insertion in 5'-flanking region of apo AI, apo CIII, apo AIV and hence some weak changes in appropriate metabolic processes.

NOVEL THERAPEUTICS AND PHARMACOLOGY

601O Clinical and pharmacokinetic (PK) results of 4 phase I studies of the second generation matrix metalloprotease (MMP) inhibitor bay 12-9566, a non-peptidic biphenyl inhibitor of MMPs 2, 3 & 9

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Introduction: MMPs are involved in invasion, metastasis and angiogenesis; MMPs 2 & 9 are overexpressed in the tumor/stroma of multiple cancers and correlate with outcome in many. MMPs are thus attractive targets for inhibition. BAY 12-9566 has nanomolar inhibitory activity against MMP 2, 3 & 9 with anti-invasive, anti-metastatic and anti-angiogenic effects in preclinical models.

Methods: 4 dose ranging trials of oral BAY-129566 were conducted in North America to define PK/safety. Dose limiting toxicity (DLT) was toxicity ≥ grade (gr) 3; symptomatic or DL gr 2; MTD was declared if > 2 patients (pts) experienced DLT. Eligible pts had PS 0–2 and acceptable organ function.

Results: 90 pts (median age 67yrs) with colon (31), breast (10), renal(10), ovary (8), sarcoma (7), melanoma (6) and other cancers (18) entered 9 dose levels. Dose related effects were limited to reduction in platelet counts (plts)(nadir d 15–27) reversible with continued therapy; in 4 heavily pretreated pts plts fell to gr 2/3 leading to prophylactic dose reduction; and mild anemia. Mild reversible transaminase elevations and GI effects (nausea, flatulence) were observed in some pts; musculoskeletal effects were not reported MTD was not reached although DLT (plts) was seen in 1 pt at DL 6, 8 & 9.6 pts remain on study (mean 236d [140–314d]). 1 pt with refractory melanoma (3 prior regimens) had PR < 4 wks duration; 1 pt with refractory ovarian cancer (7 prior regimens) has SD after 9.5 months.

Dose Level (DL)	1	2	3	4	5	6	7	8	9
Number of pts (N)	10	3	3	3	16	10	15	12	18
Total/day (mg)	100	125	150	200	400	800	1200	1600	1600
Dose (mg)	100	125	150	200	400	400	400	400	800
Schedule	OD	OD	OD	OD	OD	BID	TID	QID	BID
D28 Trough (mean; mg/L)	38	37	51	64	72	125	125	117	132
AUC_{0-24} D28 (mean, mg/h/L)	1161	–	–	1739	1411	2300	3035	2275	3135

Conclusions: Oral BAY 12-9566 (800 mg bid) is well tolerated with transient and usually clinically insignificant decreases in plt counts and mild anemia the only dose related toxicities.

602O Updated results of a phase I trial of Tomudex® (T) in combination with oxaliplatin (L-OHP) in advanced solid tumors: A promising and active combination

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Introduction: The aim of the study is to determine the maximum tolerated dose and the recommended dose for subsequent phase II trials. The different mechanisms of action and toxicity profiles of T and L-OHP are the rationale to test their combination

Methods: T was administered as a 15 minutes infusion followed by L-OHP as a 2 hours infusion, repeated 3 weekly. Dose escalation is shown below:

Dose level	1	2	3	4	5	6	7
T/L-OHP (mg/m^2)	2/85	2.5/85	2 5/110	3/110	3/130	3.5/130	3.75/130
Number of (pts/cycles)	3/10	3/21	3/12	3/10	16/63	14/61	5/6

Patients: so far, 47 patients (pts) have been entered: 30 M/17 F, median age 57 years (29 – 72), PS (WHO)· 0 = 15, 1 = 25, 2 = 7. Primary neoplasms were malignant mesothelioma (17), gastrointestinal malignancies (14), renal carcinoma (5), lung cancer (4), other (7). Thirty six pts were pre-treated.

Results: During the first 4 levels, no dose-limiting toxicity was observed. An asymptomatic increase in transaminases was frequent whatever the step. During the subsequent steps, grade 3 + 4 toxicities included: pts (cycles)

Step 5: vomiting 3 (3), diarrhoea 2 (3), neutropenia 1 (2), thrombocytopenia 1 (1), anemia 2 (2), peripheral neutoxicity 1 (1), asthenia 1 (1)

Step 6: vomiting 2 (2), neurotoxicity (fugax amaurosis) 2 (2), asthenia 3 (4), anemia 1 (1), thrombocytopenia 1 (1), diarrhoea 1 (1)

Step 7: is ongoing and no grade 3–4 toxicity was observed. However, gastrointestinal toxicities and asthenia seem dose-limiting.

Fourty four pts are evaluable for response and 3 pts are too early: 9 partial responses (7 mesothelioma, 1 pancreatic cancer, 1 renal carcinoma) 18 stable disease and 17 progressive disease.

Conclusion: This combination is well tolerated and has shown activity. In the light of these good results, we are planning two phase II trials at a dose of 3 mg T and 130 mg of L-OHP: one in mesothelioma and another in advanced colorectal cancer.

603O Phase I study of RPR109881A, a new taxoid administered as a three hour intravenous infusion to patients (pts) with advanced solid tumors

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RPR109881A has shown a broad spectrum of activity in *in vivo* and *in vitro* tumor models and is able to cross the blood brain barrier. Five phase I studies are ongoing to define the recommended dose and schedule (1-, 3-, 6-, 24-hour and 1-hour dl-d8 q3w). We report the preliminary results of the 3-hour schedule with an oral premedication with dexamethasone (−25, −13, 1-hour). The starting dose of 75 mg/m^2 was defined according to the safety profile of pts treated with other schedules (1-hour/6-hour). Dose escalation was done according to the modified Fibonacci's schedule. 13 pts (9 males/4 females – median age: 52) previously treated with ≤ 2 prior chemotherapies (CT) were included. The dose limiting toxicities (DLTs) are as follows:

Dose mg/m^2	≤ 1 prior CT		≤ 2 prior CT	
	Nb of pts	DLTs at the first cycle	Nb of pts	DLTs at the first cycle
75	1	no	2	no
90	6	febrile nuetropenia (1)	4	toxic death, acute respiratory distress syndrome* (1)
				diarrhea gr.3, fatigue gr3 (1)
				diarrhea gr.3, febrile neutropenia (1)
				neutropenia gr.4 > 7d (1)

*in NSCLC pt with pulmonary fibrosis secondary to radiotherapy

50% pts presented neutropenia Gr.4. Alopecia Gr.2/3 was universal; other toxicities were: arthralgia, nausea, rash of mild to moderate severity. One pt died because of viral infection while neutropenic after the 4th cycle. Blood samples were collected over a 0–48 h period for PK analysis. PK parameters were similar over the 2 tested doses with mean values of plasma clearance, volume of distribution and terminal half-life of ≈ 40 $L/h/m^2$, 1000 L/m^2 and 30 h, respectively (n=11). Additional pts will be treated at 90 mg/m^2 (≤ 1 previous CT) or 75 mg/m^2 (≤ 1 previous CT + RT) and randomized between 1-h versus 3-h to establish the best schedule and to confirm its feasibility for phase II study. Two confirmed partial response in 2 NSCLC pts has been observed at 90 mg/m^2: one untreated pt presented brain metastases and responded in both lung and brain lesions.

604O Evidence for the duration of the antifolate action of the thymidylate synthase (TS) inhibitor ZD9331 using plasma dUrd as a surrogate marker of enzyme inhibition

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Introduction: Inhibition of TS by raltitrexed (Tomudex™; Zeneca) or the non-polyglutamatable drug ZD9331 leads to a rise in the level of intracellular dUMP and hence plasma dUrd in mice and humans. Plasma dUrd levels were measured in four phase I dose escalating trials of ZD9331, including two trials where a 30 min infusion was given either on day 1 or on days 1 and 8, with cycles repeated every 3 weeks.

Methods: Pre- and post-treatment blood samples were immediately cooled on ice and spun to separate the plasma (stored at −70°C). Following de-proteinisation and solid-phase extraction, samples were analysed for dUrd by isocratic reverse-phase HPLC using a spectral scanning UV detector.

Results: Both trials started at a dose of 4.8mg/m^2/d. A rise (~2-fold) in dUrd was seen at this dose that was of ~48h duration (~d2-3/d9-10). As doses increased, a more prolonged effect and in some patients a greater rise in dUrd levels was seen e.g. at 19.2mg/m^2/d, 3 patients had 3-4-fold rises on d2 that had not returned to pre-treatment levels by d5. In those patients who had a second dose on d8, a further rise in dUrd of the same magnitude occurred on d9 with return to pre-treatment levels by d15-22. At 32mg/m^2/d, some patients had plasma dUrd that had not completely returned to pre-treatment levels by d8. One patient had 5, 2, 8 and 3-fold rises on days 2, 8, 9 and 15 respectively. These data provide evidence of TS inhibition that is of longer duration with increasing doses of ZD9331. Two patients at 4.8 and 9.6mg/m^2/d on the d1 and 8 schedule showed a partial and minor tumour response respectively. The trials are ongoing and the MTD has not yet been reached.

Conclusions: A rapid, sensitive and reliable method has been developed for the measurement of plasma dUrd in patients receiving antifolate drugs. These data suggest that the duration of TS inhibition is dose-related and will help in the choice of dose and schedule for Phase II trials of ZD9331 and understanding the relationship of duration of target inhibition and response/toxicity.

605O Strategies for improvement in dose escalation using the continual reassessment method (CRM) in phase I clinical trials

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The CRM has been proposed as an alternative dose escalation method in the phase I clinical trial design of antineoplastic agents, with the aim of exposing a greater proportion of patients (pts) to therapeutic drug doses than traditional approaches. The statistical model utilized is a sequential Bayesian estimation scheme in which a prior distribution function of the maximum tolerated dose (MTD) and a dose toxic-response model are selected before the trial. The MTD is the dose at which a pre-determined percentage (e.g. 30%) of the pt population would experience dose-limiting toxicity (DLT, e.g. Gr 3 non-hematologic or Gr 4 hematologic). In response to the practical and safety concerns of cytotoxic chemotherapy, modifications of the CRM (MCRM) were implemented which include the use of a conventional starting dose and the fixation of dose levels a priori, customarily by applying the modified Fibonacci sequence. However, our experience with this dose escalation method has been problematic due to the dependence on non-clinical toxicity information prior to the trial, and the difficulty of predicting a fixed number of dose levels. Therefore, we have designed a "dual-stage" escalation scheme. The initial stage involves utilization of a conventional starting dose with doubling of the dose in single-pt cohorts until moderate toxicity (e.g. Gr 2 non-hematologic or Gr 3 hematologic) is encountered, at which point 2 additional pts are accured and dose escalation proceeds in a more conservative manner (e.g. at 33% to 50% increments). The second stage begins once DLT is reached, and the CRM is used to guide subsequent assignment of dose levels. Instead of the Bayesian methodology, a maximum likelihood approach (O'Quigley and Shen) is applied which offers greater flexibility without restriction by the paucity of prior data. Practical examples and simulations of models will be provided to illustrate this proposed dose escalation method.

606O Synergistic antitumor effect by novel modified oligonucleotides targeting PKAI combined with cytotoxic drugs or monoclonal antibodies

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Introduction: Protein kinase A type I (PKAI) plays a key role in neoplastic transformation and conveys mitogenic signals of different growth factors and oncogenes. Moreover, PKAI is overexpressed in cancer cells with an active TGFα-epidermal growth factor receptor (EGFR) autocrine pathway and shows a structural and functional interaction with EGFR. Inhibition of PKAI, or its regulatory subunit RIα, results in cancer growth inhibition *in vitro* and *in vivo*.

Methods: A novel class of mixed backbone oligonucleotides (MBOs) targeting PKAI (ASRIα), with improved pharmacokinetic and bioavailability, and a humanized monoclonal antibody which blocks activation of EGFR, MAb C225, have been tested *in vitro* and *in vivo* on several human cancer cells.

Results: A dose-dependent inhibition of soft agar growth was obtained in all cancer types tested with the AS RIα MBOs, as compared to mismatched control oligos. Non-inhibitory doses of each MBO resulted in a synergistic growth inhibition and increased apoptosis, when combined with taxanes, platinum-derivatives and topo II-selective drugs. When the MBOs administered either i.p. or *p.o.* were added to paclitaxel, a cooperative effect was also obtained *in vivo*, causing tumor growth inhibition and increase of survival in nude mice bearing human cancer xenografts. Finally, combined treatment of human breast and renal cancer cells, which overexpress PKAI and EGFR, with the ASRIα MBO and MAb C225, caused a cooperative antitumor effect *in vitro* and *in vivo*.

Conclusions: Since both the AS RIα MBOs and the MAb C225 are currently studied in clinical trials, the combination between them or with selected cytotoxic drugs may represent a feasible novel therapeutic strategy.

607O Pharmacokinetic (PK) interaction of the combination of doxorubicin (DOX) and Taxotere (TXT)

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Introduction: Combination of DOX with TXT has been shown to be highly effective in advanced breast cancer recently introduced into adjuvant treatment. Purpose of the present study was to detect a potential PK interaction between DOX and TXT, as already proven for Paclitaxel + DOX leading to increased DOX-AUC and enhanced cardiotoxicity (Gianni et al). Therefore PK behavior of both, DOX and TXT, was analyzed using 2 different time schedules: DOX 50mg/m² 30min inf. followed immediately (A) of after 1HR interval (B) by TXT 75mg/m² 1HR infusion.

Methods: All pts received TXT alone at cycle 1 for baseline determination followed by DOX + TXT (18 pts schedule A, 13 pts B, sampling for both DOX and TXT), followed by DOX baseline analysis (12 pts A, 6 pts B, TXT then given delayed after end of DOX sampling). Sampling period 4HR for TXT and 6HR for DOX, measured by HPLC, Win Nonlin noncompartimental analysis performed.

Results: of the respective AUC last:

AUC	Taxotere				Doxorubicin			
ng/ml.H	n	TXT	DOX/TXT	p	n	DOX	DOX/TXT	p
A	18	1484	1956	0.03	12	859	848	0.9
B	13	1703	2450	0.05	6	906	833	0.6

Conclusion: No influence of TXT on DOX-AUC documented, DOX-cl conc (n=8) with or without TXT n.s. different (p 0.2 – 0.8), thus explaining low cardiotoxicity of the combination. In contrast, TXT-AUC was significantly increased when combined with DOX, suggesting interference at the hepatic microsomal level, partly explaining high clinical efficacy. A 1HR delay between end of DOX and start of TXT does not change the respective PK behaviour of both drugs.

608P Gemcitabine (GEM) – cisplatin (CDDP): A schedule finding phase I/II study

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Introduction: Gem and CDDP are active against various solid tumors. Since preclinical studies demonstrated the efficacy of various schedules we evaluated the tolerability and clinical efficacy of 4 different Gem/CDDP schedules as part of a pharmacokinetic and -dynamic (PK/PD) study.

Methods: Gem 800 mg/m² was administered as a 30 min infusion on d 1, 8, 15, and CDDP 50 mg/m² over 1 hr on d 1, 8 every 28 days; Gem 4 hr before CDDP (10 pts), or vice versa (14) and Gem 24 hr before CDDP (9), or vice versa (9), after one cycle followed by the reversed schedule. Pts (19 male/23 female, median age 54 years [31–77], and performance status 1 [0—2]) included, 9 ovarian, 7 non-small cell lung (NSCLC), 5 head/neck squamous cell (HNSCC), 5 esophageal, 4 melanoma, 4 cervix, 3 adenocarcinoma, 2 pancreatic, 2 colon and 1 small cell lung (SCLC). 26 pts received prior chemotherapy, of which 21 platinum based.

Results: A mean of 4.2, 2.6, 3.8 and 3.5 cycles was given in the four schedules, resp. The most frequent overall grade 3/4 CTC-toxicity was thrombocytopenia, 6/10, 4/14, 2/9 and 6/9 (overall 60%), followed by leukopenia, 8/10, 5/14, 6/9 and 6/9 (43%), in the 4 schedules, resp. Therefore, Gem was not given on d 15 in 36% of pts in cycle 1. Anemia was observed in 64% of pts. No serious bleeding occurred. Myelotoxicity was cumulative, but not schedule dependent. Non-hematological toxicity consisted mainly of grade 1/2 nausea/vomiting and fatigue. One patient died of toxicity following severe neutropenia and sepsis. Creatinine clearance decreased slightly during therapy. Anti-tumor effects in 36 evaluable pts: HNSCC, 1 CR; esophageal, 1 CR/2PR; ovarian, 2 PR; NSCLC, 1 PR; melanoma, 1 PR and adenocarcinoma, 1 PR.

Conclusion: (Cumulative) myelosuppression was the major toxicity, although it was not schedule dependent. Based on toxicity, efficacy and PK/PD data a phase II study, CDDP 24 hr before Gem, has been started in pts with upper gastro-intestinal tumors.

609P MTA (LY231514): Relationship of vitamin metabolite profile, drug exposure, and other patient characteristics to toxicity

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Introduction: MTA is a novel multitargeted antifolate with inhibitory activity against multiple enzymes. Phase I/II studies have shown activity in a variety of tumors. Historical data on other antifolates have suggested that a patient's nutritional status may play a role in the likelihood of experiencing severe toxicity. The purpose of this study was to assess the relationship of vitamin metabolites, drug exposure, and other prespecified baseline patient characteristics to toxicity following treatment with MTA.

Methods: Homocysteine (Hcys), cystathionine and methylmalonic acid were measured in 139 phase II patients with tumors of the colon, breast, pancreas, and esophagus at baseline and once each cycle thereafter. Stepwise regression modeling, multivariate analysis of variance, and discriminant analysis were implemented to determine which predictors might correlate with severe toxicity after one course of MTA. Prognostic factors considered were age, gen-

der, prior treatment, baseline albumin, liver enzymes, ANC, platelets, vitamin metabolites, and AUC.

