pts/DL experienced DLT. Irofulven was given over 30 min with anti 5-HT3, steroids and 1000cc hydration.

Results: As of 4/2001, 24 pts with AST were treated, receiving 43 cycles. M/F: 10/14, median age: 55 (21-73). Sch. B: DL2 (10 pts/21 cycles), DL3 (3 pts/3 cycles). Sch C, DL2 (8 pts/16 cycles), DL3 (3 pts/3 cycles). Clinical toxicity was mild with no grade 3/4 events; Thrombocytopenia (T) Gr1-2 was prevalent in both sch at both DLs without cumulative effects. Gr3 T and neutropenia were seen in 2 and 1 pts respectively (sch C, DL2). Gr2 transient visual disturbance (modification of color vision and contrast with normal acuity) in 1 pt (sch C, DL2). DLTs were seen in sch C in 2 pts (1 with prior mitomycin C therapy) at DL 2. Activity: 24 pts were evaluable, with 7 too early, 1 PR (renal carcinoma), 5 pts SD = or >3 cy.

Conclusion: Irofulven given as a 30 min infusion is a well-tolerated regimen at DL2 (planned DI 12 mg/m2/w) in the two sch explored, and has evidence of antitumor activity. Enrollment is ongoing at DL3. Updated results will be presented.

257 POSTER

Effects of ZD6474, an orally active inhibitor of VEGF receptor tyrosine kinase, in patients with solid tumors: Results from a phase I study

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ZD6474 is a novel, orally active inhibitor of the tyrosine kinase associated with vascular endothelial growth factor (VEGF) receptor-2 (KDR). A phase I study with this agent is being conducted at 5 sites (in the US and Australia). Patients with measurable progressive malignancies despite treatment, or tumors for which there are no treatments, are given a single dose of ZD6474 followed 1 week later by the initiation of chronic once-daily dosing at the same level. Samples for pharmacokinetic analysis are collected after the single dose and during chronic treatment. ZD6474 administration continues at the assigned dose level until disease progresses, dose-limiting toxicity intervenes, or the patient withdraws consent. To date, 41 patients have been treated at 5 dose levels; 50, 100, 200, 300 and 500 mg/d. Treatment for over 100 days has proved feasible at the first 4 dose levels and for over 30 days at the 500 mg/d level to date. All patients are evaluable for safety. No hematologic, renal, hepatic or GI toxicity has been observed. Skin changes ranging from Grade I to III have been observed. At this time, dose-limiting toxicity has not been observed and the maximum tolerated dose not determined. Pharmacokinetic analysis demonstrates dose-dependent increases in exposure to ZD6474. For example, Cmax and AUC in the 50mg cohort were 21.8 ng/ml and 3.22 ug-hr/ml, respectively, whereas in the 300mg cohort, they were 222 ng/ml and 23.8 ug-hr/ml, respectively. Elimination half-life ranged between 71.7 and 206 hours across all dose levels. Accrual is continuing at higher doses, and markers of biological activity are being evaluated.

258 POSTER

A phase I study of BAY 38-3441 given as a short infusion daily for five days every 3 weeks. a National Cancer Institute of Canada Clinical Trials Group Study

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Purpose: BAY 38-3441 consists of camptothecin conjugated to a carbohydrate moiety with a peptide spacer. The peptide-carbohydrate portion of the molecule stabilizes the active lactone form of camptothecin in blood and thereby increases the proportion of the lactone available for uptake into tumour cells. The compound is active in a range of human tumour xenografts, including MX-1, LXFL529, CXF280 and HT29. A phase I study of BAY 38-3441 given as a short infusion for 5 days was initiated in May 2000.

Methods: The starting dose was 14mg/m2 (1/10th the MTD in the most sensitive species). 3-6 pts were enrolled to each dose level (DL) and doses were doubled in the absence of * grade 2 toxicity. Endpoints included the definition of the recommended phase II dose (RP2D), the maximum dose (MTD) administered, toxicity and pharmacokinetics (PK). Eligible patients (pts) included those with ECOG PS 0-2, no more than 2 prior chemotherapy regimens for metastatic disease, no prior history of life threatening allergic reactions, and acceptable organ function.

