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 thromboctyopenia (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

Fibonacci series. A fixed-dose regimen of 25 mg/day was also tested as there was little correlation between body surface area, toxicity and drug exposure in previous cohorts.

Results (see table): To date, 74 pts have been treated. Of 13 pts entered at 25 mg/day, 1/8 pts who have completed cycle 1 had a DLT, and 1 pt with cancer of the fallopian tube, and 2 pts with colorectal cancer have achieved SD.

Conclusions: These preliminary results indicate that a fixed dose of 25 mg/day is both feasible and generally well tolerated. ZD9331 showed promising efficacy, particularly in pts with colorectal cancer. Further efficacy studies are warranted.

1151 POSTER

Phase I trial of doxil plus cisplatin (DDP) in patients (pt) with advanced malignancies

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Purpose: To determine the MTD of the combination Doxil with DDP.

Methods: In the first 3 dose levels (DL), the dose of Doxil was 40 mg/m^2 while the dose of DDP was escalated from 40 mg/m^2 (5 pt) to 50 mg/m^2 (4 pt) and 60 mg/m^2 (4 pt). At the 4th and 5th DL, the dose of DDP was 60 mg/m^2 while the dose of Doxil was escalated to 50 mg/m^2 (4 pt) and to 60 mg/m^2 (8 pt). All DL were administered q4w with dexamethasone-ondansetrone premedication. 25 pt received a total of 140 cycles between 2/97 and 10/98, 24 pt are evaluable for toxicity and 23 pt for antitumor response. Median age 58 y (21–73). Median performance status 80 (60–90). 17 pt received prior chemotherapy. Main diagnoses: soft tissue sarcoma (6 pt), non-small cell lung cancer (5 pt), ovarian cancer (4 pt), mesothelioma (3 pt).

Results: At the 1st and 2nd DL, there were no dose-limiting toxicities. At the 3rd and 4th DL, 2 pt had grade (g) 3 stomatitis. At the 5th DL, stomatitis occurred in 1 pt at g 4, and in 2 pt at g 3. 1 pt had neutropenic fever. Overall, palmar-plantar erythrodysesthesia (PPE) g 2 occurred in 4 pt and moderate hair loss in 2 pt. Partial responses were documented in 6 pt (3 with ovarian cancer). In 4/6 responders, the time to disease progression exceeds 1 y. Stabilization (>3 months) was observed in 8 pt. The mean Doxil C_{max} (mg/L plasma) increased gradually with dose from 14.7 ± 1.9 for 40 mg/m^2, to 17.3 ± 3.0 for 50 mg/m^2, and 23.1 ± 5.1 for 60 mg/m^2.

Conclusion: Doxil can be administered at full MTD (50–60 mg/m^2 q4w) in combination with 60 mg/m^2 DDP, with no evidence of major overlapping toxicities. PPE incidence and severity appears to be diminished, in comparison to data available for single agent Doxil.

1152 POSTER

Pediatric phase I trial and pharmacokinetic study of 'Tomudex' (Ralitrexed)

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Objectives: 'Tomudex' (raltitrexed) is a selective thymidylate synthase inhibitor, and effective in adult patients (pts) with advanced colorectal cancer. A Phase I trial of 'Tomudex' administered as a 15-min infusion every 21 days was performed in pediatric pts with refractory solid tumors.

Methods/Results: Pts (median age 15 [range 1.2–21] yrs), were treated at dose levels of 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0 and 7.5 mg/m^2. At the adult recommended dose (4.0 mg/m^2, US study), eligibility criteria were modified to include only less heavily pre-treated patients. 48 pts with osteosarcoma (n = 14), glioblastoma multiforme (n = 3), Ewing's sarcoma/PNET (n = 6), neuroblastoma (n = 4), rhabdomyosarcoma (n = 3), colon cancer (n = 2) and other tumors (n = 16) were entered. Hepatotoxicity (persistent grade III SGPT elevation) was observed in 1 pt each at 2.0, 3.5, 6.0 and 7.5 mg/m^2. Grade III diarrhea occurred in 1 pt each at 3.0 and 7.5 mg/m^2. 1 pt at 3.5 mg/m^2 developed sepsis. At 7.5 mg/m^2, 2/3 pts experienced DLT, including myelosuppression, hepatoxicity, diarrhea, and rash. At 6.0 mg/m^2, only 1/6 pts developed DLT. Non-DLTs included reversible elevations in hepatic transaminases (n = 29), mild diarrhea (n = 7), and mucositis (n = 5), fatigue (n = 4), rash (n = 2) and neutropenia (<500/mm3 for <7 days, n = 3). 1 pt with glioblastoma multiforme had disease stabilization for 9 months, and 1 pt with metastatic osteosarcoma had a mixed response. The pharmacokinetics of 'Tomudex' were studied in 44 pts using an enzyme inhibition assay (LLQ 0.005 μM). 'Tomudex' displayed tri-exponential elimination from plasma, with a rapid initial decay followed by a prolonged terminal elimination phase (terminal half-life = 44 h at 7.5 mg/m^2), presumably due to the release of 'Tomudex' from intracellular polyglutamated pools. Peak 'Tomudex' plasma concentrations ranged from 1.0 (SD 0.3) μM at 2.0 mg/m^2 to 2.8 (SD 0.3) μM at 7.5 mg/m^2. 'Tomudex' was cleared from plasma at a median of 55 (range 30–80) ml/min/m^2.