Results: Statistically significant predictors of Grade 4 neutropenia (n=21 pts) were albumin ($p = 0.0006$) and Hcys ($p = 0.0012$), while Grade 4 thrombocytopenia (n=8) was highly predicted by Hcys ($p < 0.0001$) and pre-treatment AST ($p = 0.0012$). Hcys $\geq 10\mu M$ predicted Grade 4 neutropenia in cycle one 75% of the time. Grade 4 neutropenia was predicted by Hcys alone in 70% of cases. Hcys and albumin levels did not appear to change from baseline during treatment with MTA. While AUC was not found to be a predictor of toxicity, little variability was observed in AUC. Maximum values were still below AUC values related to hematologic toxicity in phase I studies.

Conclusions: Toxicities resulting from treatment with MTA appear to be predictable from pretreatment homocysteine levels. Elevated baseline homocysteine levels ($\geq 10\mu M$) highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA. Homocysteine was found to be better than albumin at predicting toxicity. These results apply to the tumor types studied. Further studies are underway in patients with renal impairment or patients who received prior cisplatin.

610P Phase I and pharmacokinetic (PK) study of Tomudex (TOM) + 5-Fluorouracil (5-FU) and levofolinic acid (LFA) in advanced head and neck and colorectal cancer

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Background: Synergism between TOM and 5-FU + LFA is observed in vitro when cells are exposed for 24 hours to TOM, followed by 5-FU + LFA. Preclinical studies support the idea that TOM might down-regulate the activity of dihydropyrimidine dehydrogenase (DPD).

Patients and methods: Patients (pts) with advanced head and neck and colorectal cancer were treated with escalating doses of TOM on day 1, and bolus 5-FU (immediately after LFA) on day 2, every 2 weeks. In the 2nd course LFA and 5-FU were administered on day 1 and TOM on day 2 with the aim of evaluating DPD and 5-FU AUC with and without pretreatment with TOM. Further treatment was given according to the sequence used in the 1st course.

Results: Available clinical data are summarized below.

Step	TOM/LFA/5FU (mg/m^2)	Pts	C/HN*	DLT	Type*	Response
1	1.5/250/600	6	1/5	0/6		0/6
2	2.0/250/600	6	5/1	0/6		1/6 (PR)
3	2.0/250/750	6	5/1	0/6		1/6 (PR)
4	2.5/250/750	6	5/1	0/6		3/6 (2CR, 1PR)
5	2.5/250/900	7	6/1	0/7		0/7
6	3.0/250/900	8	8/0	1/8	N 4	1/8 (CR)
7	3.0/250/1050	16	9/7	3/15	N 4, N 4; N 4	6/13 (1CR, 5PR)
8	3.0/250/1200	3	2/1	2/3	N 4, M 3, R 3	1/3 (PR)
Total		58	41/17			OR

*C = colorectal cancer; HN=head & neck cancer. C = 6/39 (15%); HN = 7/16 (44%); * N = neutropenia; M = mucositis, R = Renal

DPD activity has been measured in 14 pts thus far. Pretherapy DPD activity was a median 34% higher than after TOM administration (95% C.I. −93 to +62%). PK data are available in 6 patients thus far, and 5-FU AUC basal values do not significantly differ from values obtained 24 hours after TOM.

Conclusions: The combination of TOM+ 5-FU/LFA is well tolerated every 2 weeks. Clinical activity looks very encouraging, since the majority of pts had already received prior chemotherapy. We are now treating some additional chemo-naive patients at step 7, in order to have a more reliable estimate of the activity of the regimen.

611P Radio-localization of pulmonary nodules using gamma-probe and resection by video-assisted thoracic surgery

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Video-assisted thoracic surgery (VATS) is emerging as safe procedure for diagnosis and treatment of peripheral pulmonary nodules. One limitation of thoracoscopic technique is the inability to detect those nodules which are very deep beneath the pleural surface, and could only be identified via manual palpation. Several methods are used to localize VATS occult lesions prior to excision, including methylene blue injection and introduction of hooked-wire; however, all suffer from limitations. Recent advancements in intraoperative radio-localization of non-palpable breast lesions prompt us to develop a new technique for detection of pulmonary nodules by VATS. CT-scan are used to guide perilesional injection of 0.2 – 0.5 ml of solution of 99m Tc-labeled human serum albumin microspheres (5–10 MBq) and 0.2 ml of iodine-non-ionic contrast medium, two hours before surgery. In VATS a gamma ray detector (Scinti Probe MR 100 – Pol hi.tech., Aquila, Italy), equipped with 11mm diameter-collimated probe, allowed us to locate that lesion for thoracoscopic resection. From June 1997 to January 1998 we treated 15 consecutive patients (pts) with sub-centimeter pulmonary nodules. Nine pts were affected by a synchronous and metachronous malignant neoplasm in other sites. Computed thomography of the chest helped in the planning of the operative procedure, the position of pts, and ideal ports. A hot-spot was easily detected, in all patients, by the probe introduced in the pleural space through a 11.5 mm trocar. The total excision of the lesion was confirmed by detection of radioactivity in the removed specimen and its absence in the resection margins of the lung. Pathological examination of specimens showed 8 benign lesions and 7 malignant lesions (4 metastases and 3 lung cancer) and it confirmed the absence of infiltration in the resection margins. The surgical procedure was extended for an average of 56.6 minutes (range 35–100 min). The average post-operative hospital stay was 3.6 days (range 3–6 days). In our experience this technique proved safe and accurate, allowing easy detection of the pleural surface projection and fast removal of the lesion. This technique offers a simple and reliable method for localization of primary and metastatic tumors by VATS.

612P Pharmacokinetic (PK) of Tomudex® (raltitrexed) (T) and oxaliplatin (O) combination: Preliminary results of an ongoing phase I study

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Introduction: The aim of this study was to evaluate the possible kinetic interactions between T and O administered to patients with advanced disease.

Methods: Patients first received T (15 min infusion), followed 45 minutes later by O (2-hour infusion). Three patients received T at a dose of 3 mg/m^2 and 3 at a dose of 3.5 mg/m^2. All of them received the same dose of 130 mg/m^2 of O.

Results: Plasma concentrations of T declined tri-exponentially after the end of the infusion. The terminal t1/2 derived from samples up to 28 hours post-dose varied between individuals from 9.3 to 193.2 h with average values of 73.4 and 33.7 for the two dose levels. The maximal concentrations varied between 323 and 1185 ng/ml with averages of 681 and 813 in the 3 mg/m^2 and 3.5 mg/m^2 groups respectively. The AUC varied between 720 and 3192 ng.h/ml with average of 1577 and 1378 in the two groups. The comparison between the two groups did not revealed any difference, probably due to the very large intra subject variability, however the mean AUC showed an approximately proportional increase with increasing dose. The estimated kinetic parameters were in agreement with the values previously published. Plasma concentrations of O declined bi-exponentially after the end of the infusion. The terminal t1/2 varied from 18 to 30 h (average of 25). Cmax ranged from 3.13 to 4.53 (average of 3.69) μg/ml. The AUC ranged from 74 to 120 (average of 195) μg.h/ml and the Cl varied between 1.76 and 3.43 (average of 2.47) 1/h. The comparison of the kinetic parameters of O to the ones previously published in the same experimental conditions seems to indicate that T induced an increase of O Cl (from 1.32 to 2.47 1/h) with a reduction of the terminal t1/2 from 38.7 to 24.8 h and a reduction of Cmax measured at the end of the infusion from 5.11 to 3.69 μg/ml.

Conclusions: These preliminary results suggest that the expected concentrations of O obtained after administration of T may be lower that the ones observed when O is administered alone. These results indicate possible PK interaction between the two drugs.

613P A phase I and pharmacokinetic (PK) study of ET-743, a novel minor groove binder of marine origin administered on a daily × 5 schedule

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ET-743 is a novel tetrahydroisoquinoline alkaloid isolated from the marine organism *Estenascidian turbinata* which binds to adenine-cytosine rich regions within the minor groove of DNA. This study is evaluating the feasibility and PK behavior of ET-743 administered as a 1-hour infusion daily × 5 every 3 weeks in patients with advanced solid malignancies. Twenty-seven patients (median age 58, range 35–79; median ECOG PS-1) have received 67 courses of ET-743 at doses ranging from 6 to 380 μg/m^2/day. At the 380 μg/m^2/day dose level, 1 patient with extensive prior treatment with 16 cycles of BCNU developed grade 4 thrombocytopenia, grade 4 neutropenia with fever, grade 3 elevation in transaminases, and acute renal failure which resulted in death. Four patients (8 cycles), at the 216 (1), 287 (1) and 380 (2) μg/m^2/day dose level developed asymptomatic elevation in hepatic transaminases of grade 3 severity that typically peaked on day 8 and resolved by day 21. Mild to moderate, dosedependent nausea and vomiting, which appeared on day 4 and resolved on day 8, was observed in 14 patients. Two patients at the 380 μg/m^2/day dose level suffered superficial venous thrombophlebitis at the drug infusion site. PK parameters obtained in 2 patients at the 216 μg/m^2/day dose level included: clearance, 137 and 589 mL/min/m^2; $t_{1/2}$, 13.7 and 23.1 L/h; and,

AUC_{0-24h}, 158 and 367 ng-min/mL. $AUC_{0-5\ days}$ (790 and 1835) were ≥ than the mouse AUC at the LD10 (854 ng-min/mL). No drug accumulation was noted from day 1 to 5. In conclusion, ET-743 produced severe toxicity with multiorgan involvement at the 380 $\mu g/m^2$/day in one exceptionally heavily-pretreated patient. Additional subjects are being evaluated at this dose level to define the MTD of ET-743 on this schedule of administration.

614P A phase I and pharmacologic study of the oral matrix metalloproteinase inhibitor, BAY 12-9566, in combination with paclitaxel and Carboplatin

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BAY 12-9566 is a biphenyl nonpeptidic inhibitor of zinc-dependent endopeptidases (matrix metalloproteinases, MMPs) that degrade the extracellular matrix and are associated with the processes of angiogenesis and metastasis in human malignancies. This phase I and pharmacologic study was performed to evaluate the feasibility and pharmacologic interaction of oral BAY 12-9566 when administered continuously with intravenous paclitaxel and/or carboplatin every 3 weeks. The study was divided into 3 consecutive cohorts of 6 patients (pts): 1) paclitaxel alone (course 1: 175 mg/m^2; course 2: 135 mg/m^2), 2) paclitaxel (175 mg/m^2) and carboplatin (AUC=6), and 3) carboplatin (AUC=6) alone. Daily oral doses of BAY 12-9566 (800 mg BID) were initiated 1 week following the first dose of intravenous chemotherapy. Thus far, 5 of 6 pts (median age, 53 [range, 25–59]; median PS, 1; prior therapy: chemo, 2; RT + chemo, 3) have been accrued to the first cohort. Hematologic toxicities include grade 1 neutropenia (1 pt) and 1 episode of grade 4 neutropenia (1 pt) lasting 2 days. Nonhematologic toxicities have been mild and include grade 1 nausea and alopecia. No dose-limiting toxicity has occurred. Pharmacologic analysis of plasma samples obtained in 3 pts following administration of BAY 12-9566 and paclitaxel, reveals plasma concentrations of BAY 12-9566 that are similar to those achieved in previous studies of BAY 12-9566 alone. The plasma concentrations of BAY 12-9566 attained with the combination are consistent with those required for *in vitro* inhibition of MMP-2 and -9; 11 and 301 nM, respectively. Accrual is ongoing and updated results of this novel interaction study will be presented.

615P Cisplatin-related anemia is linked to pharmacokinetic abnormalities

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Cisplatin-related anemia remains a toxicity with a significant impact on patient quality of life We performed a retrospective study on 40 head&neck cancer patients who received at least 3 courses of a combination chemotherapy. The population included 5 females and 35 males, the median age was 60 years (range:38–71). The chemotherapy regimen including cisplatin 100 mg/m^2, and 5-FU 1000 mg/m^2/day by continuous infusion over 5 days, every 21 days. An initial hemoglobin (Hb) value was higher than 11 g/dl in all study patients Total (T) and ultrafiltrable (UF) platinum (Pt) were measured 16 hours after the end of cisplatin administration according to a single point strategy (*Cancer Chem Pharm 21: 75–77, 1988*) 5-FU pharmacokinetic (full cycle AUC) was also determined. The median value of T and UF Pt were 209 ng/ml (range: 47–361) and 40 ng/ml (range: 10–100) respectively. The median value of 5-FU AUC was 30966 (range 12978–48372). The median Hb loss between course 1 and 3 was 2.2 g/dl (6.6-0). Fifteen patients were considered as undergoing significant anemia because they required a red cell transfusion or because they lost more than 3 g/dl of Hb between course 1 and 3. When comparing these 15 patients with other patients in the study, no significant relationship was found between age, gender, and 5-FU AUC. In contrast, T Pt and UF Pt concentrations were significantly higher in the 15 patients with severe anemia in comparison with the others (median value of T Pt, 266 versus 199 ng/ml, p = 0.015; median value of UF Pt, 52 versus 30 ng/ml, p = 0.004). The incidence of severe anemia was four-fold higher in 12 patients exhibiting UF-Pt concentration above an optimal cut-off at 50 ng/ml than in 28 patients with a UF-Pt concentration below cut-off value (p < 0 001). Early cisplatin pharmacokinetics appear to be a powerful and independent predictor of severe anemia, and may allow better management of cisplatin-related anemia by selecting patient candidate for prophylactic erythropoietin administration.

616P Phase I trial and pharmacikinetics of beta-D-glucosylisophosphoramide mustard (D-19575) administered as a 6-hour infusion every three weeks: An EORTC-ECSG study

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Introduction: D-19575 is a beta-D-glucose-linked isophosphoramide mustard aiming to exploit the transmembrane glucose transporters overexpressed in tumour cells. This compound was taken into clinical testing because preclinical data showed a higher selectivity and less myelosuppression than ifosfamide.

Methods: The present study employed a two-step 6-hour intravenous infusion (1/4 of the dose in 30-minutes, followed by 3/4 over 5½ hours) in order to increase the exposure and cellular uptake of the drug that has a short half-life. Treatment was given once every 3 weeks. Blood and urine samples for PK analysis were collected in all patients at the first course of treatment. Thus far, 17 patients (8F/9M, median age 54, range 33–72) with refractory solid malignancies have been treated over the range of 800 to 6000 mg/m^2 and a total of 44 courses of treatment have been given

Results: Nephrotoxicity was dose-limiting at 6000 mg/m^2 which was defined as the MTD for this schedule. Additionally, a short lived grade 4 neutropenia or leucopenia was seen in 3/6 patients at this dose level. Renal toxicity occurred in 2/6 patients as shown by tubular dysfunction and reversible impairment of glomerular filtration that developed eight days after the second and third course of treatment respectively and required hospitalisation. Main findings consisted of prolonged metabolic acidosis, polyuria, grade 3 hypokalaemia, prolonged hypophosphataemia with phosphaturia, renal glycosuria, proteinuria, a high urinary beta 2-microglobulin excretion, and a mild transient increase of serum creatinine level. Evidence of antitumour activity was seen in 3 patients. Minor changes on CT scan and a fall in tumour markers was seen in two patients with refractory colon adenocarcinoma and objective response in a patient with pancreatic adenocarcinoma.

Conclusion: The dose-limiting toxicity of D-19575 given as a 6-h infusion every 3 weeks consisted of renal tubular dysfunction and MTD was 6000 mg/m^2. Currently, the dose level of 4500 mg/m^2 is being investigated with close monitoring of renal function and acid-base balance. No toxicity has been seen in the first two patients at this dose level after two courses of treatment and an objective response has been documented. The clinical trial and pharmacokinetic analysis is ongoing.

617P Daunorubicin and daunorubicinol levels in human glioma tumors after administration of liposomal encapsulated daunorubicin (Daunoxome)

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Introduction: Daunoxome is a liposome formulation containing Daunorubicin (DM) currently used in patients with Kaposi's sarcoma. In mice tumor levels of DM were higher after Daunoxone then after free drug treatment. This work was performed to evaluate DM and DMol levels in different areas of glioblastoma of patients receiving Daunoxome.

Methods: Nine recurrent glioblastoma patients, previously operated and treated with radiotherapy and chemotherapy gave informed consent to enter the study. 50 mg of Daunoxome were given as a 1 h i.v. infusion. Surgery was performed in 8 cases 24 h after the end of the infusion and in one case after 48 h. Tumor biopsies were divided in three parts: peripheral, intermediate and central. A complete pharmacokinetic study was conducted taking plasma samples during the 48 h post infusion and at the time of tumor dissection. DM and DMol were determined by HPLC.

Results: The drug was rapidly cleared from the body. At 48h DM and DMol were in the range of < 5–50 ng/ml and < 5–20 ng/ml. At 24 h, concentrations of DM and DMol in the central part of tumor were in the range of 0.020–0.80 $\mu g/g$ and 0 030–1.58 $\mu g/g$ (median 0.11 and 0.250 $\mu g/g$) for DM and Dmol, respectively. In all cases except one similar concentrations were found in the intermediate and peripheral areas of the tumor. High concentrations were also found in the case studied at 48h (0.4 and 2.8 $\mu g/ml$), indicating prolonged permanence of DM and DMol in tumor tissues.

Conclusion: This study shows that after Daunoxone treatment, cytotoxic levels of DM and DMol are achieved in brain tumor for a long time with low drug plasma levels These data should be taken with caution as previous therapies could have impaired the Blood Brain Barrier, thus increasing the drug penetration.

618P Phase I study of different sequences of MTA (LY231514) in combination with cisplatin in patients with solid tumours

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Introduction: The novel multi-targeted antifolate (MTA) is a potent inhibitor of thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyltransferase. MTA has shown encouraging antitumour activity in vitro and in vivo and in single-agent phase I and phase II trials. The purpose of this study was to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT), pharmacokinetics and antitumour activity of MTA in combination with cisplatin (C).

