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POSTER DISCUSSION

Phase I trial of ZD9331 in adult patients with refractory solid malignancies administered by 30-min infusion on days 1 and 8 with the cycle repeated every 3 weeks

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Introduction: ZD9331 is a novel, potent, folate-based inhibitor of thymidylate synthase. Unlike raltitrexed, ZD9331 does not require polyglutamation for activity and thus may have a different spectrum of antitumour activity.

Methods and Results: Eleven escalating dose levels of ZD9331 (4.8 to 162.5 mg/m²/day × 2) have been administered by 30-min infusion on days 1 and 8 of a 3-week cycle to adult patients (pts) with refractory solid malignancies. To date, 54 pts have received up to 11 cycles of treatment. Tumour types comprised ovary (18), colorectal (19), breast (1), melanoma (3), lung (3), sarcoma (3), gastric (1), bladder (1), renal (1), pancreas (1), head and neck (1), and mesothelioma (1). The major toxicity has been myelosuppression with grade IV (CTC grading) neutropenia and/or thrombocytopenia occurring in 1 or more pts at doses of 32, 55, 69, 130 and 162.5 mg/m²/day. Other toxicities have included fatigue, rash, diarrhoea, nausea, vomiting, and mucositis; mild to moderate transient rises in liver transaminase activity have been seen at all dose levels. 1 pt at 130 mg/m²/day developed severe tiredness necessitating a dose reduction to 108 mg/m²/day. Of the 5 pts who have been treated at 162.5 mg/m²/day, 2 pts experienced dose-limiting toxicity (DLT) [1 pt had grade IV neutropenia, thrombocytopenia, and grade II mucositis and diarrhoea, and 1 pt had grade III diarrhoea after 3 days of treatment]. Due to the toxicities observed at a dose of 162.5 mg/m²/day, the 130 mg/m²/day dose level is to be expanded (8 pts have been treated to date). AUC and C_{max} increased with increasing dose level. The mean (SD) clearance, V_{ss}, and elimination t_{1/2} were 13.5 (5.9) mL/min, 28.3 (12.2) L, and 62.8 (28.1) h, respectively. Plasma deoxyuridine levels were elevated following treatment, suggesting in vivo inhibition of thymidylate synthase by ZD9331. Encouraging evidence of antitumour activity has been seen in melanoma, ovarian, colon, pancreatic and breast cancer.

Conclusion: The maximum tolerated dose has been reached at 162.5 mg/m²/day. Further patients are to be recruited at the likely recommended dose of 130 mg/m²/day.

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Evaluation of the factors influencing the clearance of the novel thymidylate synthase inhibitor ZD9331

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Objectives: ZD9331 is a novel, potent specific thymidylate synthase inhibitor which does not require polyglutamation for its activity. This Phase I study was conducted to evaluate the feasibility of a once 3-weekly regimen of ZD9331.

Methods and Results: ZD9331 was administered to 42 patients (pts) (age range 37–81 yrs) as a 30-min infusion once every 3 weeks at escalating dose levels of 4.8 (3 pts), 9.6 (3 pts), 19.2 (3 pts), 32 (3 pts), 48 (6 pts), 67 (3 pts), 89 (6 pts), 118 (3 pts), 157 (3 pts), 209 (3 pts), 278 (3 pts), and 370 (3 pts) mg/m². Grade IV myelosuppression was experienced by 1 pt at 48 mg/m² and another at 89 mg/m², although no grade IV hematologic toxicity was observed at the higher dose levels. 2 pts at 67 mg/m² and 1 pt at 89 mg/m² developed grade IV diarrhea. Transient, isolated, asymptomatic grade I–III transaminase elevations occurred at all dose levels. Other mild to moderate sporadic toxicities included nausea, vomiting, skin rash and fatigue.

