pts/DL experienced DLT. Irofulven was given over 30 min with anti 5-HT3, steroids and 1000cc hydration.

Results: As of 4/2001, 24 pts with AST were treated, receiving 43 cycles. M/F: 10/14, median age: 55 (21-73). Sch. B: DL2 (10 pts/21 cycles), DL3 (3 pts/3 cycles). Sch C, DL2 (8 pts/16 cycles), DL3 (3 pts/3 cycles). Clinical toxicity was mild with no grade 3/4 events; Thrombocytopenia (T) Gr1-2 was prevalent in both sch at both DLs without cumulative effects. Gr3 T and neutropenia were seen in 2 and 1 pts respectively (sch C, DL2). Gr2 transient visual disturbance (modification of color vision and contrast with normal acuity) in 1 pt (sch C, DL2). DLTs were seen in sch C in 2 pts (1 with prior mitomycin C therapy) at DL 2. Activity: 24 pts were evaluable, with 7 too early, 1 PR (renal carcinoma), 5 pts SD = or >3 cy.

Conclusion: Irofulven given as a 30 min infusion is a well-tolerated regimen at DL2 (planned DI 12 mg/m2/w) in the two sch explored, and has evidence of antitumor activity. Enrollment is ongoing at DL3. Updated results will be presented.

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Effects of ZD6474, an orally active inhibitor of VEGF receptor tyrosine kinase, in patients with solid tumors: Results from a phase I study

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ZD6474 is a novel, orally active inhibitor of the tyrosine kinase associated with vascular endothelial growth factor (VEGF) receptor-2 (KDR). A phase I study with this agent is being conducted at 5 sites (in the US and Australia). Patients with measurable progressive malignancies despite treatment, or tumors for which there are no treatments, are given a single dose of ZD6474 followed 1 week later by the initiation of chronic once-daily dosing at the same level. Samples for pharmacokinetic analysis are collected after the single dose and during chronic treatment. ZD6474 administration continues at the assigned dose level until disease progresses, dose-limiting toxicity intervenes, or the patient withdraws consent. To date, 41 patients have been treated at 5 dose levels; 50, 100, 200, 300 and 500 mg/d. Treatment for over 100 days has proved feasible at the first 4 dose levels and for over 30 days at the 500 mg/d level to date. All patients are evaluable for safety. No hematologic, renal, hepatic or GI toxicity has been observed. Skin changes ranging from Grade I to III have been observed. At this time, dose-limiting toxicity has not been observed and the maximum tolerated dose not determined. Pharmacokinetic analysis demonstrates dose-dependent increases in exposure to ZD6474. For example, Cmax and AUC in the 50mg cohort were 21.8 ng/ml and 3.22 ug-hr/ml, respectively, whereas in the 300mg cohort, they were 222 ng/ml and 23.8 ug-hr/ml, respectively. Elimination half-life ranged between 71.7 and 206 hours across all dose levels. Accrual is continuing at higher doses, and markers of biological activity are being evaluated.

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A phase I study of BAY 38-3441 given as a short infusion daily for five days every 3 weeks. a National Cancer Institute of Canada Clinical Trials Group Study

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Purpose: BAY 38-3441 consists of camptothecin conjugated to a carbohydrate moiety with a peptide spacer. The peptide-carbohydrate portion of the molecule stabilizes the active lactone form of camptothecin in blood and thereby increases the proportion of the lactone available for uptake into tumour cells. The compound is active in a range of human tumour xenografts, including MX-1, LXFL529, CXF280 and HT29. A phase I study of BAY 38-3441 given as a short infusion for 5 days was initiated in May 2000.

Methods: The starting dose was 14mg/m2 (1/10th the MTD in the most sensitive species). 3-6 pts were enrolled to each dose level (DL) and doses were doubled in the absence of * grade 2 toxicity. Endpoints included the definition of the recommended phase II dose (RP2D), the maximum dose (MTD) administered, toxicity and pharmacokinetics (PK). Eligible patients (pts) included those with ECOG PS 0-2, no more than 2 prior chemotherapy regimens for metastatic disease, no prior history of life threatening allergic reactions, and acceptable organ function.