Patients and Methods: Patients (pts) with solid tumours with no proven treatment options were entered into this trial. In cohort 1, both drugs were administered on day 1; in cohort 2 MTA on day 1 and C on day 2. Treatment was repeated every 3 weeks. In cohort 1 the starting dose was MTA 300 mg/m^2 and C 60 mg/m^2; in cohort 2 the starting dose was MTA 500 mg/m^2 and C 75 mg/m^2.

Results: In cohort 1, 40 pts were evaluable for toxicity. The MTD was reached at MTA 600 mg/m^2 and C 100 mg/m^2, with thrombocytopenia and febrile neutropenia as DLTs. In cohort 2, 11 pts were evaluable for toxicity. In this schedule, thrombocytopenia grade 4 occurred in 1 pt at MTA 500 mg/m^2 and C 75 mg/m^2, and in 1 pt at MTA 600 mg/m^2 and C 75 mg/m^2. Grade 4 infection was observed in 1 pt at each dose level, rash grade 3 in 1 pt at each dose level. Grade 4 diarrhoea occurred in 1 pt at MTA 500 mg/m^2 and C 75 mg/m^2, and grade 4 mucositis in 1 pt at MTA 600 mg/m^2 and C 75 mg/m^2. At both dose levels 1 pt died due to therapy-related toxicities. Pharmacokinetic parameters of MTA were not influenced by C administration and hydration. Several responses were observed: in cohort 1, 11 pts, including 4 of 7 pts with mesothelioma; in cohort 2, 3 pts had minimal responses, and remain on study.

Conclusion: The MTD of this combination is MTA 600 mg/m^2 and C 100 mg/m^2, if administered on day 1, with myelosuppression as the DLT. The day 1 schedule was clinically superior. This combination of MTA and cisplatin shows encouraging antitumour activity.

619P Reduction of micrometastatic tumor load by monoclonal antibody therapy: Influence of tumor antigen heterogeneity

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Introduction: Disseminated cancer cells in bone marrow (BM), are regarded as suitable targets for adjuvant immunotherapy, because they are easily accessible for both immunoglobulins and immune effector cells. This pilot study was designed to examine the influence of the individual antigen profile of such target cells on the potential treatment efficacy.

Methods: Individual breast cancer cells in BM were identified by the anti-cytokeratin (CK) monoclonal antibody (mAb) A45-B/B3. To evaluate the antigen profile of these cells, we applied a quantitative double-marker assay and typed for four potential therapeutic targets (17-1A, MUC-1, Lewis^Y, c-erbB-2). In a pilot study, five breast cancer patients with a CK$^+$ BM finding were treated with a single dose of 500 mg Panorex™, and were monitored for the elimination of 17-1A co-expressing CK$^+$ cancer cells after 5–7 days.

Results: CK$^+$ cells from 20 breast cancer patients typed in this study for the expression of the four antigenic targets were found to represent a heterogeneous cellular population. The mean percentage of double-positive cells per total no. of CK$^+$ cells was 44% (0–75%) for 17-1A, 41% (0–67%) for MUC-1, 34% (0–59%) for Lewis^Y, and 42% (0–92%) for c-erbB-2. This was contrasted by a mean count of 70% (34–100%) cocktail$^+$/CK$^+$ cells if all four antigens were targeted simultaneously by the antibody-cocktail consisting of all four antigens. Thus, we considered tumor antigen heterogeneity a potential cause for incomplete tumor cell elimination by monovalent therapeutic approaches. This assumption was supported by our pilot study. Prior to treatment patients presented with 17, 67, 97, 115, 524 CK$^+$ cells per 10^6 BM cells, and a mean percentage of 61% (range: 41–100%) CO17-1A$^+$/CK$^+$ double-positive cells per total no. of CK$^+$ cells. In all five patients we assessed a remarkable reduction in both the no. of CK$^+$ cells (17→5, 67→11, 97→2, 115→20, 524→26) per 10^6 BM cells, and the percentage of 17-1A$^+$/CK$^+$ cells (41%→0%, 48%→0%, 54%→10%, 60%→15%, 100%→17%) per total no. of CK$^+$ cells after the administration of Panorex™.

Conclusion: Genomic instability of carcinoma cells resulting in the reported polyclonal phenotype of the disseminated tumor cell population may limit the efficacy of monovalent immunogenetic treatment strategies. Individual immunocytochemical monitoring of therapeutic tumor cell elimination is feasible and suggest that Panorex™ might be able to eliminate 17-1A$^+$ breast cancer cells.

620P A phase I and pharmacokinetic (PK) study of the multitargeted antifolate (MTA, LY231514) with folic acid (FA)

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Introduction: MTA, a new antifolate that inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase, demonstrated notable broad antitumour activity when infused 10 min i.v. every 21 days. Myelosuppression precluded dose escalation above 500–600 mg/m^2. As preclinical evaluations indicate that FA supplementation increases the therapeutic index of MTA, this study was initiated to determine if FA supplementation permits significant dose-escalation above the recommended phase II dose of MTA alone. Vitamin metabolites were measured to determine their value as potential prognostic markers with this combination.

Methods: So far, 33 minimally- and heavily-pretreated pts received 90 courses of FA (5 mg/day) for 5 days starting 2 days before MTA at 600, 700, 800 925 mg/m^2. Vitamin metabolites were evaluated during cycles 1 and 2 as potential determinants of principal toxicities and effects.

Results: Principal drug-related toxicities include neutropenia, anaemia and thrombocytopenia, which were more severe in heavily-pretreated pts. Other toxicities (grade (G) 1–2) include rash, somnolence, fatigue, leg oedema, and a decrease in creatinine clearance (CrCl). Severe toxicities in 2 pts, 1 who had taken a non steroidal anti-inflammatory agent and 1 with severe hypoalbuminaemia, resolved after administration of leucovorin and thymidine. Preliminary vitamin metabolites in 26 pts reveal: 2 and 3 of 11 pts with homocysteine ≥ 10 had G4 thrombocytopenia and neutropenia, respectively; 1 and 2 of 15 pts with homocysteine < 10 had G4 thrombocytopenia and neutropenia, respectively; 1 and 2 of 9 pts with elevated cystathionine levels (cystathionine upper limit of normal 342 nM/L) had G2 somnolence and G1–2 fatigue, respectively; 1 and 10 of 16 pts with normal cystathionine levels had G2 somnolence and G1–2 fatigue, respectively; 1 of 4 pts with elevated methylmalonic acid (methylmalonic acid upper limit of normal 271 nM/L) had G2 fatigue while 12 of 22 pts with normal levels had G1–2 fatigue. 7 of 15 pts with elevated homocysteine, cystathionine, or methylmalonic acid levels had a significant decrease in CrCl. Based on information from these 15 pts, addition of FA may reduce the usefulness of vitamin metabolites as predictors of toxicity.

Conclusions: FA supplementation appears to permit MTA dose escalation by ameliorating toxicity. Heavily- and minimally-pretreated pts tolerate MTA at 700 and 925 mg/m^2 and accrual continues at 800 and 925 mg/m^2, respectively.

621P Pharmacokinetic (PK) and pharmacodynamic (PD) analysis of a phase-I study of Taxol®(T), Carboplatin (C) with P-glycoprotein (P-gp) modulator PSC-833 (PSC)

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Introduction: Cyclosporine analogues such as PSC reduce the clearance of P-gp substrates (i.e. T) and their maximum tolerated dose (MTD). This trial was designed to assess the MTD, PK and PD of T and C with oral PSC in patients (pts) with refractory solid tumors.

Methods: All patients were planned to receive a fixed dose of PSC (5 mg/kg, p.o, 6 hr x 12, days 0–3) and T (baseline dose 54 mg/m^2, 13.5mg/m^2 increments, 3 hr infusion, day 1) and C (target AUC 6–9 mg/mL.min, day 1), 3-weekly. C AUCs derived from a limited sampling model, and T PK parameters fitted to a 2-compartment model.

Results: 58 pts entered into 7 dose levels (DL), 41 had previous chemotherapy, (34, 1 prior regimen). PK for DL 1–7 summarized below.

DL	T Dose mg/m^2	Target C-AUC mg/m.hr	# pts	C-AUC mg/ml.hr	T-AUC μM.hr	T-Cl L/hr/m^2	Time (hr) T > 0.05μM
1	54	6	3	5.4	4.8	13.19	20.46
2, 6, 7	67 5	6, 7.5, 9	28	6.3, 7 15, 7.55	5.94	13.31	26.52
3, 5	81	6	23	5.2	7.46	13.47	28.0
4	94 5	6	4	6.7	12.1	9.14	37.32

No PK interaction was noted between C & T or PSC & C. The T and C doses showed a linear correlation with % change nadir ANC (R^2 = 0.95 respectively), their AUCs correlated less well with % change nadir ANC or platelets. PSC prolonged the time T > 0.05 μM at T 94.5 mg/m^2 > than T 175 mg/m^2 alone. DL-2 and DL-5 were the MTDs of prior treated & chemonaive pts respectively.

Conclusions: PSC by reducing T's clearance, prolongs the time T > 0.05 μM, without influence on C PK. PSC reduced the MTD of the T & C combination.

622P A phase I and pharmacokinetic (PK) study of ZD9331, a nonpolyglutaminated thymidylate synthase (TS) inhibitor, administered once every 3 weeks

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The antifol ZD9331, a potent nonpolyglutaminated TS inhibitor, had an elimination half-life ($t_{1/2}$) of 5 hours in preclinical studies. Following the demonstration of a prolonged $t_{1/2}$ in humans of 73 h [Ratain, Proc ASCO, 1997], this study was begun to evaluate the feasibility and pharmacokinetic behavior of ZD9331 administered as a 30 min. infusion once every 3 wks. To date, 23 pts (median age 56 yrs, median WHO PS 1) have received 47 courses of ZD9331 over the following dose levels: 4.8 mg/m^2 (3 pts, 8 courses), 9.6 mg/m^2 (3 pts, 6 courses), 19.2 mg/m^2 (4 pts, 8 courses), 32 mg/m^2 (3 pts, 7 courses), 48 mg/m^2 (6 pts, 10 courses), 67 mg/m^2 (3 pts, 7 courses), and 89 mg/m^2 (2 pts, 3 courses). The 48 mg/m^2 dose level was expanded due to gr 4 thrombocytopenia and gr 3 neutropenia in a heavily-pretreated pt. No other pts have experienced severe hematologic toxicity. Two minimally-pretreated pts at the 67 mg/m^2 dose level with colorectal cancer developed severe gastrointestinal toxicity: one pt had gr 4 vomiting and gr 4 diarrhea during her second course, and another pt had gr 3 diarrhea during his third course. Transient, asymptomatic grade 1–3 elevations in hepatic transaminases, which typically peak 8 to 15 days post-treatment and resolve prior to the next scheduled treatment, have occurred at all dose levels. Drug exposure (C_{max} and AUC) increased proportionally with dose. The PK parameters were well described by a 3-compartment linear model, resulting in the following mean (± SD) parameter values: terminal $t_{1/2}$ = 82.8 ± 43.5 h, V_{ss} = 27.7 ± 13.5 L, and Cl = 10.1 ± 6.7 ml/min. Preliminary plasma deoxyuridine data have confirmed the activity of ZD9331 as a TS inhibitor. Given the gr 3/4 diarrhea seen during the last course in 2 out of 3 pts at the 67 mg/m^2 dose level, the 89 mg/m^2 dose level will be expanded to 6 pts. These results confirm that there are substantial interspecies differences in the PK behavior of ZD9331 and that less frequent dosing schedules are rational from a PK perspective.

623P All-trans retinoic acid (ATRA) ± α interferon (IFN) in squamous cell carcinoma (SCC): A randomized phase II study

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Based on previous in vitro and in vivo data demonstrating synergy between IFN and retinoids in SCC, we designed a randomized phase II study comparing ATRA alone or associated with IFN in metastatic patients (pts) with SCC of head and neck (HNC), lung (NSCLC) and cervix cancers (CC).

Methods: pts were randomly treated with either ATRA, 45mg/m^2/d p.o. for 7 d every other week, or ATRA (same regimen) plus subcutaneous IFN (Roferon, Roche) 9.10^6 IU 3 times a week, every week, until progression of the disease or unacceptable toxicity. Tumor evaluation was repeated every 6 weeks.

Results: 48 pts have been enrolled in this study. All the pts with NSCLC and CC had been previously treated, while all but 2 pts with HNC were untreated. As initially designed, an interim analysis after enrollment of 18 pts in each arm demonstrated the lack of response in the ATRA alone arm; we thus stopped this arm and are continuing the study as a phase II study of ATRA + IFN association. Tolerance was satisfactory, and toxicity was mainly attributable to IFN. ATRA induced around 50% of skin toxicity ≤ grade 2 and few cases of mild hypertriglyceridemia. Among 30 pts treated in the combined arm (HNC=15, NSCLC=8, CC=7), we observed 2 responses in HNC (2 CR) but none in NSCLC and CC. The 2 responders were untreated and had lung metastases.

Conclusion: ATRA alone is unefective in SCC. Moreover, despite some activity in non pretreated HNC, ATRA combined with IFN is poorly efficient in SCC.

624P A phase I dose escalation study of docetaxel (TXT) with lenograstim support in patients (pts) with solid tumours

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In previous studies of 3 weekly TXT, dose limiting toxicity (DLT) was neutropenia and its complications. To explore the potential for dose intensification of TXT, G-CSF was used in an ongoing phase I study. The maximum tolerated dose (MTD) was defined as the dose at which ≥ 3 out of 6 pts in cycle one developed a DLT (NCI CTC neurotoxicity ≥ grade II on day 21, prolonged febrile neutropenia, or other toxicities ≥ grade III). Eligible pts were performance status 0-2, with maximum of one prior chemotherapy regimen. A 3 day steroid prophylaxis was given, and pts received G-CSF (lenograstim) 5μg/kg/day sc from day 2 until neutrophil recovery. 23 pts have been entered to date, with NSCLC the most common tumour type. Median age was 60 yrs (29–76) and 12 pts had previously received chemotherapy.

Dose TXT (mg/m^2/3 wks)	Number of patients			Type of DLT event
	entered	evaluable	with DLT	
110	3	3	0	
120	3	3	0	
130	6	6	2	neuropathy and skin desquamation in both pts
140	5	5	0	
150	3	3	0	
160	3	1	0	

On cycle one, grade IV neutropenia was seen in only 5 pts: 2 pts given TXT 130mg/m^2, and 1 pt each at the 140, 150 and 160 mg/m^2 levels. Four pts had febrile neutropenia. Two pts had DLT with TXT 130mg/m^2, and for both pts, toxicities were transient and TXT was continued at reduced dose. The MTD has not yet been reached and the study is ongoing. Final results will be presented.

625P The new long-acting somatostatin analogue Lanreotide in neuroendocrine tumors (NETs)

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Introduction: Somatostatin analogues induced symptomatic and biochemical responses, but few tumor regressions in NETs. In the present study we report the activity of the new long-acting somatostatin analogue Lanreotide in carcinoids and other NETs.

Methods: From June '96 to April '98, 20 patients (pts) with NETs (10 gastrointestinal NETs, 9 pancreatic NETs, 1 lung carcinoid) received Lanreotide 30 mg i.m. every 14 days (IPSTYL 30 mg, IPSEN Spa). The treatment was continued until tumor progression. Pts characteristics: 9 male, 11 female; median age 62 years (range 31–78 years); metastatic sites: liver 17, peritoneum 4, nodes 5, lung 2; 15 pts were symptomatic; 6 pts were pretreated with s.c. octreotide, 3 with chemotherapy, 2 with hepatic metastases alcoholisation. All pts were assessed with octreotide scintigraphy, neuroendocrine markers, urinary 5-HIAA. Median treatment duration was 7.5 months (range 2–24). Responses were classified as objective, symptomatic or biochemical (PR: reduction > 50% in neuroendocrine marker level; CR: normalization).

Results: Objective responses were observed in 5/15 pts with measurable disease (33%): 1 CR (6.5%) and 4 PR (26.5%); 7 pts had SD 47%, 3 pts progressed (20%). The CR was observed in a naive pt with liver metastases. The duration of CR was 5+ months. Complete control of symptoms was obtained in 7/15 pts (47%). A biochemical response was achieved in 8/15 evaluable pts (53%), with 2 CR (13%) and 6 PR (40%); 4/15 pts had stable values (27%) and in 3/15 pts markers increased (20%).

Conclusions: This treatment is active in terms of symptomatic relief and biological markers normalization. The observed 33% objective response rate with 6.5% CR, is of particular interest. Lanreotide depot is well tolerated and its schedule of administration may improve the pt compliance.

626P Effects of peripheral stem cell or bone marrow transplantation on peripheral serotonin metabolism

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During reinfusion of autologous peripheral stem cells or bone marrow, patients (pts) often complain about flushing, palpitations, dyspnea and nausea. Because some of these side effects can be prevented by ondansetron, a selective $5HT_3$ receptor antagonist, we hypothesized that these side effects are due to infusion of serotonin overload coinciding reinfusion of peripheral stem cells or bone marrow. Therefore, we determined serotonin concentrations in the bags with penpheral stem cells or bone marrow and monitored effects of reinfusion of these cells on platelet serotonin and urinary 5-hydroxyindole acetic acid (5-HIAA) concentrations in 26 pts who received a total of 32 reinfusions for treatment of different solid tumors. Mean total serotonin concentration in the bags was 2404 nmol/L (n=17). Mean total amount of reinfusion was 575 mL (n=17). After reinfusion, the mean (± SD) levels of serotonin in platelets in pts increased from 3.2 ± 1.4 nm/10^9 at baseline to 3.8 ± 2.0 nm/10^9 (p = 0.02). The mean levels of urinary 5-HIAA remained stable 1.4 ± 0.4 mmol/mol creatinine. The latter is probably due to the measurement over 24 h, whereas platelet serotonin was measured 1 h after reinfusion. In addition, as is known from a previous study, after chemotherapy there is a depletion of total body serotonin, and this probably contributes to a rapid removal of the serotonin load. These results suggests that reinfusion of peripheral stem cells or bone marrow is accompanied with alterations in serotonin metabolism, which might cause the observed side effects.