Conclusion: Younger patients appear to tolerate higher doses of 'Tomudex' than adults. The recommended pediatric Phase II dose is 6.0 mg/m^2. A phase II trial in pediatric pts with solid tumors and brain tumors is planned.

'Tomudex' is a trade mark, the property of Zeneca Ltd.

1153 POSTER

A bio-availability study of OGT 719 following oral and intravenous administration

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Introduction: OGT 719 is a carbohydrate-linked-fluoropyrimidine designed to target the asialoglycoprotein receptor on hepatocytes to treat hepatocellular carcinoma or hepatic metastases. An ongoing phase I intravenous study has demonstrated that OGT 719 is well tolerated with some evidence of efficacy. Pre-clinical data have suggested that this drug is orally bio-available. We have therefore conducted the following study.

Methods: Initially 8 patients were randomised to receive 400 mg oral OGT 719 followed by a 250 mg/m^2 3 hour intravenous (i.v.) infusion one week later or vice versa. Subsequently, following interim analysis of pharmacokinetic data, a further 8 patients received 800 mg orally randomised as above. In total 16 patients (9 F, 7 M), ECOG performance status < or = 2, were treated in this phase of the study. Patients completing the pharmacokinetic phase were able to continue OGT 719 therapy at 1000 mg/m^2 or 1750 mg/m^2 given weekly as a 3 hour i.v. infusion.

Results: No sequence effect on pharmacokinetics of oral and i.v. OGT 719 was observed. The mean bio-availability calculated from the plasma AUC and urinary clearance following the 400 mg dose was 26.43% (±10.52) and 26.29% (±10.80) respectively. Following the 800 mg dose bio-availability was 17.53% (±10.35) and 25.88% (±15.28) respectively. The median tmax for the four treatment groups after oral dosing ranged from 4.08 hours to 6.17 hours. The AUC and Cmax for oral OGT 719 were dose linear. Fourteen patients entered the continuation phase of the study. OGT 719 was well tolerated and no significant adverse events could definitely be attributed to study drug.

Discussion: This is the first study to demonstrate oral bio-availability of OGT 719 in man. Dosing at 1000 and 1750 mg/m^2 given as a 3 hour i.v. infusion on a weekly basis was well tolerated. A maximum tolerated dose using this dosing regimen was not defined. This study suggests that OGT 719 is a possible candidate for extended oral administration.

1154 POSTER

A phase I study of OGT 719 in patients with advanced solid tumours

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Introduction: This study aims to define the maximum tolerated dose (MTD) and pharmacokinetics of the novel nucleoside analogue OGT 719 given as a three hour iv infusion. OGT 719 is structurally related to 5-fluorouracil (5-FU), and has a carbohydrate modification designed to target the hepatic asialoglycoprotein receptor. Potential indications include primary hepatocellular carcinoma and intrahepatic metastases.

Methods: At present 55 patients with advanced solid tumours (predominantly colorectal) have been recruited in cohorts of three. The first dose was 500 mg/m^2 given once every three weeks. The OGT 719 dose or dose frequency was then increased for each cohort based on a tolerability and pharmacokinetic data assessment after three patients received one cycle of treatment. Dose frequencies of 1, 3 and 5 times a week have been examined. The target dosing schedule is daily administration for 5 days every 4 weeks.

Results: Currently, patients are receiving 12500 mg/m^2 on days 1 to 5 every four weeks and OGT 719 has been well tolerated to date. One dose limiting toxicity (DLT) of grade 3 mucositis was seen in cohort 10 (1750 mg/m^2 on days 1 to 5), however no further DLTs were found on recruiting three additional patients at this dose and dose escalation continued. One