Results: 13 pts have been entered to 4 DLs and have received a total of 30 cycles of BAY 38-3441; 2 pts received 9 and 4 cycles of BAY 38-3441, respectively. Currently, 10 pts are evaluable; 6 pts are male, the most common tumour types are head and neck cancer (3 pts) and ovarian cancer (2 pts), 7 pts had PS of 0 or 1, 7 pts had 2 or more sites of disease and 3 pts had had 2 prior regimens. Grade 1 or 2 nausea, stomatitis, dyspepsia, alopecia, pruritis, fever and ocular symptoms have been the only toxicities noted to date; 1 patient had grade 1 granulocytopenia and occasionally pts have had grade 1 increases in liver function tests. No antitumour activity has been seen to date. PK appears to be dose dependent but not linear with some evidence of accumulation for the lactone form of camptothecin on day 5; T1/2 is 1.5 &2 hours for parent compound and ± 40 hours for camptothecin.

Conclusions: Toxicity to date has been minor, and dose escalation continues.

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Phase I study of Caelyx and Carboplatin (Cp) in patients with advanced or metastatic solid tumors

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Pegylated liposomal doxorubicin (Caelyx,Doxil) has a unique toxicity profile, minimal hematological toxicity but dose limiting skin toxicity. Caelyx (C) is active in ovarian carcinoma. We combined C and Cp in phase I dose escalating trial to determine the maximal tolerated dose (MTD), dose limiting toxicity (DLT) and recommended phase II doses (RD) of this schedule. Cp AUC 5 was given as 30min iv infusion followed by 1hour rest and C as 60min iv infusion or inverse sequence, every 3 weeks. DLT were: grade (gr) 4 neutropenia (np) > 7 days, febrile np, gr 4 thrombopenia, gr 3 or 4 non hematological tox or persistence of gr >2 hematological tox at day 35.

22 pts were enrolled at 3 dose levels (C in mg/m2: 30, 35,40). Dose escalation followed continued reassessment method. Median age 53 [19-70]. Tumor type: cervix (1), head and neck (6), lung (3), endometrial (2), esophagus (2), melanoma (1), sarcoma (1), ovarian (4), rectal (1), renal (1). Median PS:1. Median number of cycles:2[1-6]. 4 pts are still on treatment. No cardiac tox, no skin tox, no toxic death occurred. Similar tox with the two sequences.

Level: 30MG/m2, DLT (3/8):Thrombopn gr4(1),prolonged np(1)Febrile np(2);level 2: 35mg/m2: DLT 2/8: Febrile np (1, prolonged np (1); level 3: 40mg/m2, DLT 2/6: abdominal pain (1) febrile neutropenia (2) thrombopenia gr4 (1)

Recommended schedule: Caelyx 35 mg/m2+Cp AUC5 in outpatient setting every 28 days lead manageable toxicity. Inverse sequence is similar. Anti tumor activity (PR2, SD1,PD5) merits further clinical evaluation.

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Phase I and pharmacokinetic study of capecitabine and cisplatin in head and neck cancer patients

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The cisplatin-5fluorouracil (5FU) combination is considered to be one of the standard treatments for patients with squamous cell carcinoma of the head and neck. Capecitabine (Xeloda) is an oral fluoropyrimidine which is preferentially activated at the tumoral level, exploiting higher TP activity in tumor tissue. Oral capecitabine mimics continuous infusion 5FU and therefore can conveniently replace 5FU in this setting. This study was conducted in patients with locally recurrent or metastatic head and neck carcinoma who were able to swallow. Treatment design: cisplatin was infused over 1 hour every 28 days followed by capecitabine twice daily from day 2 to day 15 with a 2-week rest period. Pharmacokinetic analysis (HPLC) included plasma levels of unchanged capecitabine, 5'DFCR, 5'DFUR and 5FU. Lymphocytic dihydropyrimidine dehydrogenase (DPD) activity was determined for each patient before and during treatment. 14 patients have been included so far. Dose (mg/m2) increments were for cisplatin and capecitabine (b.d.), respectively: level 1: 80, 1000 (4 patients, 11 cycles); level 2: 100, 1000 (6 patients, 14 cycles); level 3: 100, 1125 (4 patients, 10 cycles). Toxicities (grades 3, 4) were observed on level 2 (1 patient with mucositis, diarrhea and hand-foot syndrome) and on level 3 (1 patient with hematological toxicity-related death). Evidence of antitumor activity was also observed in 4 patients achieving an objective response.