627P Preclinical synergy of oxaliplatin in combination with other antitumor agents

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Oxaliplatin (L-OHP) was evaluated in combination with nucleoside analogues (5-FU or gemcitabine), topo I inhibitors (SN38 or CPT-11), thymidilate synthase inhibitors (AG337 or ZD1694), paclitaxel, cisplatin, and carboplatin. *In vitro*, drug combinations were tested on cancer cell lines, including colonic (HT29, HT29-5-FU, HCT 116, CaCo2, Colo 320 DM), ovarian (2008, A2780, A2780-DDP), breast (MCF-7, MCF-7mdr, MDA-MB-231), cervix squamous cell (KB), and leukemia (CEM, L1210) using the Chou and Talalay method. *In vivo*, combinations were tested against human MV-522 lung, HT29 colon cancer, L1210 leukemia xenografts, and hormone-independant GRI mouse mammary tumor. The table shows cell lines and xenografts in which the combinations elicited synergistic effects *in vitro* and potentiation of antitumor activity *in vivo*.

Combinations	*In vitro*	*In vivo*
L-OHP + 5-FU	HT29, HT29-5-FU, CaCo2, 2008, A2780, A2780-DDP MDA-MB-231	HT29 xenograft GR1 tumor
L-OHP + gemcitabine	HCT116, Colo 320 DM, CEM	
L-OHP + SN38 (*in vitro*) or CPT-11 (*in vivo*)	HT29	GR1 tumor
L-OHP + AG337	HT29, 2008	GR1 tumor
L-OHP + paclitaxel		MV-522 xenograft
L-OHP + cisplatin	KB, A2780	L1210
L-OHP + CBDCA	KB, A2780	L1210

The synergistic effects of L-OHP in combination with gemcitabine were observed in mismatch repair deficient, p53 proficient HCT116, c-myc amplified Colo 320 DM cancer cells. The effects of the L-OHP/5-FU combinations were maintained in 5-FU-resistant CaCo2 and HT29-5-FU colon cancer, and A2780-DDP ovarian cancer cells. Our results give basis to L-OHP-based combinations in clinical trials.

628P Phase I trial of ZD9331 given as a 30 minute infusion on days 1 and 8 with cycles repeated every 3 weeks

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Introduction: ZD9331 is a novel folate analogue and potent thymidylate synthase (TS) inhibitor, which unlike raltitrexed (Tomudex™), does not undergo polyglutamation and may therefore have a different spectrum of antitumour activity and toxicity profile. Due to the long half-life (about 4 days) seen in the initial phase I trials of ZD9331 using a 5 day regimen, an alternate schedule was investigated.

Method: A phase I dose escalating trial of ZD9331 given as a 30 minute IV infusion days 1 & 8 q 3/52 in patients (pts) with refractory solid malignancies.

Results: To date, 23 patients median age 52 years (range 37–75) have received 1 to 9 cycles of ZD9331 at: 4.8 (3), 9.6 (3), 19.2 (3), 32 (5), 42 (3) and 55 (6) mg/m^2 × 2 per cycle. The tumour types treated comprise ovary, colorectal, sarcoma, melanoma, bladder, gastric, and head and neck. At 32 mg/m^2 × 2, one pt developed grade 4 neutropenia, grade 2 thrombocytopenia and maculopapular skin rash, and grade 1 diarrhoea. At 42 mg/m^2 × 2, one pt had grade 3 neutropenia, and grade 2 thrombocytopenia, nausea and vomiting. At 55 mg/m^2 × 2, one pt developed acute renal failure (possible drug interaction between ZD9331 and diclofenac, trimethoprim or benzylpenicillin), grade 4 thrombocytopenia, grade 3 neutropenia and mucositis. Her renal function recovered as measured by EDTA clearance. A further pt at this dose level had grade 4 thrombocytopenia but toxicity in the remainder was limited to grade 1 and 2 neutropenia, grade 2 nausea and vomiting and grade 1 diarrhoea. Patients at all dose levels have experienced mild to moderate lethargy and transient asymptomatic rises (grade 1–3) in liver transaminases. Two pts with ovarian cancer had a fall in serum CA-125, one of whom (at 4.8 mg/m^2 × 2) had a partial response and the other (at 9.6 mg/m^2 × 2) had stable disease on CT scan. Pharmacokinetics appear to be linear with mean clearance (± SD) of 10.6 ± 5.37 ml/minute (3.81 – 21.2), mean volume of distribution of 24.1 ± 8 91 L (10.9 – 46.3) and terminal elimination half-life of 59.1 ± 32.2 hours (21.1–150). The first 2 pts with grade 4 toxicity had disproportionately high plasma ZD9331 levels. Preliminary assessment of a possible pharmacokinetic toxicity relationship shows that the toxicity threshold for AUC may be around 200,000 ng h/ml. Preliminary plasma deoxyuridine data has confirmed the activity of ZD9331 as a TS inhibitor.

Conclusions: The maximum tolerated dose using this schedule has not yet been reached and dose-limiting toxicity is likely to be myelosuppression. Antitumour activity has been seen in ovarian cancer.

629P Phase I dose escalation and sequencing study of Gemcitabine and docetaxel in advanced cancers

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Purpose: Docetaxel (D) and gemcitabine (G) are active as single-agents in a variety of solid tumors. This study was designed to determine the maximum tolerated dose, toxicities, and the effect of drug sequence on toxicities with D and G given in combination.

Patients and Methods: 23 evaluable patients with advanced cancer were enrolled in this phase I study. Patients were treated with both drugs on Days 1 and 8 every 21 days. Dose escalation was not permitted within individuals. Toxicity was assessed using NCI Toxicity Criteria. At each dose level, 3 patients were enrolled on either Arm 1 (G→D) or Arm 2 (D→G) to evaluate the effects of drug sequence on toxicity. If a dose limiting toxicity (DLT) occurred that specific arm and dose level was expanded to 6 patients. Pharmacokinetic (PK) sampling was performed from 0–24 hours. Doses were escalated as follows: dose level 1 (D 30 mg/m^2 and G 800 mg/m^2); dose level 2 (D 40 mg/m^2 and G 800 mg/m^2); and dose level 3 (D 40 mg/m^2 and G 1000 mg/m^2).

Results: Grade 3/4 neutropenia occurred in 8/23 (35%) of patients and was the most common DLT. The majority of Grade 3/4 neutropenia occurred in patients that had received 2 or more prior chemotherapy regimens. At Dose Level 3, the MTD was exceeded as 2/3 patients experienced dose limiting neutropenia and stomatitis. No fluid retention (with steroid medication), myalagias, or neuropathy was observed. No difference in clinical toxicity was observed with either sequence (PK data will be presented at the meeting). Minor and partial responses were observed in 7/23 (30%) of patients with non-small cell lung (2/5), gastric (2/3), head and neck (1/2), and hepatocellular cancer (1/1).

Conclusions: This preliminary study suggests that the combination of G and D administered on Days 1 and 8 every 21 days was active in a variety of solid tumors and was well tolerated. Based on this study, the recommended phase 2 dose(RP2D) in untreated or minimally pretreated patients is dose level 3 and in pretreated patients, the RP2D is dose level 1.

630P Influence of the Antacid Maalox® on the pharmacokinetics (PK) of Xeloda™ in cancer patients

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Introduction: Capecitabine (Xeloda™) is a novel fluoropyrimidine carbamate which was rationally designed as an orally administered and tumor-selectively activated cytotoxic agent. The present study was performed to investigate the influence of the antacid Maalox® on the PK of capecitabine and its metabolites.

Methods: Twelve cancer patients received a single oral dose of 1250 mg/m^2 of capecitabine (treatment A), a single oral dose of 1250 mg/m^2 followed immediately by 20 mL of Maalox® (treatment B) and a single oral dose of 1250 mg/m^2 followed two hours later by 20 mL of Maalox® (treatment C) in an open, randomized 3-way cross-over fashion. Serial blood and urine samples were collected up to 24 hours after each administration. Concentrations of capecitabine and its metabolites were measured in plasma using LC/MS-MS and in urine using NMRS.

Results: Administration of Maalox® either concomitantly with capecitabine or delayed by 2 h did not influence the time to peak plasma concentrations and the elimination half-lives of capecitabine and its metabolites. Minor increases of the C_{max}- and $AUC_{0-\infty}$-values of capecitabine and 5'-DFCR were observed when Maalox® was administered together with capecitabine. However, these increases were not statistically significant ($p > 0.05$). There was no indication of consistent changes in the plasma concentrations of the main metabolites, 5'-DFUR, 5-FU and FBAL. C_{max}- and $AUC_{0-\infty}$-values of these three metabolites increased and decreased in a stochastic manner. The magnitude of these changes was low (< 13%) and not statistically significant. Total recovery of capecitabine and its metabolites in urine was similar in the 3 treatment groups.

Conclusions: There were no significant changes in the plasma concentrations of capecitabine and 5'-DFCR when Maalox® (20 mL of suspension) was administered together with capecitabine and there was no evidence of an effect on the 3 main metabolites (5'-DFUR, 5-FU and FBAL). The effect of Maalox® on the PK of capecitabine is not clinically significant and therefore there is no need to adjust the dose and timing of capecitabine administration in patients treated with Maalox®.

631P A phase I study of TLC D-99 (liposome encapsulated doxorubicin) with G-CSF in patients with refractory solid tumours

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Single agent efficacy has been demonstrated with doxorubicin (DOX) in

patients with different types of cancer, including patients who failed other therapies. TLC D-99, a liposome encapsulated from of DOX, was designed to increase the amount of drug delivered to tumours and decrease the amount going to healthy organs, such as the heart. TLC D-99 therefore has a toxicity profile that differs from free DOX. A phase I dose escalation study to define the maximum tolerated dose (MTD) of TLC D-99 with G-CSF support was conducted in patients who failed first line curative or palliative chemotherapy for a metastatic or inoperable form of cancer. Eligibility also included histological documentation of the tumour, Eastern Cooperative Oncology Group performance status between 0 and 2, life expectancy > 2 months, cardiac ejection fraction > 50% and no prior anthracycline therapy. Dose-limiting toxicity was defined as neutropenia

(ANC < 0.5 × 10^9/L) or thrombocytopenia (< 20 × 10^9/L) for > 7 days in any two patients. Thirty patients, 17 male (57%) and 13 female (43%) entered the trial. Median age was 52.5 years (range 27–67). The most common malignancies were non-small-cell lung cancer (37%), small-cell lung cancer (17%), colorectal cancer (13%) and soft tissue sarcoma (13%).

Results: As per protocol-defined criteria, neutropenia was the dose-limiting toxicity and the MTD of TLC D-99 with G-CSF support was determined to be 150 mg/m^2 every 3 weeks. The objective response rate in the evaluable population was 22% (5/23). Cumulative doses ranged from 90 to 788 mg/m^2. One patient had a decrease in LVEF < 50% after a cumulative TLC D-99 dose of 289 mg/m^2. No patients developed cardiomyopathy Grade 3/4 nausea/vomiting, mucositis, infection, and neutropenic fever were seen in 10%, 47%, 53%, and 13% of patients, respectively. Neutropenia (ANC < 500/μL), thrombocytopenia (platelets < 20,000/μL) and anemia (haemoglobin < 8 g/dL) occurred in 58%, 43% and 16% of the cycles, respectively.

Conclusion: The MTD of TLC D-99 with G-CSF support was 150 g/m^2 every 3 weeks. Neutropenia was the dose limiting toxicity.

632P Malignant mesothelioma of the pleura: A phase II study of mitoxantrone, methotrexate and mitomycin in 18 patients

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Introduction: Malignant mesothelioma is a neoplasia of special interest because of its increasing frequency, poor prognosis and direct association with asbestos exposure. Considered an uncommon neoplasia in the past, it can now no longer be seen as such. The extensive diffusion of asbestos in this century has brought a sharp increase in malignant mesothelioma incidence and mortality, since asbestos is a potent mesotheliomatogen. The lack of uniformity in approach and the small number of patients in most studies precludes at present any standardized treatment of this neoplasia.

Methods: Between July 1995 and February 1998, 18 patients with malignant pleural mesothelioma were enrolled in the study. Patients with histologically and/or cytologically confirmed diagnosis, at least one measurable or assessable tumor parameter and performance status (according to Karnofsky) ≥ 70% were eligible for this trial. Patients pretreated with other chemotherapeutic drugs, with previous or concomitant tumor, with leucocytes < 4,000 μl, platelets < 100,000 μl, serum creatinine > 1.5 mg/dl, serum SGOT, SGPT and bilirubin > 50% of baseline and severe cardiac dysfunctions were excluded. The patients were treated with mitoxantrone (10 mg/m^2 iv or ipl), methotrexate (35 mg/m^2 iv) and mitomycin (7 mg/m^2 iv). The treatment was repeated every 3 weeks, with mitomycin in alternate cycles, up to progression.

Results: All patients were evaluated for response. One complete response (CR = 5.5%) and 4 partial responses (PR = 22.2%) were achieved; response rate (CR + PR) was 27.8%; 5 patients were stable under this treatment (NC = 27.8%). The median survival time from onset of early symptoms and signs and from onset of chemotherapy was respectively 14 months (range 4–32) and 8 months (range 1–27). This treatment produced a significant improvement of subjective symptoms (dyspnea, pain) and pleural effusion. Hematological toxicity was the main side effect. Neutropenia WHO grade IV was observed in 58.8% of patients, anemia grade IV in 5.9% and thrombocytopenia grade IV in 17.6%. All side effects were reversible.

Conclusions: The combination chemotherapy with mitoxantrone, methotrexate and mitomycin used in this study has demonstrated objective activity (response rate 27.8%). This treatment has also produced improvements in subjective symptoms and pleural effusion. From the data presented here, this chemotherapy combination can be considered active in the treatment of malignant pleural mesothelioma.

633P Influence of paclitaxel (PAC) on topotecan (TPT) pharmacokinetics (PK) in advanced cancer patients

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Introduction: Combination therapies of TPT with other cytostatic agents are currently under investigation for first line treatment of lung or ovarian cancer. In order to establish a PK base for combining TPT with PAC, two PK studies were performed using TPT at a dosage of 1 mg/m^2 30 min infusion dl-5.

Methods: In study 1, TPT-PK was compared between dl and d5, including separation of Lactone (L) and Carboxylate (C) (n=5). In study 2, a potential influence of PAC on total TPT-PK was tested using a cross over design (n=7) with baseline TPT-PK determination on dl of the first cycle, then analysis of TPT-PK was repeated on dl of cycle 2 when preceeded by PAC 175 mg/m^2 3HR infusion. Sampling period was 6HR, TPT measured by reversed phase HPLC with fluormetric detection (for L and C separation bed side preparation of serum samples with cold acetonitril was performed), noncompartimental analysis calculated by WinNonlin.

Results:

	Cmax (ng/ml)	AUC last	Cl (ml/min)	VSS (l)
n = 5		*Study 1*		
L d1	28	1662	941	100
L d5	33	1956	742	104
C d1	22	3813	368	69
C d5	29	3809	291	100
n = 7		*Study 2*		
TPT	69	7653	267	44
TPT/PAC	52	7367	172	36

Conclusions: No significant difference of TPT-PK parameters (L or C) could be documented between dl and d5 indicating no drug accumulation during 5 days treatment. The addition of PAC did not change the PK behavior of total TPT (AUC last ng/ml.min p < 0.8).

634P Schedule-dependent antitumor efficacy of irinotecan (CPT-11) and 5-Fluorouracil (5-FU) in nude mice bearing colon tumor xenografts that are resistant to 5-FU

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The antitumor efficacy and schedule-dependent interactions of CPT-11 and 5-FU were evaluated in athymic nude mice (nu/nu) bearing xenografts of 5-FU resistant human colon carcinoma HT29R1 cells. Drugs were given at their maximum tolerable doses (MTD): 5-FU (300 mg/kg, i.v. bolus); CPT-11 (20 mg/kg i.v., d 1-5). HT29R1 tumor xenografts showed nearly complete resistance to 5-FU treatment (overall response rate 8.3%, no cures). In contrast treatment with CPT-11 at its MTD produced a tumor response in 80% of mice including 20% complete tumor regression (cures). No differences in toxicity in terms of maximum weight loss (MWL) between 5-FU or CPT-11-treated mice were observed (MWL: 17.6 ± 7.2% and 14.2 ± 6.5%, respectively) and no treatment-related deaths occurred. The activity and toxicity of the combination of 5-FU and CPT-11 were highly schedule dependent. The sequence of CPT-11 (10 mg/kg i.v d 1-5) followed by 5-FU (100 mg/kg i.v. d5) was significantly more active than the reverse sequence (5-FU d1; CPT-11 d 1-5) in terms of tumor response but also resulted in higher toxicity.

Conclusions: CPT-11 showed significant antitumor activity against 5-FU resistant colon tumor xenografts. The data reported herein suggest that the administration of CPT-11 followed by 5-FU may result in superior antitumor efficacy against 5-FU resistant tumors when compared with a schedule of 5-FU followed by CPT-11, but may also produce increased toxicity.

635P A sequential chemo-radiotherapeutic treatment for anaplastic gliomas: A phase II pilot study

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Introduction: Despite the significant advances in surgery, radiotherapy and chemotherapy, the prognosis of patients with newly diagnosed high grade gliomas remains dismal and virtually none are cured of their illness. The propose of our study was to evaluate the activity and toxicity of the sequential chemo-radiotherapeutic treatment on the basis of early report by Grossman (ASCO 1989).

