1143 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

R. Plummer[1], C. Rees[2], I. Judson[2], H. Calvert[1], M. Highley[1], J. Trigo[2], A. Jackman[2], R. Smith[3], M. Hutchison[3], M. Smith[3]. [1]*University of Newcastle upon Tyne;* [2]*Institute of Cancer Research, Surrey;* [3]*Zeneca Pharmaceuticals, Alderley Park, United Kingdom*

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/m[2]/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/m[2]/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/m[2]/day developed severe tiredness necessitating a dose reduction to 108 mg/m[2]/day. Of the 5 pts who have been treated at 162.5 mg/m[2]/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/m[2]/day, the 130 mg/m[2]/day dose level is to be expanded (8 pts have been treated to date). AUC and Cmax increased with increasing dose level. The mean (SD) clearance, Vss, and elimination tΠ 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/m[2]/day. Further patients are to be recruited at the likely recommended dose of 130 mg/m[2]/day.

1144 POSTER DISCUSSION

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

S.G. Diab[1], S.Y. Rha[2], C. Britten[2], S.D. Baker[2], R. Smith[3], L. Hammond[2], A. Newman[2], E. Douglass[4], D. Von Hoff[2], E. Rowinsky[2]. [1]*University of Texas Health Science Center, San Antonio, TX;* [2]*Cancer Therapy and Research Center, San Antonio, TX, United States;* [3]*Zeneca Pharmaceuticals, Alderley Park, United Kingdom;* [4]*Zeneca Pharmaceuticals, Wilmington, DE, United States*

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/m[2]. Grade IV myelosuppression was experienced by 1 pt at 48 mg/m[2] and another at 89 mg/m[2], although no grade IV hematologic toxicity was observed at the higher dose levels. 2 pts at 67 mg/m[2] and 1 pt at 89 mg/m[2] 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/m[2] and 89 mg/m[2], 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/m[2]. 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.

1145 POSTER DISCUSSION

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

H. Dumez[1], M. Louwerens[2], D. Tonelli[4], I. Avril[4], A. Pawinski[3], A.T. Van Oosterom[1], J. Verweij[2]. [1]*University Hospital Gasthuisberg, Leuven, Belgium;* [2]*Rotterdam Cancer Institute, Rotterdam, Netherlands;* [3]*Curie Memorial Cancer Center, Warsaw, Poland,* [4]*Rhone-Poulenc Rorer, Antony, France*

A phase I study was performed to determine the feasability of T + G, repeated every 3 weeks. At the recommended dose (G: 800 mg/m^2, d1&8, T: 85 mg/m^2, 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.

1146 POSTER

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

A.H. Calvert, A.N. Hughes, P.M. Calvert, R.E. Plummer, M.S. Highley. *Department of Medical Oncology, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE, United Kingdom*

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/m^2 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.

Conclusion: MTA and carbo have been safely administered to date. One pt of 6 evaluable for response has a PRNM. 5 pts have stable disease and no pt has progressed. Recruitment continues to establish the MTD of this active combination.

1147 POSTER

Pharmacokinetics (PK) of BMS-184476, a new taxane analog, given weekly in patients with advanced malignancies

A.H. Calvert[1], C. Sessa[2], A. Hughes[1], U. Jochim[2], P. Calvert[1], M. Ghielmini[2], J. Renard[3], E. Gupta[4], D. Sonnichsen[4], G. Gallant[3]. *[1]Newcastle General Hospital, Division of Oncology, Newcastle-upon-Tyne, United Kingdom; [2]Ospedale San Giovanni, Department of Oncology, Bellinzona, Switzerland; [3]Bristol-Myers Squibb, Oncology Clinical Research Europe, Waterloo, Belgium; [4]Bristol-Myers Squibb, Human Pharmacology and MAP, Princeton, United States*