The trial is still ongoing in order to identify the maximal tolerated dose and to define recommended doses for further phase II studies, taking into account the pharmacokinetic-pharmacodynamic data.

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Phase I and pharmacokinetic study of irinotecan and paclitaxel in patients with lung cancer

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Purpose: Paclitaxel and Irinotecan have shown significant anti-tumor activity in lung cancer as a single agent. In order to determine maximum tolerated dose(MTD) and recommended dose, and to examine pharmacokinetic character in this combination.

Methods: Eligibility criteria included age 75 or less than years old; performance status 1 or 2; adequate organ function; unresectable non-small cell lung cancer (NSCLC) or extensive disease of small cell lung cancer (ED-SCLC). Irinotecan was administered over 90 min. on day 1 and 8, paclitaxel was given over 3 h. infusion on day 8 after 90 min. from the end of irinotecan infusion. The treatment was repeated every three or four weeks. After MTD was determined without preventive G-CSF support, we tried dose-up with preventive G-CSF support from day 9. We also examined the pharmacokinetics of irinotecan, its metabolites and paclitaxel on both day 1 and 8.

Results: This study reached MTD without preventive G-CSF support in the doses: irinotecan(C) 60 mg/m2 and paclitaxel(P) 135 mg/m2. The dose limiting toxicities are neutropenia and febrile neutoropenia. The study is still going on in the following doses: C 60 mg/m2 and P 175 mg/m2 with G-CSF support. Until now 27% (4/15) patients with NSCLC achieved partial response, and all (5/5) patients with ED-SCLC achieved partial response.

In pharmacokinetic analysis, remarkable drug-drug interaction between irinotecan and Taxol was observed. To date we analyzed 13 patients' pharmacokinetic data. The AUCs of irinotecan and its metabolites on day 8 are significantly higher than on day 1. Apparent rebound increases of plasma concentrations of irinotecan and its metabolites is also observed in some patients. It may be considered that Taxol is excreted with irinotecan and its metabolites competitively, and that Taxol chenges their distribution volume.

AUC:	CPT-11	SN-38	SN-38G (μg.ml-1.min)
day 1:	201.53 ± 100.17	5.02 ± 4.56	99.16 ± 106.13 (mean ± S.D.)
day 8:	276.16 ± 130.14	7.64 ± 6.42	182.70 ± 195.00

p-value: <0.0001; 0.0159; 0.0441. p-values are calculated by paired t test.

Conclusion: The toxicities of this combination is mainly hematologic toxicities. Non-hematologic toxicities are mild. Taxol makes AUCs of irinotecan and its metabolites higher in this combination chemotherapy.

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A phase I trial of ZD9331 administered by infusion to Japanese patients with refractory solid malignancies

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Aims: ZD9331 is a direct-acting, cytotoxic antifolate which is a product of rational structural design. ZD9331 is actively transported into cells and, because it does not require polyglutamation, it is not affected by the folylpolyglutamyl synthetase/hydrolase status of tumours. The primary aim of this Phase I study was to investigate the tolerability of ZD9331 when administered by iv infusion to Japanese patients with refractory solid tumours. Secondary objectives included the assessment of the efficacy and pharmacokinetic (PK) parameters of ZD9331 to allow a preliminary comparison of the PK data with those from a similar study in the UK.

Methods: Three escalating dose levels of ZD9331 (69, 108 and 130 mg/m2) were administered by a 30-min infusion on D1 and 8 of a 3-wk cycle. Blood samples were collected for PK analysis during the first cycle.

