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