colorectal (3), lung (3), liver (2), head and neck (1), melanoma (1), and other (4). 12/21 patients had received prior chemotherapy. 71 cycles were administered with a median 3 cycles (range, 1-10). There were no dose reductions or omissions. 17/25 dose delays were due to scheduling conflicts; myelosuppression (5), nasopharyngitis

Pemetrexed/ paclitaxel (mg/m^2)	Cohort (#pts)	DLT (# pts)	Other Clinically Significant Toxicity (#pts)
400/30	1 (6)	G3 bilirubin (1)	G4 neutropenia (1) G3 anemia (1)
500/30	2 (6)	G4 thrombocytopenia + + G4 febrile neutropenia + G3 edema (1)	G3 asthenia (1) G3 bilirubin (1)
500/40	3 (6)	G3 bilirubin + G3 alkaline phosphatase (1)	G3 hyperglycemia (1) G3 thrombocytopenia (1) G4 hemorrhagic ulcer (1)
500/50	4 (3)	None	G3 fatigue (1) G3 nausea (1) G3 transaminitis (1)