Results: 13 pts have been entered to 4 DLs and have received a total of 30 cycles of BAY 38-3441; 2 pts received 9 and 4 cycles of BAY 38-3441, respectively. Currently, 10 pts are evaluable; 6 pts are male, the most common tumour types are head and neck cancer (3 pts) and ovarian cancer (2 pts), 7 pts had PS of 0 or 1, 7 pts had 2 or more sites of disease and 3 pts had had 2 prior regimens. Grade 1 or 2 nausea, stomatitis, dyspepsia, alopecia, pruritis, fever and ocular symptoms have been the only toxicities noted to date; 1 patient had grade 1 granulocytopenia and occasionally pts have had grade 1 increases in liver function tests. No antitumour activity has been seen to date. PK appears to be dose dependent but not linear with some evidence of accumulation for the lactone form of camptothecin on day 5; T1/2 is 1.5 &2 hours for parent compound and ± 40 hours for camptothecin.

Conclusions: Toxicity to date has been minor, and dose escalation continues.

259 POSTER

Phase I study of Caelyx and Carboplatin (Cp) in patients with advanced or metastatic solid tumors

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Pegylated liposomal doxorubicin (Caelyx,Doxil) has a unique toxicity profile, minimal hematological toxicity but dose limiting skin toxicity. Caelyx (C) is active in ovarian carcinoma. We combined C and Cp in phase I dose escalating trial to determine the maximal tolerated dose (MTD), dose limiting toxicity (DLT) and recommended phase II doses (RD) of this schedule. Cp AUC 5 was given as 30min iv infusion followed by 1hour rest and C as 60min iv infusion or inverse sequence, every 3 weeks. DLT were: grade (gr) 4 neutropenia (np) > 7 days, febrile np, gr 4 thrombopenia, gr 3 or 4 non hematological tox or persistence of gr >2 hematological tox at day 35.

22 pts were enrolled at 3 dose levels (C in mg/m2: 30, 35,40). Dose escalation followed continued reassessment method. Median age 53 [19-70]. Tumor type: cervix (1), head and neck (6), lung (3), endometrial (2), esophagus (2), melanoma (1), sarcoma (1), ovarian (4), rectal (1), renal (1). Median PS:1. Median number of cycles:2[1-6]. 4 pts are still on treatment. No cardiac tox, no skin tox, no toxic death occurred. Similar tox with the two sequences.

Level: 30MG/m2, DLT (3/8):Thrombopn gr4(1),prolonged np(1)Febrile np(2);level 2: 35mg/m2: DLT 2/8: Febrile np (1, prolonged np (1); level 3: 40mg/m2, DLT 2/6: abdominal pain (1) febrile neutropenia (2) thrombopenia gr4 (1)

Recommended schedule: Caelyx 35 mg/m2+Cp AUC5 in outpatient setting every 28 days lead manageable toxicity. Inverse sequence is similar. Anti tumor activity (PR2, SD1,PD5) merits further clinical evaluation.

260 POSTER

Phase I and pharmacokinetic study of capecitabine and cisplatin in head and neck cancer patients

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The cisplatin-5fluorouracil (5FU) combination is considered to be one of the standard treatments for patients with squamous cell carcinoma of the head and neck. Capecitabine (Xeloda) is an oral fluoropyrimidine which is preferentially activated at the tumoral level, exploiting higher TP activity in tumor tissue. Oral capecitabine mimics continuous infusion 5FU and therefore can conveniently replace 5FU in this setting. This study was conducted in patients with locally recurrent or metastatic head and neck carcinoma who were able to swallow. Treatment design: cisplatin was infused over 1 hour every 28 days followed by capecitabine twice daily from day 2 to day 15 with a 2-week rest period. Pharmacokinetic analysis (HPLC) included plasma levels of unchanged capecitabine, 5'DFCR, 5'DFUR and 5FU. Lymphocytic dihydropyrimidine dehydrogenase (DPD) activity was determined for each patient before and during treatment. 14 patients have been included so far. Dose (mg/m2) increments were for cisplatin and capecitabine (b.d.), respectively: level 1: 80, 1000 (4 patients, 11 cycles); level 2: 100, 1000 (6 patients, 14 cycles); level 3: 100, 1125 (4 patients, 10 cycles). Toxicities (grades 3, 4) were observed on level 2 (1 patient with mucositis, diarrhea and hand-foot syndrome) and on level 3 (1 patient with hematological toxicity-related death). Evidence of antitumor activity was also observed in 4 patients achieving an objective response.