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

partial response was demonstrated after 6 cycles of OGT 719 at 250 mg/m^2 on days 1 to 5 (renal cell carcinoma with liver metastases). Two patients had stable disease after 6 cycles of OGT 719 at 1000 mg/m^2 on days 1, 3 and 5 (metastatic adenocarcinoma) and 1750 mg/m^2 on days 1 to 5 (melanoma with lung metastases). Pharmacokinetic data show no accumulation with daily dosing and dose linearity for AUC and Cmax up to 10000 mg/m^2 is apparent.

Conclusions: These data indicate that OGT 719 has predictable pharmacokinetics with more variability at the higher doses. Structural modification of 5-FU with a carbohydrate ligand significantly affects potency on a mg/m^2 basis.

1155 POSTER

Phase I and pharmacokinetic study of BBR 2778

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BBR 2778, a novel anthracenedione, induces DNA intercalation and inhibition of the topoisomerase-II enzyme. In this study BBR 2778 was given as a 1 h intravenous infusion weekly for 3 weeks (w) every 4 w. The aims were (1) to study the pharmacokinetics (PKs), (2) to determine the maximum tolerated dose (MTD), (3) to define dose-limiting toxicities (DLT), and (4) to recommend a dose for phase II studies. Dose escalation proceed according to the following weekly dose-levels (mg/m^2): 5 (4 pts, 9 cycles), 10 (3 pts, 3 cycles), 16.5 (3 pts, 5 cycles) 25 (6 pts, 9 cycles), 37.5 (1 pt, 1 cycle), 75 (4 pts, 5 cycles), 112.5 (6 pts, 10 cycles), 150 (3 pts, 4 cycles). Plasma PKs followed a multiexponential profile with a rapid distribution phase followed by a prolonged elimination phase. BBR 2778 had a large volume of distribution and was efficiently cleared from the plasma compartment. DLT was neutropenia. Other toxicities were mild to moderate including lymphopenia, thrombocytopenia, alopecia, and moderate nausea/vomiting. No cardiac toxicity was reported. The MTD was 150 mg/m^2/w for 3w, q4w (2/3 DLT) and the recommended dose for phase II studies was 112.5 mg/m^2/w for 3w, q4w.

1156 POSTER

Biweekly docetaxel (DOC), gemcitabine (GEM), oxaliplatin (LOHP) in heavily pretreated patients with solid tumors – Preliminary results of a phase I study

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Purpose: In vitro data suggests a schedule-dependend synergistic antineoplastic activity of Doc/Gem/LOHP. To evaluate the toxicity of this novel triple combination, a pilot trial with 10 pts with refractory tumors was conducted with a biweekly application of this combination. Protocol (dose-level 0): Doc 35 mg/m^2 1 hr-infusion d1 (with standard premedication), followed after 1 hr rest by Gem 800 mg/m^2 30 min-infusion, followed by LOHP 65 mg/m^2 2 hrs infusion on d2; q d15 until progression. Based on the results of this 10 pts, a dose-escalation study was initiated. At time of this interim analysis 17 pts are evaluable for toxicity, 13 for response.

Patient characteristics: 12 male/5 female, median age 58 yrs, median ECOG-Status 1, median prior chemotherapies 2. Type of treated tumors: Squamous cell carcinoma of head and neck (10 pts), sarcoma (2 pts), CUP, gastric cancer, adrenal-, nasopharyngeal- and ovarial-carcinoma 1 pt.

Results: Toxicity (CTC-NCI-criteria): To date, 90 cycles are evaluable, median 5 cycles/pt (range: 3–10). Diarrhea II°: 1 pt, mucositis II° 1 pt, nausea/vomiting I/II° 4 pts, neurotoxicity I° 3 pt, IV° 1 pt (this patient has received 10 applications), no hematologic toxicity >2°; alopecia II° 5 pts, no other toxicity occurred.

Response: 3 (23%) objective remissions (sarcoma, head and neck, CUP) were seen. 8 pts (62%) showed disease stabilisation, 4 of them with clinical benefit (decrease of clinical symptoms or tumor markers). 2 pts (15%) progressed under therapy.