Results: 12 patients (5M/7F; mean age 57 yrs [range 36-70]) underwent a total of 37 cycles of treatment. Tumour types were gastric (5 pts), colorectal (2), breast (1), gall bladder (1), leiomyosarcoma (1), lung carcinoid (1) and myxoma (1). Dose-limiting toxicities were identified in 2 patients at the 69 mg/m2 (G4 neutropenia, G4 thrombocytopenia) and 130 mg/m2 dose (G4 febrile neutropenia, G4 thrombocytopenia). The maximum tolerated dose has yet to be reached. ZD9331 showed a variable toxicity pattern, generally of myelosuppression including G3/4 lymphocytopenia (6 pts), neutropenia (3), leucocytopenia (2), haemoglobin decrease (2), thrombocytopenia (1) and hepatic transaminase elevation (3). Across the range of doses, similar toxicities to the UK study were seen (neutropenia, leucocytopenia, haemoglobin decrease, nausea and hepatic transaminase elevation). Disease was stabilised in 3 patients who had received >4 cycles of treatment. An improvement in clinical symptoms was seen in 1 gastric cancer patient. AUC and Cmax increased as treatment dose increased.

PK parameters (CL, Vss and t1/2) were similar to those in the UK study. Mean (SD) values at 69, 108 and 130 mg/m2 dose levels were: CL 13.0 (3.70), 19.6 (5.23) and 11.0 (1.57) mL/min; Vss 15.5 (3.81), 29.0 (12.3) and 16.8 (5.77) L; t1/2 35.5 (7.0), 39.1 (13.2) and 44.1 (8.2) h.

Conclusion: Intravenous ZD9331 was well tolerated and showed evidence of efficacy in Japanese patients with refractory solid malignancies. Preliminary PK and toxicity data from this study are similar to those from an earlier UK study.

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ZD9331 in combination with gemcitabine in patients with refractory solid tumours - a phase I study

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Rationale: ZD9331 is a novel antifolate rationally designed as a selective thymidylate synthetase (TS) inhibitor with no requirement for polyglutamation. Thus, it may overcome resistance to other TS inhibitors arising due to alteration in folylpolyglutamate synthetase expression. This Phase I dose-escalation study was designed to determine the recommended dose schedule for ZD9331 in combination with gemcitabine (GEM), a nucleoside analogue antimetabolite, and to describe the toxicity, pharmacokinetics and antitumour activity of this combination. As both agents may decrease the deoxynucleotide triphosphate pools, some synergistic cytotoxicity was expected.

Methods: Sequential cohorts of patients with refractory solid tumours and WHO PS 0/1 were recruited. On the initial schedule, patients received ZD9331 and GEM on Days 1 and 8 of a 21-day cycle. Each drug was given as a 30-min infusion, with GEM infused 30 min after completion of the ZD9331 infusion.

Results: To date, 23 patients (pts) have been recruited (M/F 9/14; mean age 49.4 years [range 26-75]) with a variety of tumour types. In the initial cohort treated with GEM 800 mg/m2 and ZD9331 65 mg/m2, dose-limiting toxicity (DLT) was seen in 5/7 pts (neutropenia with fever [2]; failure to deliver on Day 8 due to myelosuppression [3]). The schedule was changed with the order of drugs reversed and ZD9331 administered 90 min after GEM. However, in this second cohort treated with GEM 500mg/m2 and ZD9331 65 mg/m2, DLT (failure to deliver on Day 8 due to myelosuppression) was seen in 5/6 pts. The schedule was again changed with elimination of the Day 8 dose of ZD9331. DLT was still observed in 2/5 pts (platelet count <25x109/L and grade 3 bilirubin [1]; grade 3 diarrhoea [1]). The treatment schedule was amended further with GEM given alone on Day 1 and GEM followed by ZD9331 administered on Day 8. Following an initial cohort at GEM 500 mg/m2 and ZD9331 65 mg/m2, the dose of GEM has subsequently been escalated to 650 mg/m2. Accrual is ongoing. Other adverse events reported include fatigue, mild nausea, mild fever, abnormal liver function tests and rash. Pharmacokinetic assays have revealed no significant interaction between ZD9331 and GEM. No objective responses have yet been observed.

Conclusion: Although the combination of ZD9331 and GEM results in significant toxicity, this trial demonstrates that a combination schedule is feasible.

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A phase I dose-escalation study of zd0473 combined with paclitaxel in refractory solid malignancies

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Aims: ZD0473 (cis-amminedichloro[2-methylpyridine]platinum [II]), a new