Methods: Eighteen patients with histologically diagnosed malignant gliomas entered the study. The median age was 54 years (36–69). Fifteen patients had glioblastoma multiforme (83%), two had anaplastic astrocytomas (11%) and one had anaplastic oligodendrogliomas (AAO). BCNU (40 mg/sqm/die) 30 minutes i.v. infusion in 4 doses a day and Cisplatin (40 mg/sqm/die) i.v. continuous infusion were administered concurrently for 3 days every 3–4 weeks. Radiotherapy was begun 30 days after the 2nd or 3rd cycle of chemotherapy and consisted of 45 Gy whole cranial irradiation plus a 15 Gy boost on the preoperative volume.

Results: We administered 45 cycles of chemotherapy. Thirteen patients had misurable desease and were evaluable for response After chemotherapy we obtained 3 CRs and 4 PRs (RR 54%). Three PRs were converted to CRs

after radiotherapy, for a complete remission rate of 46% (6/13). The median duration of response was 10 months. The median survival of the entire patients population was 9 months with 33% survival rates at 1 year. The patient with AAO is free of desease at 82 months from the beginning of chemotherapy. Vomiting grade 3, hematologic toxicity grade 4 in one patient and grade 3 in two patients were the major complications due to chemotherapy, while nephrotoxicity and neurotoxicity were usually mild.

Conclusion: Our sequential chemo-radiotherapy regimen appears to have significant activity in adults with newly diagnosed high-grade gliomas.

636P Æ-941 (Neovastat), an inhibitor of angiogenesis: Phase I/II lung cancer clinical trial results

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Introduction: Æ-941 is a complex derived from cartilage that has shown both antiangiogenic and antimetalloproteinase activities. Oral administration of Æ-941 (125 mg/kg) resulted in approximately 50–70% reduction in the number of lung metastases using the Lewis Lung Carcinoma mouse model. No signs of toxicity were observed.

Methods: Æ-941 is currently in Phase I/II clinical trials in Canada and in the US for the treatment of lung, prostate and breast cancers. Patients were administered escalating doses (4) of Æ-941 for 12 weeks. Tolerability and clinical benefits (tumor assessment, ECOG, body weight and analgesic consumption combined) were evaluated

Results: Results obtained from 25 assessable patients of the Phase I/II trial for lung cancer show a trend in favor of a dose/response effect of patients' clinical benefits. Doses ranging between approximately 10 to 80 mg/kg were administered orally. Including the Canadian Special Access Program that started in July 1996 and the ongoing Phase I/II clinical trials, approximately three hundred and thirty (330) patients have been exposed to Æ-941 for up to 20 months without reporting any serious adverse events definitively associated with it.

Conclusions: Oral administration of Æ-941 demonstrates a favorable safety profile and show a positive trend in favor of a dose/response improvement in clinical parameters. Complete results of Phase II lung and Phase I breast and prostate trials will be available Q3-98.

637P In vitro cytotoxicity of Tomudex (TOM) in combination with 5-Fluorouracil (5-FU) and levofolinic acid (LFA) in head and neck and colon cancer cell lines

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Tomudex is a pure thymidylate synthase inhibitor, with clinical activity in colorectal cancer and in other solid tumors. TOM has recently been reported to down-regulate the activity of dihydropyrimidine dehydrogenase (DPD), and this implies a potential role for TOM in combination with 5-FU.

We have evaluated the citotoxicity of TOM, 5-FU and LFA, when used in several different schedules in three colon cancer cell lines, (LOVO, GEO and SW620) and in one oral epidermoid carcinoma cell line (KB), using the SRB colorimetric assay.

LFA 5 μM alone had no effect on cell proliferation, while in combination with 5-FU it reduced by about 50% 5-FU IC50 in all tested cell lines, as expected. If 5-FU was added simultaneously to TOM, a slightly additive effect was observed. When LFA, alone or in combination with 5-FU, was added simultaneously to TOM, it significantly inhibited TOM-induced citotoxicity by increasing TOM IC50 up to 30 fold. The same effect was observed if cells were treated with LFA alone or in combination with 5-FU followed 24 hrs later by TOM. In this case TOM IC50 was increased up to 10 fold. When 5-FU alone was followed 24 hours later by TOM, an additive effect was observed. Interestingly, if cells were exposed for 24 hours to TOM and then to 5-FU + LFA, a clear synergism was observed in all tested cell lines, while only an additive effect was shown when 5-FU alone was added, thus indicating an important role for LFA in this schedule-dependent synergistic effect.

In conclusion, our preliminary in vitro studies suggest that LFA does not interfere with TOM cytotoxicity if a 24 hour interval elapses between the two drugs. In addition, this study also indicates that the combination of TOM followed 24 hours later by LFA+5FU is a worth pursuing approach for clinical investigation. Finally, we are currently measuring DPD activity in all tested cell lines in order to find out a possible correlation with in vitro synergistic effect.

638P Resistance to Gemcitabine (GEM) in a Fas-ligand (FasL)-resistant cell line is not dependent on the Fas/FasI (CD95/CD95L) system

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Introduction: The T-cell lymphoma HUT78B1 cells were selected by exposure to a Fas-agonistic Ab and, in contrast to the parental HUT78, are resistant to Fas-mediated apoptosis owing to the expression of both a wild-type and a truncated Fas receptor. HUT78B1 retain sensitivity to apoptosis from various anticancer drugs, but are resistant to the cytidine analog GEM.

Methods and results: Cytotoxicity was evaluated by vitality assay and apoptosis by flow cytometry and fluorescence microscopy. In comparison with HUT78, HUT78B1 exhibited a high (about 100-fold) resistance to the cytotoxic and apoptotic effects of GEM. They were moderately cross-resistant to cytarabine, but retained sensitivity to fludarabine or hydroxyurea. To clarify whether the Fas/FasL system plays a role in the cellular response to GEM, we evaluated the effects of GEM in HUT78 after pretreatment with FasL- (NOK1, NOK2) or Fas-(ZB4, DX2) blocking antibodies or the inhibitor of caspase 8 YVAD-cmk. Overall, we did not observe any clearcut effect of such blocking reagents on GEM-induced apoptosis and cytotoxicity, in spite of an increase in FasL levels after 4 or 8 h of exposure to GEM, as shown by Western blotting assay. However, the apoptotic effects of GEM were suppressed by Z-VAD, a wide spectrum inhibitor of caspases. Finally, HUT78B1 accumulated about 10-fold less 3H-GEM than HUT78.

Conclusions: The antitumor effects of GEM on HUT78 cells do not correlate to the Fas/FasL pathway, whereas they seem to be dependent on the caspase cascade. GEM accumulation by the cells might account for the response to GEM in this model The possible interactions between the Fas/FasL system and chemotherapeutics agents deserve further investigations and might have relevance to cancer therapy. Supported by Eli Lilly.

639P Ecteinascidin-743 (ET-743) 24 hours continous infusion (CI): Clinical and pharmacokinetic phase I study progressive report

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Introduction: ET-743, a tetrahydroisoquinoline alkaloid isolated from the Ecteinascidia Turbinata, a minor grove DNA binding agent specific for the guanine rich regions, with potent activity in murine tumor models and in human lines in vitro and in vivo. Bone marrow and liver function toxicity were shown in preclinical studies. A phase I study with ET-743 I.V. 24 hours C.J. every 21 days is ongoing, in solid avanced stages tumors.

Methods: Since may 1996, 31 pts were treated over 9 dose levels (DL) from 50 to 1800μg/m^2. Median number of cycles/pts: 2 (1–8), median age: 55 (26–74). F/M: 18/13, ECOG PS: 1 (0–2). Tumor types: colo-rectum (7), ovary (4), sarcoma (7), renal (3), breast (4), bladder (2), larynx (1), gastric (2) and ACUP (1), all refractory to standard chemotherapy. Nausea/vomiting (grade 2) and reversible (4–6 days) transaminase elevation starting 2–4 days after treatment were seen from 600μg/m^2 DL. This toxicity is self limiting (resolved by day 7–10). Maximal transaminase (ASAT-ALAT) elevation, and neutropenia, at the five highest DL is shown below (NCIC-CTC)

Dose level μg/m^2	Pts/Cy	Neutropenia		Transaminitis	
		Grade 0–2	Grade 3–4	Grade 0–2	Grade 3–4
600	3/8	3/8	–	3/8	
900	3/8	3/8	–	2/7	1/1
1200	5/19	5/19	–	3/17	2/2
1500	4/16	1/9	3/7	1/9	3/7
1800	4/7	2/2	2/5	1/2	3/5

Conclusion: The incidence of reversible grade 4 transaminates and frequency of grade 4 neutropenia suggest that MTD is close to 1800μg/m^2

640P Optimization of tumor suppressor genes delivery using original cationic lipids in malignant mesothelioma cells

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Human malignant mesothelioma (MM) displays chromosomal abnormalities, particularly homozygous deletions of the p16 tumor suppressor gene.

In attempt to replace altered genes in MM cell lines in culture and in nude mice xenograft, we developed a non viral gene delivery technique, using original synthetic cationic liposomes V14 and V5, and a DNA compacting agent spermine. Transfection using naked DNA or commercialized cationic lipids is inefficient in MM cells. Cell lines were established from the MM of patients in accordance with pathological criteria, and prior to therapy.

The first step was to test the ability of different carriers: DOTAP, lipofectine, and original V5 and V14. Therefore, we studied the β galactosidase (βgal) gene expression in 3 human MM cell lines in culture (RAV, FER, BLA), after transfection of a βgal reporter gene (pCMVβ CLONTECH) complexed to lipids. 2.10^5 cells were transfected with 0.5 to 9 μg of pCMVβ alone, condensed with spermine, then complexed to cationic lipids. The βgal activity was measured by chemoluminescence (Galactolight® TROPIC) 48 hours after transfection. The

endogenous βgal activity was determined in cell extracts, reduced using heat inactivation, and subtracted from the measured level. Significant βgal gene expression was seen only in cells exposed to DNA-V5 or V14 complexes. There was low βgal activity in cells exposed to DNA alone, demonstrating that the cationic lipid carrier was required for transfection in MM cells. More, no significant βgal activity was detected in cells exposed to DNA complexed to DOTAP (Boehringer) or lipofectine (GIBCO BRL). In FER cells using V5 ou V14, we obtained 4.10^5 relative light unit per mg of total protein, corresponding to a ratio 20:1 in comparison with the endogenous measured level. Moreover, XGAL essay revealed a transfection efficiency about 70% (ratio between transfected and total cell numbers).

Finally, the cytotoxicity of the lipid-pCMVβ complexes was tested with MTT assay, showing no significant toxicity for V5 or V14 up to tenfold concentration used for transfection. Currently, transfection assays using both pCMVβ and pCMVp16 are proceeded with the same procedures. The results will be reported in the final presentation.

641P Phase I trial of docetaxel (DOTAX) and topotecan hydrochloride (TOPO) in patients with advanced solid tumors

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This is a follow up on our phase I study with DOTAX and TOPO in pts with solid tumor maligancies, both DOTAX a promoter and stabilizer of microtubule assembly and TOPO a topoisomerase I inhibitor have demonstrated antitumor activity in various solid tumor malignancies. A phase I study was designed to assess the dose limiting toxicity DLT, maximum tolerated dose MTD, and pharmacokinetics of the combination. DOTAX was administered first as 1 hour infusion on day 1 of the odd number of courses, and day 4 of the even number of courses, and TOPO was administered as a 30 min. infusion on days 1, 2, 3, 4. of each course every 21 days. Fourteen patients (pts) have been treated so far: six in cohort I DOTAX/ TOPO 60/0.75 mg/m^2 respectively without G-CSF and 2 pts. developed febrile neutropenia; four pts. in cohort II, same dose level with G-CSF and no DLT was observed; and four pts. were treated in cohort III, DOTAX/TOPO 80/0.75 mg/m^2 with G-CSF, and 2 developed febrile neutropenia. Patient profile: 9 females, 5 males, median age 52 (43–72), median ECOG PS 1 (0–2). Four pts. had ovarian carcinoma (CA), 2 pts breast CA, 5 pts. Head and Neck CA, 1 patient (pt) cervical CA, 1 pt gastric CA, and 1 pt. fallopian tube CA. Hematologic DLT was defined as neutropenic fever or any grade IV hematologic toxicity that did not recover within 7 days. G-CSF 5 mcg/kg was started on days 5 through 14 of each course if hematologic DLT, excluding thrombocytopenia and anemia, was achieved. Forty courses were administered. Median absolute neutrofil cout (ANC) for cohort I was 400 cells/mm^3 (0-5372), median platelet count (plt.) 64,000 cells/mm^3 (30–479,000), median hemoglobin (Hb) 9.9 g/dl (6.9–11.6). For cohort II median ANC was 3726 cell/mm^3 (162–11,716), median plt. 110,000 cell/mm^3 (46–182,000), median Hb 10 g/dl (5.7–11.2). Cohort III median ANC is 4285 cells/mm^3 (216–25,740), median plt. 120,000 cells/mm^3 (77,000–280,000), median Hb 9.7 g/dl (7 5–12.9). Other mild grade I/II non-hematologic toxicities were seen such as constipation, nausea, myalgias, fatigue, facial flushing, weakness, alopecia. One pt. had partial response and 5 pts had stable disease. MTD was reached at DOTAX/TOPO dose level 80/0.75 mg/m2 with G-CSF, and the dose will be deescalated to 70/0.75 mg/m^2 with G-CSF.

642P Phase I trial of docetaxel and short infusion Gemcitabine given every two weeks for advanced solid tumors

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Introduction: Docetaxel and gemcitabine have broad antitumor activity as single agents. Their modes of action suggest non-cross resistance. We designed this dose-ranging trial to define the optimal Phase II doses of docetaxel and gemcitabine when given in a novel two week schedule.

Methods: Patients (pts) with advanced solid tumors receive docetaxel (1 hour IV infusion) followed by gemcitabine (30 minute IV infusion) every 2 weeks. Dose levels (mg/M2) of docetaxel/ gemcitabine: I: 40/2000; II: 45/2000; III: 45/2500; IV: 50/2500; V. 50/3000; VI: 55/3000; VII: 55/3500. Twenty-eight evaluable pts enrolled; median age 57 years (range: 41–70); 20 previously treated with chemotherapy; 27 with performance status ≥ 80%.

Results: Pts with grade 3–4 adverse events:

Dose level	I	II	III	IV	V	VI
Total pts	3	4	3	8	6	3
Nausea			1	1	1	
Neutropenia	1	1	2	2	3	
Thrombocytopenia				1		
Anemia		1		1		
Fatigue				1		

Maximal tolerated dose (MTD) has not yet been defined. Responses have been observed in nonsmall cell lung, head/neck, breast, and gastric cancers.

Conclusions: The combination of docetaxel and gemcitabine can be given every 2 weeks with acceptable toxicity, and responses have been seen. Dose escalation and accrual continue. Docetaxel pharmacokinetics will be studied using a limited sampling model at the MTD. Phase II trials in several tumor types are anticipated.

643P Chylomicron metabolism is altered in ovarian carcinoma

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Introduction: Chylomicrons are triglyceride-rich lipoproteins that carry in the bloodstream the dietary lipids absorbed in the intestine for energy supply of the tissues. Their triglyceride content is hydrolisised by lipoprotein lipase on the vessel wall and the resulting remnants are taken up by the liver. Altered chylomicron metabolism has been shown in some malignancies and may have important implications in nutritional managent of the patiens. Currently, chylomicron metabolism was evaluated in patients with ovarian neoplasm using a labeled artificially-made emulsion that mimics natural chylomicrons as a study tool.

Methods: Patients were assigned to two groups: those with advanced disease (AD) and those without active disease (WD). The chylomicron-like emulsion labeled with 14C-cholesteryl esther (CE) and 3H-triglicerid(TG) was injected intravenously into 3 AD patients and 5 WD patients. Blood samples were taken aat regular intervals during 60 min for determination of the plasma decaying curves of the isotopes. Fractional clearance rate(FCR, in min) of the labels was calculated from the curves.

Results:

	AD	WD
TG-FCR	0 33 ± 0.017	0.043 ± 0.018 N
CE-FCR	$2\,2 \times 10^{-9} \pm 1\,1 \times 10^{-9}$	0 013 ± 0.006 ($p < 0\,05$)

Conclusions: The results show that patients with advanced disease develop alterations of chylomicron metabolism characterized by diminished hidrolysis of triglycerides (expressed by FCR-TG) and diminished removal of the generated remnants from the circulation (FCR-CE). This finding is suggestive that cachexia that frequently accompanies this disease can be related with deficient dietary fat assimilation by the organism resulting from defective chylomicron metabolism.

644P Phase I and pharmacokinetic (Pk) study of an orally active drug, 2-deoxy-2-methylidenecytidine (DMDC) in patients with advanced malignancies

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Introduction: DMDC is a potent 2'-deoxy-cytidine analogue, which is phosphorylated by deoxycytidine kinase into its active forms which inhibit ribonucleotide reductase and DNA polymerase within tumor cells to impair DNA synthesis. In human tumor xenograft models DMDC given orally markedly reduced growth of tumors including colorectal, non-small cell lung (NSCL), breast, esophageal, renal cell, gastric and pancreatic, particularly those with high levels of cytidine deaminase activity. The objectives of Phase I study were to investigate maximum tolerated dose (MTD), tolerability and Pk profiles of DMDC and its metabolite DMDU when given orally twice a day for 7 or 10 days, every 21 days in patients with advanced malignancies.

Methods: Initially, a cohort of 6 patients with advanced NSCLC for whom no standard chemotherapy was available, was enrolled at a starting dose of 12 mg/m^2, bid × 10 days, p.o, q21d (10q 21d). For the second cohort of 6 patients, the dose was deescalated to 9 mg/m^2, bid, ×10days. The second schedule of dosing enrolled a cohort of 6 advanced NSCLC and colorectal cancer (CRC) patients, at the dose of 12 mg/m^2, bid × 7 days, p.o, q21d (7q21d). For the second cohort of 6 patients, the dose was escalated to 15 mg/m^2, bid ×7 days, q21d. Blood samples were collected for Pk analysis, safety assessment and dose modification purposes. Tumor assessments were performed to preliminarily assess anti-tumor activity.