Conclusion: The application of Doc/Gem/LOHP is feasible in an outpatient setting and shows promising activity. One pt was taken of study due to neurotoxicity IV° after 10 applications. The patient cohort of this dose level was escalated to 6 pts. No further neurotoxity >II° occurred in this cohort in pts with a nearly similar number of applications. Dose-escalation continues further. Updated results of the dose-escalation study will be presented at the meeting in September 1999.

1157 POSTER

Escalated dose docetaxel (TXT) with G-CSF support in patients (PTS) with solid tumours

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Patients received TXT with G-CSF (lenograstim) support in a phase I dose escalation study, aiming to reduce dose limiting toxicities (DLTs) of neutropenia and sepsis. A 3 day steroid prophylaxis was given and pts received G-CSF 5 (ug/kg/d sc) from day 2 until neutrophils >1 × 10 9/l. 35 pts with various solid tumours were entered. Median age was 59 yrs (29–76) and 16 pts had previously received chemotherapy. TXT dosing was escalated by 10 mg/m^2 for cohorts of 3–6 pts, commencing at 110 mg/m^2 q21 days. At TXT170 mg/m^2, 2/3 pts experienced DLTs: grade III neuropathy and grade III skin toxicity respectively. Only two pts had DLTs at lower dose levels (130 mg/m^2). Twelve pts have now been treated at the recommended dose of 160 mg/m^2 without DLTs. The median neutrophil nadir occurred prior to day 8 with day 8 being the median day of cessation of lenograstim. Grade IV neutropenia was observed in 10/29 pts (35%). Only 3 pts developed febrile neutropenia which was not prolonged. Mobilisation of progenitor cells has been examined during cycle one for patients at all dose levels. Median CD34+ cell levels rose to 2.2 × 10 6/l on day 8 and 60% of pts had peak levels >1 × 10 6/l. A Phase II trial of TXT 160 mg/m^2 and lenograstim is currently being undertaken of pts with breast cancer who have not previously received chemotherapy for advanced disease.

1158 POSTER

A dose finding and pharmacokinetic study of docetaxel (TXT) and methotrexate (MTX) in patients with epithelial cancer

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TXT and MTX, very active drugs in epithelial cancer, were associated and evaluated in a phase I study. TXT was given on day 8 as 1 hour infusion with dose escalation and MTX on d1 and 8 at fixed dose (40 mg/m^2). DLT was defined as NCI-CTC >2 toxicity, vomiting, diarrhea and stomatitis gr. >3 or a prolonged (>7 d) or febrile gr. 4 neutropenia (FN). 28 pts have been treated. Pts characteristics are: median age 55 [44–71], 5 females/23 males, PS 0:8 pts, 1:15 pts, 2:5 pts, tumor type: urothelial: 12, head and neck: 12, lung: 3, cervix: 1. All 28 patients are evaluable for toxicity. PK data were analyzed using NONEM, according to a 3 compartment model for both drugs. Co-variables were mainly age, body weight and surface area, sex, renal and hepatic parameters, α 1-acid glycoprotein. Major DLTs on cycle 1 were: FN (4), thrombocytopenia (3), cytolysis (3), stomatitis (2). Combination of TXT and MTX is feasible without severe toxicity and has notable activity. Adjunction of cisplatinum will be evaluated in a new phase I study

Dose Level		Toxicities (Nb of pts)		Obj.	PK Data (mg l^{-1}·h)	
TXT mg/m^2	MTX mg/m^2	Entered/ Evaluable	with cy 1 DLT	Resp.	AUC TXT 16 pts/28	AUC MTX 19 pts/28
60	40	3/3	0	1/3	2.32 ± 0.34	7.54 ± 1.71
70	40	6/6	0	1/6	3.48 ± 1.19	7.59 ± 1.63
80	40	7/6	2	2/7	4.27 ± 1.47	7.37 ± 1.97
90	40	6/6	3	1/6	4.59 ± 1.07	7.97 ± 1.44
100	40	6/6	2	–	–	–

1159 POSTER

Phase I trial and pharmacokinetic (PK) study of S16020 according to a weekly and every 2 week (W) schedule in cancer patients (PT)

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In a previous phase I study carried out with the new Olivacine derivative S16020 according to a single dose schedule (1 or 3 hour infusion) every