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

generation platinum drug designed to have an extended spectrum of antitumour activity and overcome platinum resistance mechanisms, has shown synergistic in vitro activity in combination with paclitaxel. The purpose of this ongoing Phase I trial is to evaluate the safety of ZD0473 in combination with paclitaxel, in patients with refractory solid malignancies.

Methods: Patients received a 3-hour iv infusion of paclitaxel, followed after 30 min by a 1-hour infusion of ZD0473, repeated every 3 weeks.

Results: To date, 17 patients (NSCLC [12 patients], mesothelioma [3], SCLC [2]) have been recruited and have received paclitaxel/ZD0473 combinations at doses of 135/60, 135/90, 135/120, 150/120, or 175/120 mg/m2. The median (range) of treatment cycles received to date is 3 (1-6), with 8 patients having received at least 4 cycles of treatment. During the first treatment cycle myelosuppression was mild: 1 patient had grade 3/4 anaemia; there were no incidences of grade 3/4 thrombocytopenia or neutropenia. Nine patients were withdrawn due to disease progression. So far, no patients have experienced dose-limiting toxicity. Stable disease was observed in 9 of the 13 evaluable patients, including 3 patients with NSCLC who experienced a reduction in tumour size of ~10%. The median number of treatment cycles received by patients with stable disease was 4 (range 2-6).

Conclusion: The ZD0473 and paclitaxel combination is well tolerated and shows encouraging stable disease in patients with solid tumours.

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A phase I study of weekly Oxaliplatin (OXA) + continous infusion (CI) fluorouracil (FU) in patients with advanced colorectal cancer (CCR)

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A combination of OXA and FU is frequently used as 1st or 2nd line treatment for advanced CCR. However, the optimal schedule for this combination has not been defined. Weekly administration of OXA may result in decreased acute toxicity and increased dose intensity compared to bi- or tri-weekly administration. The purpose of this study was thus to identify the MTD of weekly OXA (4 dose levels: 60-70-80-90 mg/m2 on days 1, 8, 15) in combination with a fixed daily dose of CI FU (200mg/m2/die d1à21) + Leucovorin (LV), with cycles repeated every 4 weeks. Since April 2000, 20 patients with progressive advanced CCR, previously treated with or ineligible for 5-FU and CPT-11 were accrued (13 males, 7 females; median age 68 years; median ECOG PS 1; median CEA 31.5 ng/ml).

Overall, 56 cycles were delivered corresponding to 163 weeks of chemotherapy. The median number of cycles administered to each patient was 2 (range 1-6) and the median number of weeks of chemotherapy was 6 (range 3-18). Fifteen of 163 weeks of chemotherapy were delayed because of toxicity while 6 of 163 weeks were delivered at a reduced dose. Considering the first 2 cycles of treatment (2 months), no grade III-IV toxicity was observed up to dose level 4 (OXA 90 mg/m2). Three patients presented grade I thrombocytopenia lasting 19, 14 and 14 days, respectively. Three out of 6 patients treated at dose level 4 (OXA 90 mg/m2) required a major change in the treatment program (discontinuation, delay longer than 14 days or dose reduction) because of constitutional symptoms (asthenia, weight loss and unbearable peripheral sensory neuropathy). This was thus deemed to be the MTD for OXA in this combination. Among 15 patients with measurable disease completing at least one treatment cycle 1 PR, 4 MR, 7 SD and 3 P were obtained. Overall, disease progression was abrogated in 12 of 18 evaluable patients. Three patients with initially unresectable liver metastases underwent secondary resection with curative intent.

These results demonstrate that the combination of weekly OXA and low-dose CI FU is feasible and well tolerated. This regimen allows to deliver a higher dose intensity of OXA compared to bi-weekly or tri-weekly schedules and shows a promising antitumor actvity in heavily pretreated patients. The study is now continuing to assess the possibility of incorporating LV (20 mg/m2, d1, 8, 15) at the OXA dose level below the MTD (80 mg/m2).

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A phase I, dose-escalation study of the novel antifolate zd9331 in combination with cisplatin in patients with refractory solid malignancies

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Introduction: ZD9331 is a new antifolate cytotoxic that inhibits thymidylate synthase and does not require polyglutamation for its activity.