Results: DMDC at 12mg/m2, p o., 10q21d, bid produced clinically significant hematological toxicities. A dose of 9 mg/m2, p.o., 10q21d, bid was well-tolerated and recommended for Phase II/III trials. DMDC when administered twice daily 7q21d, a dose of 15mg/m^2, bid produced clinically significant but acceptable tolerability profile and this dose was recommended for Phase II/III trials. Dose limiting toxcities for both schedules were neutropenia and thrombocytopenia with nadir counts occurring on day 17 and 14 respectively, and recovery by day 21. Grade 3 asthenia occurred only in 10q21d schedule. Other non-hematological toxicities were generally mild to moderate in nature and

reversible. Pks of DMDC and DMDU appear to be linear. Oral bioavailability of DMDC is estimated as 41%, with terminal half-life of approximately 2–3 hours. No accumulation of DMDC was reported after repeated dosing.

Conclusions: DMDC when administered orally twice a day for 7 or 10 days is well tolerated. Patient enrollment continues to substantiate safety profile and to investigate anti-tumor activity of DMDC in both NSCLC and CRC patients. [Acknowledgement – C. Brindley, Quintiles, Scotland (Ltd), Edinburgh, UK performed Pk analysis of blood samples].

645P Resistance to the multitargeted antifolate (MTA, LY231514): Multifactorial in human leukemia, breast, and colon carcinoma cells

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Introduction: MTA is a structurally novel antifolate that inhibits multiple folate-requiring enzymes. MTA is readily polyglutamated, and the pentaglutamate inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARFT) with Ki values of 1.3, 7.2, and 65 nM, respectively.

Methods and Results: We sought to determine the mechanistic basis for antifolate resistance in several human tumor cell lines adapted to escalating MTA concentrations. The degree of resistance in growth inhibition assays was 729-fold for CCRF-CEM leukemia, 140-fold for GC3 colon carcinoma, and 117-fold for HCT-8 colon carcinoma cells. Strong collateral resistance (> 3500-fold) was noted for the selective TS inhibitor, raltitrexed in all three cell lines. In contrast, only modest cross-resistance was noted for methotrexate and the GARFT inhibitor, LY309887. Cellular resistance to MTA was stable upon removal of selective pressure. Only $GC3_{MTA}$ cells showed increased (~40-fold) TS activity. Accumulations of MTA at 24 hours in CCRF-CEM_{MTA}, HCT-8_{MTA}, and $GC3_{MTA}$ cells were 2, 6, and 46% of wild-type values. Thymidine totally lacked protective activity in the MTA-resistant cells. The resistant cells with TS amplification demonstrated a GARFT-like reversal pattern (complete protection by hypoxanthine), whereas the other MTA-resistant lines demonstrated a DHFR-like reversal pattern (complete protection by hypoxanthine plus thymidine).

Conclusions: Resistance to MTA is multifactorial, and MTA appears to have the unique ability to shift target enzymes through development of resistance.

646 Euregenethy/regulation of gene therapy: A European network of users – DGXII/ E.5 BIOMED II/ ELSA-CA

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The development of recombinant DNA technology has induced in the public fears and speculation regarding its potential risks. In fact, implementation of gene therapy involves technological approaches which might not be devoid of potential side effects (as with many conventional therapeutic means addressing severe conditions). The regulation of Gene Therapy is intended to assess for potential risks in order to restrict them; but also to delineate a margin where safety can be secured. This should also contribute to better understanding and improved public acceptance. Within the EU, three Directives have been adopted in respect of the use of genetically modified organisms (GMOs)- in fact, national authorities have often interpreted them in ways that generate heterogeneity. Such heterogeneity justifies the need to conduct a survey of national regulations and to circulate to potential users expert information on European regulation. This should ultimately contribute to harmonisation via the dissemination of knowledge and expertise. In this project a series of tasks will be undertaken which include: **1.** making a record of regulatory information from each member state; **2.** translation (into a language understood Europe-wide) and circulation; **3.** circulation of information including both national and overall regulation by means of printed reports, telematics & support of Europe-based journals, specialising in this field; **4.** a record of regulatory information from the EU relevant to the fields of gene transfer and gene therapy in humans; **5.** a survey of the opinions of the Europena Group on Bioethics and the declarations of the Unesco I BC; **6.** Interaction with the European Commission; EMEA, OECD Biotechnology Unit, industrial platforms; **7.** establishment of a booklet of recommendations for users.

This project involves the contribution of expert users; some partners have already conducted clinical trials in their countries. Extended audience will be addressed taking advantage of identified networks and suitable contacts with professional associations, regulatory bodies, bioethics groups, public authorities and services, as well as industrial platforms, under the form of multidisciplinary fora. Our purpose is to provide users with relevant information and to contribute to harmonisation.

http://193.48.40.240//www/euregenethy/euregenethy.html

647 Cytotoxic effects of topotecan combined with various active G2/M phase anticancer drugs in panel of human tumor derived cell lines

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TPT acts as cell cycle specific drug (Topoisomerase I inhibitor) recruiting cells at S and G2/M phases of the cell cycle. Particularly G2 phase cell arrest has been associated to accumulation of relatively inactive cyclinB1/cdk2 complexes. The aim of our study was to analyze cytotoxicity due to sequential combination of TPT and G2/M-phase active drugs in a panel of human tumor cell lines: TPT-Bleomycin in HEp-2 (derived from SCCHN), TPT-Docetaxel in SKBr-3 (derived from breast cancer) and TPT-Etoposide in NCI-H23 (derived from NSCLC). We first determined optimal conditions to obtain maximum TPT-induced G2/M-phase cell arrest. Secondly, we used these G2/M-arrest intervals to assess cell toxicity due to specific G2/M drug administration. These combination schedules were always synergistic when Bleomycin, Docetaxel or Etoposide administration overlapped the interval of maximum TPT-induced G2/M-phase cell arrest. Conversely, opposite sequential schedule Etoposide-TPT was only additive in NCI-H23, whereas Docetaxel-TPT and Bleomycin-TPT yielded a less than additive effect in SKBr-3 and HEp-2 respectively. Our in vitro assay shows that: 1) combination between Bleomycin, Taxotere or Etoposide and TPT is highly synergistic when the optimal sequential administration schedule is applied; 2) synergistic combinations are found in all three cell lines despite of their mutated p53 status; 3) in contrast to different schedules presented to date, we obtained encouraging results in both sequential administration schedules using Topoisomerase I and Topoisomerase II inhibitors in NSCLC.

648 Hemolytic uremic syndrome with Gemcitabine therapy?

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Introduction: Hemolytic Uremic Syndrome (HUS) is a rare clinical condition occasionally reported in cancer patients. It can be caused by the malignancy itself and has been implicated with some chemotherapeutic agents. It has been recently observed that gemcitabine may be rarely associated with this condition. This review examines the validity of this observation and attempts to identify the incidence of and risk factors for such occurrences.

Methodology: The manufacturer's safety database was searched from 01 Aug 1987 to 31 Dec 1997, the ten-year period since gemcitabine was first studied in human subjects. In addition to the terms HUS and thrombotic thrombocytopenic purpura (TTP), a comprehensive search of possible terms related to renal and hematologic abnormality was conducted. All cases generated were reviewed individually to evaluate patient demographics, dosing, clinical presentation, and outcomes. Clinical (microangiopathic hemolytic anemia, thrombocytopenia and acute uremia) or pathologic (renal biopsy) criteria was used to confirm the cases. Attempts were made to validate individual cases and examine risk factors that may have predisposed patients to HUS. A crude incidence rate was calculated using worldwide patient exposure data from clinical trial and commercial use.

Results: Twelve cases were identified in the review. Based on an estimated worldwide patient exposure of 78,800, a crude incidence rate of 0.015% was determined. Cases included 7 males (58%) and 5 females (41%) with a median age of 55 5 years (range 37–73). Two-thirds of these patients were between 50 and 69 years. Primary malignancies were pancreas (50%), lung (33%), stomach (8.5%), and biliary tract (8.5%). Median duration of therapy was 5.8 months (range 3.8–13.1). The median cumulative dose was 18,252 mg/m^2 (range 2,450–40,269). Eight patients developed HUS within 1 month from the time of last infusion and 4 patients developed the condition between 1–2 months. Outcomes showed that 6 died, 5 improved and 1 outcome was unknown. Among the 6 deaths, 3 patients died from cancer progression, and 1 died from an unrelated myocardial infarction. Two patients died of HUS or related complications. For the 5 patients who improved, treatment was either dialysis, plasmapheresis, splenectomy or a combination. Confounding factors were fairly common. Two of the 12 patients had prior chemotherapy treatments with mitomycin-C. Most other patients had either advanced stage cancers or pre-existing renal dysfunction.

Conclusions: Despite a comprehensive review of our database, very few cases of confirmed HUS were found. The crude rate suggests that the incidence is extremely rare (< 0.02%). Confounding factors such as malignancies or other underlying conditions may have contributed to some of these cases. No consistent risk factors were identified. There is no structural similarity between gemcitabine and mitomycin-C, or cisplatin, nor known mechanism for this occurrence. In view of the large patient exposure, HUS remains a rare event. As with other treatments for malignancy, clinicians should exercise prudent judgment in weighing the appropriate risk versus benefit ratio in using this chemotherapy in their patients.

649 Phase I dose finding trial of irinotecan (CPT-11) combined with ifosfamide (IFO) in patients with advanced solid tumors

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Purpose: CPT-11 and Ifosfamide are two very active chemotherapeutic agents that have already demonstrated efficacy for different advanced solid tumors. To determine the maximum tolerated dose (MDT), the toxicity profile and the feasibility of an Irinotecan (CPT-11) plus Ifosfamide (IFO) combination, in patients with advanced solid tumors, a Phase I trial with a simultaneously dose escalation of Irinotecan (CPT-11) and Ifosfamide (IFO) has been set up.

Method: IFO is given dI, 60 min. i.v. infusion, and it is followed by CPT-11, 30–90 min. i.v. infusion. Cycles are repeated q3w. Mesna uroprotection is also administered. DLT is defined: granulocytes $\leq 500\times10^9$/l; platelets $\leq 25{,}000\times10^9$/l, febrile neutropenia (fever $\geq$ 38.5°C with concomitant grade 3/4 neutropenia), grade 3/4 neutropenia with sepsis, and any grade 3/4 non hematological toxicity appeared in the first cycle except alopecia, nausea & vomiting. Dose escalation runs as follows:

Level	CPT-11	IFO
1	65	1500
2	75	1500
3	75	1800
4	100	1800
5	100	2100
6	150	2100
7	150	2400
etc	(mg/sqm)	

Toxicity	No pts	G1	G2	G3
N & Vom.	5	5	0	0
Astenia	8	7	1	0
Anorexia	5	4	1	0
Diarrhea	3	3	0	0
Hematuria	1	1	0	0
Neutropenia	1	0	0	1

Status: Since October 97, 12 patients, 8 male, 4 female, have been treated in levels 1 to 4. 2 more are under screening to level 5. Median age: 57.3 (44–67); PS 0(1), PS 1(10), PS 2(1). Indications are: Hepatocarcinoma (3) Lung cancer (2), Cervical cancer (2), Colorectal (1), Melanoma (1), Lymphoma (1), Head & Neck (1), Small Intestine (1). 37 cycles have been administered. 9 patients have received more than 3 cycles and are evaluable for efficacy. No dose limiting toxicities have been reported on first cycle until now. Main toxicities have been astenia, anorexia, nausea & vomiting, diarrhea and neutropenia with no fever. Although this trial is not designed to evaluate efficacy, 5/9 patients have progressed and 4/9 had stable disease after 3 cycles of treatment. Dose escalation is still ongoing.

Conclusions: CPT-11 and IFO combination seems to be feasible. Toxicity profile at dose levels tested is not severe and manageable. MDT of this scheme is not yet reached. Final results will be presented.

Trial supported by a grant of Prasfarma S.A.

650 IL-2 liposome inhalation therapy for patients with lung and mediastinal metastases of solid tumors

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Introduction: IL-2 has a therapeutic activity in patients with metastatic renal and colon cancer and disseminated melanoma It has been shown (Huland E. et al., 1997) that inhalation of IL-2 is highly effective and safe in patients with lung metastases of renal cancer. Liposomal formulation of IL-2 can (Khanna C. et al., 1997) increase the circulating half-life of IL-2, targeting tissues of the immune system and lungs and decrease toxicity. The purpose of our study was to evaluate efficacy and toxicity of liposomal IL-2 for the treatment of the pts with lung and mediastinal metastases of solid tumors.

Methods: In the study we included pts with lung metastases of renal, colon cancer and melanoma. A recombinant IL-2 (Proleikin; Chiron, Netherland) has been used. The liposomal IL-2 is prepared by original technology without lyophylization[2]. The liposome preparation contains natural phospholipids with 25% of phosphatidylholine. Liposomes entrapment of IL-2 is 80–85% Nebulization of liposomal IL-2 involved the use of Sunmist Plus compressor (De Vilbiss Health Care UK Ltd.).

The dose of liposomal IL-2 was escalated on the following dose-levels:

I – 1.8×10^6IU twice daily for 10 days; II – 3.6×10^6 IU twice daily for 10 days; III – 4.5×10^6 IU twice daily for 10 days; IV – 6.0×10^6 IU twice daily for 10 days.

Results: overall 8 pts were treated on these levels. The treatment with liposomal IL-2 was well tolerated. Registered toxicity were: fever gr.I (5/8 pts), vasomotor rhinitis (3/8 pts), hemoptysis gr.I (2/8 pts). A 9-months stabilization was registered in 1 pt. There were no objective responses (CR,PR). The trial is ongoing.

Conclusions: The use of inhalation of liposomal IL-2 is a well tolerated promising method of lung metastases therapy

651 Phase I trial of the bombesin receptor antagonist RC-3095 in patients with refractory solid tumors

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Introduction: The growth-inhibitory effects of the bombesin/gastrin-releasing peptide (GRP) antagonist RC-3095 were demonstrated in various murine tumors, as well as in human tumor xenografts implanted in nude mice. These effects are due to interference of the drug with autocrine signals in tumor cells expressing bombesin-like/EGF cell receptors. Preclinical toxicology studies of RC-3095 in Beagle dogs using SC daily administration did not disclose toxic effects, and no MTD was reached in the dose range from 0.3 to 1000 μg/kg.

Patients and methods: In this phase I trial, adult patients with refractory solid tumors, preferably those believed to express the above mentioned autocrine pathways, having adequate liver, renal and cardiac function, and who signed a written informed consent, were included. Serial plasma samples were collected for analysis, including gastrin levels prior and following drug administration. The starting dose was 8 μg/kg, administered SC daily continuously, patients being evaluated for toxicity (NCI-CTC) and response (WHO) every 3 weeks. Dose-escalation was planned as follows: 8, 16 and 32 μg/kg SC daily in groups of 3–5 patients per each dose level, with no intra-patient dose-escalation. In case no toxicity was observed at the latter dose level, the next group of patients should be treated with a twice-daily SC schedule (to enhance drug-receptor interation) at the dose of 32, 64 and 128 μg/kg, respectively, until clinical toxicity and/or inhibition of plasma gastrin levels are observed.

Results: So far, 3 patients were entered in each of the two initial dose-levels (8 and 16 μg/kg, respectively), while 1 patient received RC-3095 at the 32 μg/kg dose level. Nineteen courses are now evaluable, and neither toxic effects, nor antitumor activity were observed. Measurements of plasma samples showed no significant inhibitory effect on gastrin release by RC-3095 at the dose-levels thus far employed.

Conclusion: The trial is open for accrual.

652 In vitro schedule-dependent cytoxicity by Ecteinascidin 743 (ET-743) against human tumor cells

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We have evaluated the cytotoxicity of Ecteinascidin 743, a new natural product, which has shown promising antitumor activities. The aim of this study is to compare the activity of different exposure schedules of ET-743 against tumor and normal cell lines, to assist clinical studies in finding a rational schedule for Phase II trials. Cells, in logarithmic phase of growth, were incubated in presence of Et-743 for 1, 3, 6, 8 & 24 hours. At present we have completed 9 cell lines (see table below):

Tumor Cells	IC50 (ng/ml)					Therapeutic Index	
	1 h	3 h	6 h	8 h	24 h	CV-1	Chang Liver
A-549	21	6	3	1.9	1.5	1 6 (3 h)	0.5 (6 h)
ACHN	5	1 5	1	0.5	0.3	6 7 (3 h)	1.5 (6 h)
DU-145	40	7	4	1 4	1	2.1 (8 h)	0.5 (8 h)
HeLa	30	5	2 5	0.9	0 5	3.3 (8 h)	0.8 (8 h)
HT-29	7 5	3 7	2	1.6	0 4	2 7 (3 h)	1.1 (3 h.)
SK-MEI-28	9	1.8	1.7	0.8	0.4	5 5 (3 h)	1.1 (3 h)
SK-OV-3	15	3	2	0.9	0 5	3.3 (3 h)	0.8 (8 h)

ET-743 is generally more cytotoxic with increasing exposure times. The magnitude of this potency represent a gain of between 14–60 times more sensitivity with time, where prostate, cervix and ovarian tumor cell lines are the most sensitive. The gain of sensitivity, although schedule-dependent, is more apparent between 3 and 8 hours, depending on the tumor. Taken together, this data supports a strategic consideration to choose infusion time for continued Phase II clinical trials based upon a balance of optimal stability and reduced toxicity as well as biological activity.

