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/m^2 30min inf. followed immediately (A) of after 1HR interval (B) by TXT 75mg/m^2 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 ng/ml.H	Taxotere				Doxorubicin			
	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-ol 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/m^2 was administered as a 30 min infusion on d 1, 8, 15, and CDDP 50 mg/m^2 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 ≥ 10μM 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 (≥ 10μM) 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/m²)	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/m² and 3 at a dose of 3.5 mg/m². All of them received the same dose of 130 mg/m² 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/m² and 3.5 mg/m² 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) l/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 l/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 *Estenaiscidian 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/m²/day. At the 380 μg/m²day 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/m²/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/m²/day dose level suffered superficial venous thrombophlebitis at the drug infusion site. PK parameters obtained in 2 patients at the 216 μg/m²day dose level included: clearance, 137 and 589 mL/min/m²; $t_{1/2}$, 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 $5\frac{1}{2}$ 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 × 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.

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