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

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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)

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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

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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

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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