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