653 Whole body hyperthermia has a stimulatory effect on the immune cell activity in cancer patients

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Introduction: Whole body hyperthermia (WHB) alone or combined with chemotherapy is known to have a number of beneficial effects. Those include a potentiation of the tumoricidal effects of specific cytotoxic agents,

induction of cytokines and surface expression of heat shock proteins. The latter has been shown to enhance the suseptibility of tumor cells to lysis by lymphokine-activated killer cells (Blood 86, 1374, 1995). The goal of this study was to investigate the effect of WBH on functional subsets of human lymphocytes.

Methods: WBH (41.8°C) in combination with chemotherapy was administered by a radiant heat device (Enthermics Medical Systems, Menomonee Falls, WI) to patients with cancer of the GI-tract or soft tissue sarcoma. Quantitative assessment of various lymphocyte subsets (CD4, CD8, CD19. CD56) and monitoring of the effector adhesion molecules LFA-1, CD2 and CD28 on the respective subsets was performed at the given timepoints using flow cytometry. Activity of purified CD56+ NK cells was examined in three patients using K562 as target cells and was compared to the stimulatory effect of IL2.

Results: Data are given as the mean ± SE of 36 WBH treatment sessions.

		37°C	41.8°C	18h post WBH
Lympho	(WBC differential, %)	21 ± 1.4	31 ± 2.7	16 ± 1.6
CD4	(%)	42 ± 2.1	28 ± 1.6	45 ± 2 1
CD8	(%)	34 ± 2 1	45 ± 2 3	35 ± 2 1
CD56	(%)	18 ± 1.4	34 ± 1.9	15 ± 1.3
CD19	(%)	6.2 ± 0.7	4.5 ± 0 5	4.7 ± 0 7

The initially high expression of LFA-1 and CD2 on CD56 and CD8-cells remained unchanged. CD28 decreased by almost 50% at 41.8°C but returned to initial values 18 h later. WBH increased NK cell cytotoxicity by 7%, 8% and 10% in the three patient samples tested. This was comparable to the effect of IL2. Treatments were accompanied by a slight increase in white blood count.

Conclusions: WBH has the potential to stimulate and to significantly increase the total number of NK cells. Results indicate that WBH might enhance the immunological responses via increased oncolytic function of NK cells known to be triggered by surface protein interaction (e.g. LFA-1/ICAM-1). Therefore, ICAM-1 expressing malignancies may be good candidates for a combined thermo-chemotherapy.

654 "Rotating" chemotherapy in the treatment of resistant and overtreated malignancy – A preliminary report

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Introduction: It is considered that multidrug resistance, in the usual way, develops during 6 cycles of chemotherapy. "Rotating" chemotherapy, means to change the composition of chemotherapy schedules from cycle to cycle, according to some rules. With this conception we are trying to overcome resistance and excessive toxicity in our patients.

Methods: Total number of 23 patients with different malignancy was included in this study (3 breast, 6 lung, 2 head and neck, 4 lymphoma, 4 gastrointestinal, 2 gynecological, 1 melanoma and 1 pancreatic cancer), 15 mail and 8 female, age 29–67 (median 52). All patients were previously treated with first to third line chemotherapy or with combined modality chemo and radiotherapy, and disease was considered as resistant or recurrent. The chemotherapy schedules were created during 5 days, trying to cover cell cycle with following rules: 1. day-tubulin active agents (vinca-alcaloids or taxans with influence on mitotic spindle), 2.- 4. day – antimetabolites + alkylating agents and 5. day – intercalators (anthracyclines or other analogues). The doses were minimal to moderate recommended for each drug.

Results: Total number of 71 cycles were completed, median 3 per patient. The following responses were observed: ORR 34.8%, 13.1% CR, 21.7% PR, 17.4% SD, 47.8% PD, the complete remission occurring in 1 patient with lung metastases of UCNT, 1 breast and 1 ovanan carcinoma. Main toxicity was hematological with 8/23 patients of leucopenia and 6/23 of trombocitopenia gr. 3–4 (1 toxic death because of GIT bleeding). There was no other toxicity grade 3–4.

Conclusion: According to this preliminary results, with acceptable toxicity and few complete remissions a "rotating" chemotherapy might be promising choice for patients with good performance status and resistant or overtreated disease. The further investigation is need for assessment of its real value.

655 Support to phase II clinical trials of oral vinorelbine (VRL, NAVELBINE®) by population pharmacokinetics (PKs): A new tool to follow drug induced toxicities

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Navelbine® is a vinca-alkaloid antimitotic agent. First registration was obtained in 1989 and since NAVELBINE has been registered in more than 70 countries for non-small-cell lung cancer and/or metastatic breast cancer.

In order to support the development of an oral form (p.o.), a PKs population study using NONMEM system was performed on data available from phase I studies conducted with the i.v. (64 patients) and the oral form (75 patients) A model was built which demonstrated that, based on few covariates, inter-individual variabilities on $Cl_{i.v.}$ and $Cl/F_{p.o}$ decreased respectively from 35% and 76% in basic model to 22% and 56% in the final model, while residual variability was estimated to 22% and 24% for i.v. and oral route respectively. Moreover, these phase I studies allowed to establish a PK/Pharmacodynamics (PDs) relationship between haematological toxicities and drug exposure, a trend for a PK/PD relationship on non haematological toxicities was suggested and has to be confirmed.

Based on this population model, a limited sampling strategy was developed in order to contribute to a better understanding of oral VRL, particularly regarding its PKs and safety profiles, in further phase II clinical trials. The best sampling time schedule only needs three blood samples to accurately determine the PK characteristics of the drug: They have to be taken around 1.5 h, 3 h and 24 h following the oral administration (end of infusion, 3 h and 24 h if i.v. administration).

This limited sampling strategy was applied to patients included in phase II studies with oral VRL. Interim results indicate that the PK behaviour of VRL is properly described by this model.

656 A phase I study of the novel antracycline analogue MEN-10755/BMS-195615 (NAA) in patients (pts) with a solid tumor: Preliminary results

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Introduction: The novel doxorubicin (Dox) disaccharide analogue NAA is synthesized by coupling the aglycone with a daunosaminyl-α(1→4) fucosil moity. Such a disaccharide structural variant is designed to expand the recognition options in this portion of the molecule. Compared with Dox NAA is characterized by its marked ability to induce DNA breaks by topoisomerase II inhibition in tumor cells, and by superior activity in a number of human tumor xenografts, including Dox-resistant tumors Preclinical studies have shown a similar degree of cardiotoxicity for Dox and NAA.

Methods: In an ongoing phase I study, NAA is given as a 15 minutes infusion once every 3 weeks in patients with solid tumors to define the MTD and pharmacokinetics (PK) at escalating doses: 4, 8, 16, 32, 55, and presently 80 mg/m2.

Results: 21 pts have entered the study: median age 53 years; lung (6 pts), oesophagus (2), pancreas (2), kidney, gastric, colon, melanoma, pulmonary, skin, parotid, basis cranii: (1 each), and unknown primary (3). At 55 mg/m2 CTC grade 4 neutropenia was observed in 1/6 pts; at 80 mg/m2 grade 3 anemia, neutropenia, and leucopenia has been observed in 1/2 pts. No responses have been achieved so far. PK from the first 4 dose levels appear to be linear, and compared with Dox, NAA shows higher systemic exposure (AUC), with lower clearance and distribution volume, and shorter half-life.

Conclusions: The MTD has not yet been reached, and dose escalations will continue.

657 Phase II trial and pharmacokinetic study of irinotecan (CPT-11) in patients with glioblastoma

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Irinotecan (CPT11) is a topoisomerase 1 inhibitor active against colorectal cancer. Preclinical data indicate a potent antitumor activity in mice bearing pediatric and adult human central nervous system tumor xenografts. The aim of the present study was to determine the antitumor activity and safety of CPT11 in patients (pts) with glioblastoma Fifteen patients (M/F=8/7) with histologically-proven glioblastoma and documented progression were enrolled. Median age were 50 years (range 34–72), and performance status according to WHO criteria was: 0 (6 pts), 1(6 pts), 2(3 pts). Surgical procedure consisted of a stereotaxic biopsy in 7 cases, a partial tumor resection in 5 cases, and a complete tumor resection in 3 cases. CPT11 was administered either before radiotherapy in 5 pts with unresectable and partially resected glioblastoma or after radiotherapy (60 Gy) in 10 pts with recurrent and progressive glioblastoma. CPT11 was given as a 90 minute infusion at the dose of 350 mg/m² every three weeks. Response to treatment was assessed after two or three cycles by cerebral CT-scan or MRI. Fifteen patients received a total of 43 cycles (median=2; range 1–9). Maximum toxicity/cycle according to the NCI classification included: grade 3–4 neutropenia (n=9), grade 1 anemia (n=10), grade 1 thrombocytopenia (n=4), grade 1 diarrhea (n=12), grade 2 diarrhea (n=3), grade 1–2 fatigue (n=4), and mild cholinergic syndrome (n=18). Median follow-up is 17 weeks. To date, no objective response was observed in 13 evaluable pts. Stable diseases including one minor response were observed in 7 pts and progressive diseases in 6 pts. Accrual and pharmacokinetic studies are ongoing. Additional results will be available at the time of the meeting. The mild toxicity observed in this population might be related to metabolic interactions due to concomitant anti-epileptic medications. Pharmacokinetic data will be available to assess these putative interactions.

658 In vitro aneuploidy induced by Taxol® on human T phytohemagglutinin-stimulated lymphocytes

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Taxol® (Paclitaxel) is derived from the bark of the pacific yew (Taxus Brevifolia). It is a novel chemotherapeutic agent which presents a great antitumoral activity (advanced ovary, breast cancers...) by inhibiting tubulin depolymerisation in mitotic tumoral cells. Although its use is increasing, very little data is available on its potential genotoxicity on normal human cells. The genotoxicity is studied here by means of *in vitro* cytokinesis-blocked human T lymphocytes micronucleus assay with Taxol® (2.5 to 10 nM) for 48 hours. This test can detect either clastogenic (loss of acentric chromosome fragments) or aneugenic (loss of whole chromosomes) DNA damage. Fluorescent *In Situ*-Hybridization (FISH) with non-specific centromeric alphoid probes can then distinguish between these 2 mechanisms.

The results obtained with 11 healthy non-smoking female donors, aged 29 to 61, demonstrated a significant ($p < 0.01$) increase in the frequency of micronuclei (MN) with a dose-response. In the FISH analysis, more than 80% of micronuclei in binucleated cells are centromere-positive. At the highest concentration of Taxol® (10 nM), multimicronuclei cells (MN > 6) appeared, suggesting the first stage of DNA fragmentation and Taxol®-induced apoptosis. Surprisingly, at these concentration levels, no significant cytotoxicity (assessed by counting the number of binucleated cells on 1000 mono- or binucleated lymphocytes) was observed. This result differs from those obtained with tumoral cell lines, suggesting that no accumulation of lymphocytes in the G2/M phase cell cycle occurred.

These findings underline the *in vitro* genotoxicity of Taxol® (with concentrations similar to plasma concentrations in clinical trials) on human phytohemagglutinin-stimulated lymphocytes, through an essentially aneugenic action. This mechanism involves interphase aneuploid lymphocytes with no significant cytotoxicity.

659 Pharmacokinetic study of temozolomide penetration into CSF in a patient with dural melanoma

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Introduction: Temozolomide (TMZ) is an orally active, synthetic imidazotetrazinone, structurally related to dacarbazine. Unlike dacarbazine, which requires enzymatic conversion in the liver, TMZ undergoes spontaneous hydrolysis to its active metabolite, 3-methyl-imidazole-4-carboxamide (MTIC), at physiological pH. TMZ effectively penetrates the blood brain barrier in a number of animal models and has shown clinical promise in the treatment of gliomas.

Methods: KH, a 41-year old white male was diagnosed with a primary dural melanoma in December of 1995. He underwent several treatments, including primary resection, radiation therapy, interferon-alfa and intrathecal therapy with methotrexate, ara-c and dexamethasone (after placement of an Ommaya reservoir). Following reappearance of melanoma cells in his CSF, he was treated with TMZ, 150 mg/m^2/day orally × 5 days q28 days for 2 cycles (in February 1998). Blood and CSF samples were obtained on days 1 and 5 of cycle 1 at the following time points: pre-treatment, 1,2,4 and 6 hr. Plasma and CSF samples were analyzed using HPLC analysis with an LOQ of 0.1 ug/ml. This assay is linear and reproducible between 0.1 and 20 ug/mL of plasma/CSF. The area under the plasma concentration-time curve from time zero to the time of final quantifiable sample (AUC(tf)) was calculated using the linear trapezoidal rule.

Results: Maximum plasma and CSF TMZ concentrations (Cmax) were reached within 1–2 hr post-dose on days 1 and 5. The respective plasma and CSF AUC(tf) values were similar on days 1 and 5, indicating lack of TMZ accumulation (accumulation ratios 0.96 and 0.91 for plasma and CSF, respectively). The ratio of CSF to plasma AUC(tf) values were 30% and 28% on days 1 and 5, respectively. Interestingly, melanoma cells seen on cytology on the pretreatment CSF were undetectable on CSF obtained after cycle 2 of treatment, cell counts and protein levels also returned to the normal range.

Conclusions: TMZ penetrates into the CSF following oral administration. These results are consistent with the previous findings in animal models. Further investigation of TMZ in primary and metastatic brain tumors is warranted.

660 Phase I and pharmacokinetic study of low-dose, three-times daily oral etoposide in patients with refractory solid tumors

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Introduction: We reported previously, that etoposide displays a more favorable therapeutic index in patients with progressing, AIDS-associated Kaposi's sarcoma when given BID and PO. This observation could be due to the prolonged maintenance of cytotoxic, topoisomerase II-inhibiting plasma drug levels, and the simultaneous avoidance of severely myelosuppressive peak concentrations.

Methods: In this phase I study, adult patients with refractory solid tumors, having adequate liver, renal and cardiac function, and who had signed a written informed consent, received etoposide TID and PO daily for 14 days in 21-day cycles. The starting dose was 15 mg/m^2 TID. At least 3 patients were included per dose-level, and dose-escalation was guided through a modified Fibonacci scheme. Plasma pharmacokinetic analyses following chloroform extraction and HPLC separation, were carried out in all patients. Toxicity and response were assessed according to the NCI-CTC, and the WHO criteria, respectively.

Results: Thus far, 3, 3, and 5 patients were evaluable at the 15, 20, and 25 mg/m^2 TID dose-levels, respectively, receiving a total of 17 courses. No significant toxicity, or only grade 1–2 nausea occurred at the 15, and the 20 mg/m^2 TID-level, respectively. At the 25 mg/m^2 TID-level, grade 3–4 bone marrow suppression was predominant, manifesting in 3/5 patients. No objective responses were documented. The pharmacokinetic analyses revealed an AUC of about 25 μg.h/ml, a peak concentration of approximately 3.5 μg/ml, and the maintenance of plasma etoposide concentrations > 3 μg/ml for about 2 h in patients treated at 20 mg/m^2 TID. At the 25 mg/m^2 TID level, these values were about 40 μg.h/ml, 7.5 μg/ml, and 4 h, respectively.

Conclusion: The main toxic effects observed in this trial were myelosuppression and nausea. The apparent MTD of etoposide at the schedule employed is 25 mg/m^2 TID. Extra patients are being entered at the 20 mg/m^2 TID dose-level to confirm its recommendation for further studies. At this dose-level, plasma drug levels > 3μg/ml are achievable for about 7.5 h per day, avoiding toxic peak concentrations.

661 The chronic administration of ion exchange inhibitors markedly suppress tumour growth in vivo

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Introduction: The extracellular pH of solid tumours is approximately 0.5 pH units below the pH of normal tissues. Previously we have demonstrated that the viability of tumour cells in acidic microenvironment *in vitro* depends on the activity of membrane exchangers that regulate intracellular pH (pHi). Two main pHi regulating transport mechanisms are Na^+/H^+ antiport and Na^+-dependent HCO_3^-/Cl^- exchanger. It is possible to inhibit Na^+/H^+ antiport by amiloride and its analogues as 5-N-ethyl-N-isopropyl amiloride (EIPA) and Na^+-dependent HCO_3^-/Cl^- exchanger by stilbene derivates as 4,4′ dilsothiocyanostilben-2,2′-disulphonic acid (DIDS). Our experiments have been designed to demonstrate the activity of ion exchange inhibitors against murine tumour *in vivo* when delivered by chronic intratumour (i.t.) administration.

Methods: Tumour-bearing mice (carrying subcutaneous mastocytoma P815 for 20 days) were divided into three experimental groups and treated with DIDS, EIPA or DIDS and EIPA together. The antitumour effects of long-term (18 days) i.t. administration of (EIPA) and/or (DIDS) were expressed as mean tumour diameter ± SE (mm). Survival rates in experimental groups have been also followed.

Results: In all three experimental groups it has been occurred significantly ($p < 0.05$) lower tumours' growth than in control group. At the end of experiment, mean tumour diameters in experimental groups were twice as small as in control group. Surviving rate in all experimental groups has been significantly higher (DIDS-69%, EIPA-76%, DIDS and EIPA-87%) than in the control group (18%) ($p < 0.05$).

Conclusions: DIDS and EIPA and their combination were equally effective in inhibition of growth of murine mastocytoma P815. Surviving rates of treated animals compared to control group were also significantly higher. These results have shown the ability to obtain anti-tumour effects and prolonged life in experimental animals using chronic administration of DIDS and/or EIPA. Our results also suggest that pharmacological inhibition of pH-regulating mechanisms might be an exploitable strategy for the therapy of solid tumour.

662 Phase I study on docetaxel and Gemcitabine in patients with advanced solid tumors

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Docetaxel (D) and Gemcitabine (G) exhibit significant activity against several tumors. Since they have different mechanism of action and non-overlapping toxicity D and G are attractive candidates for combination therapy.

We evaluated this association in patients with advanced solid tumors in an open label phase I trial. A minimum of 3 patients were to be entered per dose level. Dose limiting toxicity (DLT) was defined as ≥ 3/6 pts with ≥ grade 3 organ toxicity, ANC nadir < 0.5 × 10^9/l for > 7 days, or ANC nadir < 1.0 × 10^9/l with fever ≥ grade 2 during > 3 days.