Pharmacokinetic analysis indicated that the 2 pts with grade IV myelosuppression had higher AUC values (430 and 691 microg.h/mL) and lower plasma clearance values (3.61 and 3.71 mL/min) compared with other pts treated at the same dose levels who did not experience hematologic toxicity (mean AUC 190 and 259 microg.h/mL; mean clearance 11.0 and 15.2 mL/min, at 48 mg/m² and 89 mg/m², respectively). To explore the variables affecting ZD9331 clearance, the administered dose, RBC folate, total protein, creatinine clearance, age, BSA, albumin and total bilirubin were evaluated in a multivariate regression model. Positive and statistically significant (p [less than] 0.05) correlations were observed between the

clearance of ZD9331 and the administered dose, RBC folate, total protein and creatinine clearance.

Conclusions: A single dose of ZD9331 administered once every 3 weeks was well tolerated up to a dose of 370 mg/m². Determination of the factors influencing the clearance of ZD9331 in other Phase I studies, and future Phase II studies, should improve our understanding of interpatient variability observed in the pharmacokinetics and pharmacodynamics of ZD9331.

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POSTER DISCUSSION

A Phase I study of taxotere (T) and gemzar (G) in patients with advanced solid tumors: Impact of drug sequence and feasibility

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A phase I study was performed to determine the feasibility of T + G, repeated every 3 weeks. At the recommended dose (G: 800 mg/m², d1&8, T: 85 mg/m², d8) the impact of the drug sequence was investigated. 14 patients were treated at 2 dose levels. 7 M/7 F; med age 55 (21–75); mad WHO PS: 1 (0–1); tumor types: breast, bladder, penis, NSCLC, melanoma, leiomyosarcoma and prostate (1 of each), ovarian (2), H&N (2), renal cell (3). 10/14 pts received previous chemotherapy.

	Dose level I G: 800 mg/m ² d1&8 T: 85 mg/m ² d8		Dose level II G: 1000 mg/m ² d1&8 T: 85 mg/m ² d8
	d8: T + G, N = 6 pts	d8: G + T, N = 4 pts	d8: T + G, N = 4 pts
Nb of cycles (cy)	25	10	12
% of cycle reduced	12	40	16
Neutropenia gr 4	51% of cy		50% of cy
DLT (gr3/4): Febrile neutropenia, diarrhea, stomatitis	2/6 pts	3/4 pts	3/4 pts
Objective response	1 CR, 2 PR ovary, kidney prostate	1 PR Head & Neck	2 PR bladder, breast

Conclusion: The combination of T + G is active in both sequences but when gemcitabine is given before Taxotere on day 8 is more toxic. Analysis of pharmacokinetic data is ongoing, will be presented and might explain the clinically observed heavier toxicity.

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POSTER

MTA (LY231514) demonstrates clinical activity against malignant mesothelioma in a phase I combination trial with carboplatin

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Purpose: MTA, a novel antifolate which inhibits multiple enzymes, has shown anti-tumour activity in non-small cell lung, breast, and colon cancers in Phase II clinical trials. The primary objective of this ongoing study is to determine the maximum tolerated dose (MTD) of the combination of MTA and carboplatin (carbo) in patients (pts) with advanced solid tumours.

Methods: Of 10 pts treated to date, all had malignant mesothelioma. Six pts entered at the 1st dose level – MTA 400 mg/m² by 10-min iv infusion, followed by a 30-min iv infusion of carbo, which was dosed to achieve an AUC of 4. Four pts have been treated at dose level 2, with MTA unchanged and carbo escalated to an AUC of 5.

Results: 49 courses of treatment have been administered [range 1–9]. One pt withdrew and 1 pt died, unrelated to treatment or disease. Of the 8 pts who have received a minimum of 2 courses, each has reported an improvement in symptoms. Of 6 pts formally assessed for response using CT scan measurements, 1 pt has measurable disease, 5 have evaluable disease only. One pt has demonstrated a partial response in non-measurable disease (PRNM) after 4 courses of treatment, with the other 5 showing stable disease. In 34 courses evaluated for toxicity, treatment has been well tolerated. Three CTC grade 3 study-drug related events have been observed on the first dose level, neutropenia in a single patient, and transient transaminase elevations in two patients. One patient at dose level 2 experienced grade 3 myelosuppression in the first two courses of treatment, but this did not lead to clinical problems.