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.

574 POSTER

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).

575 POSTER

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.

576 POSTER

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)

(1), fever (1) and unspecified reason (1) accounted for the remaining delays. Toxicity data are presented in the table on p. S174.

There has been 1 therapy related death, due to malignant ulcer hemorrhage associated with G4 plts (500/40). Two patients discontinued due to toxicity: pancytopenia (1) and thrombocytopenia (1). Preliminary analysis does not reveal any overt alterations of the pemetrexed pharmacokinetic profile on coadministration with paclitaxel. Responses have been noted in thyroid, gastric, penile and renal cell cancers.

Conclusions: Overall, this schedule of pemetrexed and paclitaxel is well tolerated. The combination appears to have a broad spectrum of activity. Study enrollment is ongoing.

577 POSTER

A phase I dose-escalation study of pemetrexed and docetaxel in patients with locally advanced or metastatic cancer: preliminary results of schedule B

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Background: Both pemetrexed (Alimta), a novel multitargeted antifolate, and docetaxel, a semi-synthetic taxane, have proven to be effective antineoplastic agents. The primary study objective was determination of the maximum tolerated dose (MTD) of the pemetrexed/docetaxel combination in 2 schedules (schedules A and B); secondary objectives were to identify dose-limiting toxicities (DLTs) and recommended doses for phase II study. Preliminary results for schedule B are presented. (For schedule A, see *Mackay H et al. Proc ASCO 2002; #2120.*)

Methods: Patients (pts) who were at least 18 years of age with advanced or metastatic cancer received docetaxel on days (d) 1 and 8 and pemetrexed on d8 (before docetaxel) every 21 days, with folic acid and vitamin B_{12} supplementation to reduce pemetrexed-related toxicity. DLT was defined as the occurrence of any of the following in cycle 1: CTC grade (G) 4 neutropenia lasting > 5 days; febrile neutropenia; G4 thrombocytopenia; G3 or 4 non-hematologic toxicity (excluding nausea/vomiting, or isolated G3 ALT or AST); or treatment delay > 2 weeks due to unresolved toxicity. The MTD was reached when DLTs occurred in 2 of 6 pts. Additional pts were then treated at the previous dose level; if DLTs did not occur in * 3 of 9 pts, that dose level was the recommended dose for phase II study.

Results: Data are currently available for 15 pts (13 males, 2 females) with a median age of 61 years (range, 31-77) in 4 dose levels (pemetrexed mg/m^2/docetaxel mg/m^2): 250/25 (3 pts), 325/25 (6 pts), 325/30 (3 pts), and 400/30 (3 pts). Tumor types include mesothelioma, colon, esophagus, stomach, rectum, and head and neck cancers. An ECOG performance status of 0, 1, and 2 was reported in 4 (26.7%), 9 (60.0%), and 2 (13.3%) pts, respectively. Fourteen pts received 1 prior chemotherapy regimens. The total number of cycles reported was 42 (median 2; range, 1-6). There were 8 delays (2 of which were due to neutropenia and increased bilirubin, respectively), 1 dose reduction (at 325/25 due to G3 diarrhea), and 1 omission (at 400/30 due to decreased weight). One pt experienced G3 diarrhea (DLT) at 325/25. Other significant grade 3/4 toxicities were G3 bilirubin (1 pt), G3 neutropenia (2 pts), and G3 anemia (1 pt). No treatment-related deaths have been reported. Two pts discontinued the study due to tendonitis and decreased weight, respectively. Of the 11 pts with response data, stable disease was reported for 4 pts (in stomach, colon, and other tumor types). Based on available data, dose escalation was continued to 500/30, and the MTD was reached when DLTs (G3 fatigue) occurred in the first 2 pts.

Conclusion: The combination of pemetrexed d8 and docetaxel d1,8 is feasible and well tolerated. The MTD appears to be 500/30. Enrollment for 400/30 is ongoing to establish the recommended phase II dose

578 POSTER

Post-transcriptional regulation of P-glycoprotein expression in human colon carcinoma cell lines.