Thirteen patients were enrolled to date (5M/8F, median age. 52 years, median PS: 1, prior chemotherapy: 12 pts, prior radiotherapy: 8 pts) in four dose levels. Tumor types included: breast (6), NSCLC (5), sarcoma (1), ovary (1).

G was given as a 30 min. infusion on days 1 and 8, and D was given as a 1

h infusion on day 8. Cycles were repeated every 3 weeks. All patients received oral dexamethasone for 5 days starting on day 8.

G/D (mg/m^2)	# Pts	# Cycles	Mean ANC	# Pts with DLT
800/50	3	12	2.56 x 10^9/L	0
1000/50	3	6+	2.30 x 10^9/L	0
1000/75	3	7+	1.07 x 10^9/L	0
1000/90	4	4+	1.22 x 10^9/L	0

Clinical toxicities included: nausea, fatigue, anorexia, dermatitis, alopecia, myalgia. Mild and reversible edema was observed in two patients. One partial response in NSCLC pt was observed. Dose limiting toxicity has not yet been reached.

663 Intratumoral cisplatin/epinephrine injectable gel: Palliative treatment of advanced solid tumors

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Introduction: Phase II/III studies are evaluating the safety and efficacy of intratumoral therapy with cisplatin/epinephrine injectable gel (CDDP/epi gel) for site-specific treatment in patients with advanced solid tumors of various primary sites. The biodegradable viscous gel is composed of cisplatin and epinephrine formulated in a purified bovine collagen as a carrier matrix. The delivery system provides enhanced retention and high tumoral drug concentrations for extended periods.

Methods: Two ongoing identical, open-label studies enrolled patients who had failed previous therapy. CDDP/epi gel was administered intratumorally (2 mg CDDP and 0.1 mg epi per cm^3 tumor) weekly for up to 8 weeks. Patients were then followed for at least 4 weeks. Evaluations included tumor response for the most troublesome tumor (MTT) (response defined as $\geq$ 50% decreased tumor volume sustained $\geq$ 28 days), tumor-related symptoms for the MTT, palliative treatment objectives (e.g. pain control), and adverse events.

Results: 81 patients (296 tumors) with both recurrent and metastatic disease are described in this report. Primary tumor types included adenocarcinoma of the breast and melanoma, plus smaller groups of other tumors. Total patient cumulative doses of 1–240 mg CDDP (median 17 mg) were administered in 1–7 injections of CDDP/epi gel. Preliminary results show that 18 of the 81 MTTs (22%) had tumor responses; MTT responses in the two larger subgroups of tumors are listed:

Primary Tumor	Median Tumor Size	MTT Responses	Median Duration
Breast AdenoCA	3 cm^3 (< 1–413)	4/20 (20%)	151 days (91–204+)
Melanoma	3 cm^3 (< 1–201)	3/19 (16%)	50 days (29–112+)

Most of the patients had received prior therapy with one or treatment modalities including surgery (83%), radiation (75%), systemic chemotherapy (75%), or other therapy (56%). Attainment of the palliative treatment objective was associated with MTT response. Common toxicities (vomiting and nausea) typically related to intravenous cisplatin were observed at a lower frequency (< 21%) with CDDP/epi gel.

Conclusion: Local tumor control with CDDP/epi gel provides a new therapeutic tool for management of solid tumors while limiting systemic toxicity of the drug.

664 Phase I study of weekly placitaxel in advanced solid tumors: A preliminary report

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Purpose: To determinate the maximum tolerated dose (MTD) and the dose limiting toxicity (DLT) of paclitaxel given weekly in patients with solid tumors.

Patients and Methods: Patients with advanced solid tumors who failed at least one prior chemotherapy regimen received escalated doses of paclitaxel (P) weekly with increments of 10mg/m^2 for 4 weeks in cycles of 6 weeks. All patients received standard premedication. Cohorts of at least 3 patients were included at each dose level. As DLT was defined: grade 4 neutropenia or febrile neutropenia or any > grade 3 non-hematologic toxicity, or any treatment delay (> 3 days) due to insufficient recovery from hematologic or non-hematologic toxicity. The staring dose of P was 60mg/m^2/week and so far, 15 patients were enrolled. Their performance status (WHO) was 0-2, the median age 64 years (range 48–74) and 11 (73%) were female and 4 (27%) male.

Results: All patients were evaluable for toxicity and response At the dose-level of P 100mg/m^2/week, 2 patients developed DLT (1 grade 4 neutropenia and 1 febrile neutropenia). Grade 4 neutropenia occurred in 2 (6%) of 34 administered cycles whilst febrile neutropenia was observed in 1 cycle. Alopecia (grade 2) was rare (< 5%) while non-hematologic toxicity was mild (< grade 2). So far, no objective response was observed in this unfavorable group of patients.

Conclusions: The MDT has not yet been reached and further dose escalation is ongoing The weekly schedule allows a significant dose intensification of P administration. Although, no responses were observed it should be noted that all patients had refractory tumors.

665 A phase I study of Taxotere (T) and Gemzar (G) in patients with advanced solid tumors

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The combination T+G given in 4-week cycle appeared to be not feasible (Proc ASCO 1998, 17). Therefore a 3-weekly schedule was investigated in a phase I study. Patients (pts) with histologically confirmed advanced solid tumors, good performance status, adequate bone marrow, renal and liver functions, who received a maximum of two regimens of previous chemotherapy (without taxoids or gemzar) were eligible. Treatment was: G: 800 mg/m2 (dose level I) or 1000 mg/m2 (dose level II), 30 min. i.v. infusion on day 1 and 8, T: 85 mg/m2, 1 hr i.v. infusion on day 8 before G, repeated every 3 weeks; a 3-day oral corticosteroid premed was given from day 14.

A total of 10 pts (6 in dose level I and 4 in dose level II) has been included: 5M/5F; median age: 55 (42–68), median WHO P.S: 1 (0-1), tumor type: ovarian (2 pts), breast, bladder, renal cell, penile, head and neck, NSCLC, melanoma and leiomyosarcoma. Eight out of 10 pts received previous chemotherapy. To date a total of 32 cycles were administered, median: 3 (1–6). Treatment delay was seen in 11 cycles because of hematological (9 cycles) or liver toxicity (2 cycles). Dose reduction was necessary in one patient. Toxicity: Neutropenia grade 3–4, 47% cycles, thrombopenia grade 3–4, 6% cycles; febrile neutropenia, 9% cycles; Severe diarrhoea (1 pt) asthenia and (1 pt) alopecia (1 pt) were most serious nonhematological toxicity observed. One CR (ovarian ca) and one PR (renal cell cancer) were seen in 5 evaluable pts. Further accrual and updated data will be given during the presentation.

666 Pharmacokinetics of mitomycin C (MMC) and doxorubicin (DOXO) during a phase I study on locoregional therapy with hypoxic stop-flow perfusion

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Background: a phase I study on a new abdominal and pelvic hypoxic locoregional treatment with percutaneous double-ballon catheters, stop of blood flow and administration of high-dose of mitomycin C (MMC) and doxorubicin (DOXO) was designed to improve the exposure of tumoral tissues to chemotherapy.

Methods: 3 patients with advanced colon-rectum cancer and not resectable pelvic recurrence, treated with stop-flow infusion of MMC, 20/25 mg/sqm plus DOXO, 75 mg/sqm were followed for MMC and DOXO pharmacokinetics. Drug concentrations were measured by HPLC methods both in extracorporeal vascular flow and in peripheral blood. We compared area under curve – AUC – in the interval 0–20 min in the two compartments during the stop-flow infusion; drug decays were also observed in peripheral plasma after the end of infusion.

Results: the $AUC_{0\,20}$,-ratios of extracorporeal/peripheral drug concentrations were equal respectively to 3.8, 34.37 and 28.8 for MMC; to 1.3, 13.1 and 11.5 for DOXO. In these patients a complete pain remission was registered; no significant toxicities were observed. One patient showed PR of the disease.

These very preliminary results indicate that stop-flow technique could allow a pharmacokinetic advantage for perfused tissues even if with a high intersubject variability. The study is ongoing; more data will be presented.

667 A phase II study in the treatment of mesothelioma with a combination of docetaxel and CPT-11 – Set up and initial results

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Introduction: No effective chemotherapy is yet available for the treatment of malignant pleural mesothelioma. We have found several human mesothelioma *in vitro* cell lines to be sensitive to docetaxel and to a metabolite of CPT-11, SN38. We chose to combine these two new drugs with different mechanisms of action: docetaxel inhibits tubulin depolymerization affecting mitosis and intracellular molecule transportation, and CPT-11 inhibits DNA-enzyme topoisomerase I, introducing DNA-based effects in malignant cells.

Methods: All patients enrolled were previously untreated, have histologically proven diagnosis, and good performance status (WHO 0-1). Treatment schedule was docetaxel (Taxotere®) 60 mg/m^2 in 1 hour infusion followed by CPT-11 (Campto®) 190 mg/m^2 in 1 hour infusion without any interval between infusions, repeated once every three weeks.

Results: Responses were defined after three cycles. Main toxicities ob-

served during the first cycle in the first five patients were neutropenia (2 Gr3, 1 Gr1), two febrile neutropenia treated with i.v. antibiotics and G-CSF. Subsequently, two cycles were given with prophylactic G-CSF. Patients had nausea (3 Gr2) and diarrhea (1 Gr3, 2 Gr2) and alopecia (5 Gr3) after the first cycle. No dose delay or dose reduction was recorded. Four patients were evaluable for response: 2 NC and 2 PD, one patient chose to discontinue treatment after the first cycle.

Conclusion: This schedule and dosing of Taxotere® and Campto® are feasible and the study is still enrolling more patients. Updated results will be presented.

668 Interaction between topotecan and cyclosporin: Clinical results and pharmacokinetics over three courses

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Introduction: The pharmacokinetics of Topotecan (T) remains poorly known with only about 30% of T found in the urines and no isolated yet metabolites. Ciclosporine (CS) is metabolized through a cytochrome isoform of the P450-3A family. We looked for a pharmacokinetics interaction between T and CS.

Methods: A liver transplanted 51 years-old woman treated with 150mg CS twice a day, received three courses of 1.25mg/m^2/day T, as a 30 minute infusion, for 5 days for a metastatic neuroendocrin tumor. Plasma maximal concentration (Cmax), area under the curve (AUC), clearance and terminal half-life of total T and T as lactone form were determined using high-performance liquid chromatography. Cyclosporinemia was determined with specific and non-speckific antibodies.

Results: During the second cycle, the patient developed clinical and biological symptoms suggesting CS overdosage: vomiting, palpebral edema and facial erythema, subictera, systolo-diastolic hypertension, headache, 2.8- and 2.6- fold increase in creatininemia and total bilirubinemia, respectively. There was a 3-fold increase both in Cmax and residual cyclosporinemia from day 0 to day 5 of T treatment. No significant variation in plasma lactone and total T was found. Starting the following cycles with halved CS doses resulted in reproducible increase of cyclosponnemia from day 0 to day 5, yet without any clinical evidence of CS overdose.

Conclusions: These results suggest a pharmacokinetic interaction between T and CS. Ongoing experiments will determine whether T activates P450-3A or competes with CS, and therefore with other drugs metabolized by P450-3A.

669 A study of cyclosporin A and imipenem associated grand mal seizures in allogeneic bone marrow transplantation(BMT)

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Introduction: Imipenem(I) is a beta-lactam antibiotic used with Cilastatin(C) in the BMT setting. Cyclosporin A(CsA) is a fungal product used in the BMT setting as an immunosuppressive agent, seizures can be seen with both I/C and CsA. Our hypothesis for study was that CNS toxicity and seizures would be increased by the concomitant administration of both CsA and I/C.

Methods: Between December of 1989 and 1996, 166 of the stem cell BMT performed at Mount Sinai Hospital were either allogeneic(n=122) or autologous(n=44) and evaluated for this study. All allogeneic patients received CsA 1.5mg/kg bid as part of their immunosuppressive regimen, starting 1 day before infusion of stem cells. Thus, 3 groups were studied: 77 patients received CsA alone without I/C(Group 1). 89 patients received I/C, of these, 45 received concomitant CsA(Group 2) and 44 patients who underwent autologous BMT received I/C only and no CsA(Group 3)

Statistical Analysis: Differences between proportions evaluated using a two-tailed Fisher's exact test. A t-test was used to compare baseline values of the patients with and without seizures with respect to blood chemistries. Wilcoxan's non-parametric test was used if the data were markedly non-normal, typically due to skewness or to extreme outliers. Changes between baseline and chemistries as the time of seizure were examined for 5 patients who seized.

Results: We observed 3(3.8%) seizure episodes in patients who were on CsA alone(Group 1), 2(4.4%) seizure episode in patients who were receiving I/C and CsA(Group 2). Group 3 had no seizures. There were no statistical differences in between Group 1 or 2. We studied whether electrolytes, liver and renal function influences which patients will seize, the only statistically significant difference found was hyperbilirubinemia. Adverse effects may be difficult to relate to a particular drug, especially for patients on multidrug regimens. There were no history of seizures and baseline multiple blood chemistries and functional parameters were not statistically different in the two groups. The number of days patients were on CsA and I/C did not differ significantly than patients who received both and did not seize.

Conclusions: The use of I/C and CsA did not cause a significant rise in the frequency of seizures comparing to CsA alone.

PALLIATIVE AND SUPPORTIVE CARE

674O A prediction model to identify cancer patients (pts) with febrile neutropenia (FN) at low risk to develop a serious medical complication: Results from a multinational survey conducted by the Infection study section of the Multinational Association for Supportive Care in Cancer (MASCC)

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To be safely adopted, a risk based treatment of FN in cancer (iv, sequential or oral therapy) requires an accurate assessment of the individual risk of poor outcome which is still controverial: Talcott's model is sensitive but lacks clinical specificity whereas the ASCORP trials from M.D. Anderson were successful using clinical eligibility criteria. MASCC prospectively surveyed cancer pts with FN (20 institutions, 15 countries) in order to derive, from a statistical model, a prediction rule for pt's outcome (resolution of FN with or without serious medical complications -including death- development) using variables measured at fever onset. The study included 1146 eligible pts with a median age of 52 (16 to 91); 493/653 with hematologic malignancies/solid tumors, BMT in 174 and profound neutropenia < 100 cells/mm3 in 754). Variables possibly related to outcome ($p < 0.10$ on univariate analysis) were tested for potential inclusion in a multiple logistic regression model. Covariates in the final model, predicting a higher probability of poor outcome were: dehydration (RR 0.36, $p < 0.0001$), previous antifungal therapy (RR 0.37, $p < 0.0001$), inpt status (RR 0.42, $p < 0.0001$), Apache score $\geq$ 40 (RR 0.47, $p = 0.0002$), lesions from infection on chest X ray (RR 0.42, $p < 0.0004$), hypotension (RR 0.24, $p = 0.0008$), poor physiologic reserve (RR 0.51, $p = 0.004$), severe signs of illness (RR 0.53, $p = 0.004$), chronic obstructive pulmonary disease (RR 0.30, $p = 0.006$), confusion (RR 0.38, $p = 0.01$), hematologic tumor (RR 0.62, $p = 0.03$), uncontrolled cancer (RR 0.68, $p = 0.05$). A prediction rule was derived from the logistic equation of this model targeting the Talcott's model sensitivity in identifying pts at low risk. The corresponding specificity improved to 43% from 31%. In conclusion, if some progress was made with an improved risk index, specificity is still low and new types of variables, like estimates of duration to hematologic recovery need to be assessed.

675O Randomized, double-blind, parallel trial of the antiemetic efficacy and safety of ondansetron (OND) plus metopimazine (MPZ) versus OND plus MPZ plus prednisolone (PRED) during multiple cycles of moderately emetogenic chemotherapy (CT)

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In patients treated with moderately emetogenic CT the antiemetic efficacy of OND is improved with the addition of the dopamine D_2 antagonist MPZ or a corticosteroid. The efficacy of OND plus MPZ plus PRED has not previously been investigated.

In all, 221 CT-naive women scheduled to nine cycles of IV CMF/CEF were randomized to three days of oral treatment with OND plus MPZ (n = 111) or OND plus MPZ plus PRED (n = 110). OND was given as 8 mg twice a day, MPZ as 30 mg four times a day, and PRED as 50 mg once a day. Patients received the same antiemetic treatment during all nine courses of CT but were withdrawn if they had $\geq$ 5 emetic episodes during any day 1–5 after CT or if they were not satisfied with the treatment. In cycle 1, complete protection from emetic episodes/nausea day 1, days 2–5 and days 1–5 was achieved in 84.4%/51.4%, 82.6%/41.3% and 79.8%/34.9% with OND plus MPZ and in 84.1%/57.0%, 86.8%/53.8% and 79.4%/ 43.0%, respectively, with OND plus MPZ plus PRED. There was no significant difference in emetic episodes, but nausea was significantly better controlled with the three-drug combination days 2–5 ($P = 0.0497$), and there was no difference in the control of nausea day 1 and days 1–5. The cumulative emetic protection rate after nine cycles was 0.52 with OND plus MPZ and 0.75 with OND plus MPZ plus PRED ($P = 0.0014$, log rank test). Constipation was more frequent with the three-drug combination, with regard to other adverse events there were no significant differences.

In conclusion, the combination of OND plus MPZ plus PRED is highly effective and superior to OND plus MPZ during nine cycles of moderately emetogenic CT.

676O Epoetin alfa treatment of anaemic breast cancer patients: Haematological and quality of life (QOL) outcomes

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Introduction: The efficacy of epoetin alfa (rHuEPO) and its clinical and QOL outcomes in anaemic breast cancer patients (pts) undergoing chemotherapy (CT) in community-based oncology practice, was studied in two community-based, 4-month, open-label, multicentre studies.