BMS-184476 is a new taxane analog with superior activity in a number of experimental tumor models and has a much reduced purified polyoxyethylated castor oil content as compared to paclitaxel. The main objectives of this study were to establish the maximum tolerated dose (MTD), the dose-limiting toxicities, and the PK of BMS-184476 given weekly on day (d) 1, 8 and 15 by a 1-hour infusion in patients (pts) with advanced malignancies. Courses were repeated every 28 d. No pre-medication was given. An accelerated Phase I design using single pt cohorts, rapid (100%) dose escalation and intra-patient dose escalation (IPDE) was used. When predefined toxicity was observed, a standard Phase I design (3–6 pts cohort) with IPDE was to be used. 36 pts (9 breast, 8 NSCLC, 4 colon, 2 sarcomas, 2 ovary, 2 SCLC, 9 others) -14 males and 21 females- with a median age of 55 years (range: 32–72) and a median performance status of 1 (range: 0–2) were enrolled. Plasma and urine PK data were obtained for 20 pts (7, 28, 40 or 50 mg/m^2); 17 with D1 & D15 data. CMAX and AUC (0–24 h) values for both D1 & D15 increased in a dose-related manner. At 40 mg/m^2, mean (SD) CMAX and AUC (0–24 h) values were 1073 (219) nM and 2038 (432) nM*h, respectively (n = 20 courses/11 patients). Across all dose levels, mean T1/2 values ranged from 33 to 42 hours, based on a 48 h sampling interval. Mean CLT and Vss values ranged between 140 to 225 mL/min/m^2 and 294 to 502 L/m^2, respectively. Relative to parent BMS-184476, plasma exposures of known metabolites were low (typically <2%). Cumulative renal elimination of BMS-184476 and metabolites was low (<5% of dose). Data from patients with PK studies on D1 and D15 support that little intrapatient variability exists for BMS-184476 PK. MTD has not been reached and the study is currently enrolling patients at 60 mg/m^2.

1148 POSTER

Phase I trial of sequential administration of tomudex and 5-iodo-2′-deoxyuridine (IdUrD)

E. Galanis[1], R. Goldberg[1], C. Erlichman[1], J. Sloan[1], J. Reid[1], H. Pitot[1], S. Safgren[1], P. Atherton-Skaff[1], T. Witzig[1], M. Ames[1]. *[1]Mayo Clinic, Rochester, MN, United States*

Tomudex (TOM) is a specific inhibitor of thymidylate synthase with clinical activity in colorectal cancer. We have demonstrated in vitro synergism between TOM and IdUrd (a cytotoxic pyrimidine analog) against colon and bladder human carcinoma cell lines as well as increased IdUrd incorporation into DNA (Pressacco J, Cancer Res 54: 3772, 1994). We have completed a phase I trial to determine the MTD, pharmacokinetics and biologic effects of escalating doses of the combination, with the IdUrd given as a 24° infusion after a TOM 15 min infusion. To date, we have treated 34 patients (pts). Pt characteristics were: median age 62 (range 29–83), M (21), F (13), ECOG PS 0 (17), 1 (16), 2 (1). Tumor types: colorectal (25), esophagus (2), small bowel (3), melanoma (2), liver (1), unknown (1). Median number of cycles was 2 (range 1–8). Dose limiting toxicity occurred at dose level 8 (TOM = 2.5 mg/m^2 and IdUrd = 10,400 mg/m^2) with 2/3 pts experiencing grade 4 neutropenia. 18 of the 34 pts had grade 3 and 4 pts had grade 4 toxicities: neutropenia (14 Gr 3, 4 Gr 4), anemia (1 Gr 3), chills (1 Gr 3), stomatitis (1 Gr 3), dermatotoxicity (1 Gr 3). Antitumor activity was observed (1 PR, 15 SD, 13 PROG, 29 evaluable pts). Mean plasma Css of IdUrd, 22 hr IodoUracil level and IdUrd incorporation in the peripheral mononuclear cells (examined by use of the monoclonal antibody BU-1) were measured and results will be presented. Our recommended phase II dose is TOM = 2 mg/m^2 and IdUrd = 10,400 mg/m^2. We are currently treating an additional cohort of 9 pts at the phase II dose in order to determine the effect of TOM on IdUrd dispositionand DNA incorporation. (Supported by grants CA69912, CA15083, RR00585.)

1149 POSTER

Phase I trial of ZD9331, a non-polyglutamatable thymidylate synthase inhibitor given as a 5-day continuous infusion every 3 weeks

J. Trigo[1], C. Rees[1], P. Beale[1], F. Mitchell[1], A. Jackman[1], R. Smith[2], M. Hutchison[2], M. Smith[2], I. Judson[1]. *[1]Institute of Cancer Research, Surrey; [2]Zeneca Pharmaceuticals, Alderley Park, United Kingdom*

Objectives: ZD9331 is a potent folate-based thymidylate synthase (TS) inhibitor, actively transported by the reduced folate carrier. It is not a substrate for folylpolyglutamate synthetase (FPGS) and may, therefore, overcome resistance due to altered FPGS expression, affecting both the toxicity profile and spectrum of antitumour activity. This Phase I study investigated a 5-day continuous iv infusion every 3 weeks.