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Background: Multidrug resistance constitutes a major obstacle for success of cancer chemotherapy. The role of MDR1 gene product P-glycoprotein (Pgp) has been well established. The regulation of MDR1 expression has been mostly related to transcriptional control of the MDR1 gene expression. Recently, it has been reported that in the colon carcinoma cell line SW620, Trichostatin A (TSA), a histone deacetylase inhibitor (DHCAi), produces an increase in MDR1 transcription. This result means a major set back, because a number of histone deacetylase inhibitors inhibit tumour growth and several of them are in clinical trials. An increase in Pgp expression mediated by these compounds would made them impossible to combine with other cytotoxic agents that are Pgp substrates. We have investigated the effect of TSA on Pgp expression in the human colon carcinoma cell lines HT29 and HT29/M6.

Material and methods: Detection of mRNA levels was performed by real time RT-PCR, using specific primers and Taqman® probe. Detection of Pgp protein was analysed using three different experimental approaches: immunocytochemistry, western blot, and calcein uptake. We have also analysed by real time RT-PCR, the subcellular distribution (nuclear *vs* cytoplasmic) of Pgp mRNA. Translation of Pgp has been analysed performing the polysome profile of mRNA in sucrose gradients.

Results: We have found an increase in Pgp mRNA in human colon cancer cell lines after TSA treatment. However, this increase does not parallel an increase in Pgp protein levels or activity. We have also found that the transport of Pgp mRNA from the nucleus to the cytoplasm is quite inefficient, being this effect independent of TSA treatment. However, significant levels of Pgp mRNA reach the cytoplasm and bind to endoplasmic reticulum-associated ribosomes. We have analysed the Pgp mRNA distribution in polysomes profiles. Our results suggest a block in Pgp mRNA translation.

Conclusions: Trichostatin A increases Pgp mRNA levels in HT29 and HT29/M6 colon cancer cell lines. This increase does not correlate with a parallel increase in Pgp protein levels or activity.

The analysis of the subcellular distribution of Pgp mRNA points to an inefficient transport from nucleus to cytoplasm.

The percentage of Pgp mRNA transported to the cytoplasm, is able to bind to endoplasmic reticulum-associated ribosomes.

A translational blockade of the Pgp mRNA may occur in human colon cancer cell lines.

579 POSTER

Significant tumor growth inhibition of glioblastoma xenografts by NNC 47-0011 - a low molecular weight tricyclic tyrosine kinase modulator with anti-angiogenic activity.

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The Neurin series of tricyclic compounds are active against chronic inflammatory conditions (Olsen et al., Eur. J. Pharmacol. 435:43-57, 2002) in which angiogenesis plays an important role as it does in the growth of malignant tumors. NNC 47-0011 [(R)-1-(3-(6,7-Dihydro-5H-dibenz[b,g]azocin-12-yl)propyl)-3-piperidinecarboxylic acid] (MW 379) was selected due to strong anti-angiogenic effects in the chicken chorio-allantoic membrane (CAM) assay. Likewise it inhibited vessel growth induced in the mouse cornea by either VEGF or bFGF in a dose-dependent manner. We therefore assessed the effect of NNC 47-0011 on the growth of a tumor that is highly dependent on angiogenesis. MG U87 (human glioblastoma multiforme) was serially inoculated s.c. in the flanks of 7-week-old nu/nu homozygotous nude male mice of NMRI background. The tumor bearing mice and control animals were randomly allocated to receive either plain drinking water or water with 100 or 500mg/liter of NNC 47-0011 from the time of inoculation. This is equivalent to approx. 20 and 100 mg/kg/day. The mice were observed twice daily and the tumors were measured daily in two perpendicular diameters. The compound did not cause any adverse effects and produced a significant retardation of tumor growth at 100mg/kg/day (Kaplan-Meier log-rank analysis). However, in vitro NNC 47-0011 did not affect proliferation or migration of endothelial cell at concentrations attained in plasma of tumor bearing mice but it affected intracellular signalling through the P-Akt pathway. We conclude that NNC 47-0011 significantly inhibits the growth rate of the human glioblastoma line U87 at doses well tolerated. The mechanism probably involves inhibition/modulation of tyrosin kinase receptor. The Neurin family of compounds thus represents a potentially important new therapy for brain cancer.