Objectives: To determine the maximum tolerated dose (MTD) for ZD9331 in combination with cisplatin and to assess the tolerability, pharmacokinetic and antitumor activity of the combination.

Methods: Thirteen patients with refractory solid tumors have been entered to date. ZD9331 was administered as a 30-min iv infusion on days 1 and 8 of a 21-day cycle. Cisplatin was administered after ZD9331 as a 30- to 60-min infusion on day 1. The MTD was defined as that which caused dose-limiting toxicity (DLT) in ~2/6 patients.

Results: Patients entered on one of three dose levels: ZD9331/cisplatin 100/50 (n=3), 130/50 (n=6) and 130/75 (n=4) mg/m2. Baseline performance status (PS) was good (PS 0 in 3 patients, PS 1 in 10 patients), and most patients had received prior chemotherapy. The majority of patients had thoracic malignancies. DLT was observed in 2 patients at 130/75. Both had grade 3/4 neutropenia requiring the day 8 dose of ZD9331 to be withheld. A third patient at this dose level experienced similar toxicity on his second cycle of treatment. Other toxicities include thrombocytopenia, anemia, fatigue, nausea, vomiting, and stomatitis. Accrual to the 130/50 dose level continues. Of the 13 patients entered, there has been 1 partial response in a patient with mesothelioma. Patients with mesothelioma and breast cancer also have stable disease.

Conclusions: The combination of ZD9331 and cisplatin is well tolerated and has antitumor activity.

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Phase I study of weekly paclitaxel and liposomal doxorubicin in patients with advanced solid tumours

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Objectives: Paclitaxel has a broad spectrum of toxicity against the most common human tumours. Weekly administration of paclitaxel may improve the toxicity profil of the drug increasing its efficacy. Liposomal doxorubicin (Caelyx) has shown similar to conventional doxorubicin's activity with much more favorable toxicity profil. A phase I study was conducted to determine the maximum tolerate dose (MTD) and the dose limiting toxicities (DLTs) of the combination of the two drugs administered weekly in patients with advanced solid tumours.

Patients and Methods: Escalating doses of Caelyx (6–12 mg/m^2) were administered as a 1 h IV infusion and a fixed dose (80 mg/m^2) of paclitaxel as a 3 h IV infusion on the same day for 4 consecutive weeks in a 6 week cycle. Nineteen previously treated patients with histologically confirmed advanced stage solid tumours were enrolled.

Results: The MTD was reached at the dose-level Caelyx 10 mg/m^2 + paclitaxel 80 mg/m^2. The DLTs were evaluated after the first cycle and consisted in all cases of grade 3 neutropenia resulting in treatment delay. A total of 55 cycles have been administered: Grade 2–3 neutropenia was observed in 7 (14%) cycles and grade 4 anemia in 1 (2%) cycle. Non hematologic toxicity included grade 2–3 nausea-vomiting in 5 (9%), grade 2–3 diarrhea in 4 (7.2%), grade 2–4 fatigue in 7 (12.7%) and grade 2 mucositis in 1 (1.8%) of the cycles. No cardiotoxicity, as determined by the development of CHF or more than 10% reduction on LVEF was observed. Among 12 evaluable patients, 1 PR was observed in a patient with ovarian cancer.

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A phase I study of the caelyx - Oxaliplatin combination in patients with advanced solid tumors

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Background: Caelyx is a liposomal doxorubicin formulation with low toxicity and high activity in various tumors. Oxaliplatin (L-OHP) is a new platinum analog with improved toxicity profile and only partial cross resistance with cisplatin and carboplatin. We conducted a phase I study to evaluate the MTD and DLT of the Caelyx-L-OHP combination.

Patients and Treatment: Caelyx was administered on day 1 as an 1-hour IV infusion at escalating doses of 25–35 mg/m^2 followed by L-OHP as a 2-hour IV infusion at doses of 80–100 mg/m^2. Cycles were repeated every 3 weeks without growth factors. Eighteen patients with advanced stage carcinomas have been entered. Median age 60, PS (WHO) 0:6, 1:9, 2:3. Treatment was 1st line for 5 (28%), 2nd line for 7 (39%) and 3rd line for 6 (33%) pts. DLT was evaluated during the first cycle of treatment and included any grade 4 hematologic toxicity, neutropenia grade 3–4 with