Methods and Results: 44 patients (16 M/28 F), median age 53 (range 31–76) years, have been treated at 0.125 (3), 0.25 (3), 0.4 (3), 0.6 (3), 0.8 (3), 1.0 (3), 1.25 (3), 1.6 (3), 2.4 (3), 3.1 (3), 4.0 (3), 6.0 (6) and 8.0 (5) mg/m[2]/day × 5 days and received 1–6 cycles. Clearance of ZD9331 was slow and non-linear. At doses up to 1 mg/m[2]/day × 5 days, the mean clearance was 4.26 ± 1.50 ml/min. At higher doses the mean clearance was 7.88 ± 1.89 ml/min. This suggests saturation of tubular reabsorption. V[ss] was low (mean 25.5 ± 6.60 L) but independent of dose. The elimination t[1/2] (mean 75.1 ± 25.0 h) was longer than predicted, prompting the study of intermittent dosing schedules. Dose levels 6.0 and 8.0 mg/m[2]/day have been expanded. At 6.0 mg/m[2]/day, 1 pt had grade IV (CTC) thrombocytopenia and grade III neutropenia after 1 cycle and grade IV thrombocytopenia and neutropenia after dose reduction to 4.0 mg/m[2]/day in the second cycle. At 8.0 mg/m[2]/day, 2 pts had grade IV thrombocytopenia plus grade III or IV neutropenia and 1 of these also had grade IV diarrhoea. Other toxicities included grade I/II anaemia, skin rash, nausea, vomiting, alopecia and diarrhoea, grade I–IV transient asymptomatic rise of liver transaminase activity, and lethargy. 1 pt with ovarian cancer had a partial response after 2 cycles and 3 pts had stable disease after 6 cycles. Plasma 2′-deoxyuridine levels are being measured as a surrogate marker of TS inhibition and have risen by day 2, remaining elevated for ~10 days at higher dose levels. The study is ongoing.

1150 POSTER

A fixed-dose phase I study of ZD9331, a novel non-polyglutamated inhibitor of thymidylate synthase, in patients with refractory cancer

D. Bertucci[1], M.J. Ratain[1], R. Smith[1], S. Mani[1], N.J. Vogelzang[1], R.L. Schilsky[1], B.C. Goh[1], M. Smith[2], E. Douglass[3]. *[1]The University of Chicago, Chicago, IL, United States; [2]Zeneca Pharmaceuticals, Alderley Park, United Kingdom; [3]Zeneca Pharmaceuticals, Wilmington, DE, United States*

Introduction: ZD9331 is a potent inhibitor of thymidylate synthase which, unlike raltitrexed, does not undergo intracellular polyglutamation. It therefore may have a different spectrum of activity and toxicity. Preclinical studies have shown that ZD9331 has a relatively short elimination half-life (6 h). A Phase I study was conducted to assess the feasibility of a 5-day, 3-weekly regimen.

Methods: Pts with solid tumors resistant to at least 1 prior chemotherapy regimen were given ZD9331 by 30-min infusion for 5 days every 3 weeks. Dose escalation followed a 2-stage procedure, with (1) initial doubling of the dose until drug-related toxicity and (2) dose escalation guided by a modified

Dose level (mg/m^2/day)	No. pts (evaluable for toxicity)	DLT (no. pts)	Toxicities (after 2 cycles)	Response
4.8	6	1	GIV thrombocytopenia (1)*	2SD, 4PD
6.0	7 (6)	0	–	6SD, 1PD
7.5	6	1	GIV thrombocytopenia (1)*	3SD, 3PD
9.0	5 (4)	0	death, not drug-related (1)	1SD, 3PD
12	6	2	GIV thrombocytopenia (1)* GIV febrile neutropenia (1)* GIV leukopenia (1) GIII rash (1)	1PR, 3SD (2 pts not scanned)
16	11 (8)	2	GIV leukopenia (2) GIV neutropenia (2) GIV thrombocytopenia (2)**	2SD, 4PD (2 pts not scanned)
25 mg/day fixed dose	13†	1	GIV leukopenia (1) GIV neutropenia (1) GIV thrombocytopenia (1)*	3SD, 1PD

*DLT; †1 pt not evaluable, 8 pts completed cycle 1