inhibition of sublethal radiation-induced DNA damage repair (advocated as the main mechanism for the radiosensitizing effect of Oxaliplatin).

This phase I study was thus started to determine the maximum tolerated doses of OXA (25-35-45 and 60 mg/m2, weekly for 6 times) and continuous infusion FU (200-225 mg/m2/die, d 1-38) in combination with standard pelvic radiotherapy (50.4 Gy - 28 fractions).

Since April 2000, 24 patients with locally advanced (cT3-T4 and/or N+) or recurrent rectal cancer were accrued (16 males, 8 females; median age 59, range 34-71 years).

Overall, 102 out of 108 courses of chemotherapy were delivered as planned. Three courses were omitted and two were delayed (1 day- 2 days) because of toxicity, while one course was given without FU (CVC dislocation). Only one patient did not complete the treatment program because of toxicity (grade III diarrhea leading to Oxaliplatin discontinuation after four doses). The first 13 patients had surgery as scheduled (6-8 week following completion of chemoradiation).

No grade IV toxicity was observed at the first four dose levels (OXA 25/FU 200; OXA 35/FU 200; OXA 45/FU 200; OXA 60/FU 200). Three episodes of grade III diarrhea were observed: two at OXA 25/FU 200, one at OXA 60/FU 200. Nine patients complained of grade I-II neurotoxicity (OXA 45/FU 200: 1; OXA 60/FU 200: 8).

All the patients had substantial tumor shrinkage with primary tumor and nodes down-staging observed in 11/13 and 6/7 cases respectively. Among 13 patients for whom final pathologic reports are available, 5 pCR were reported.

These results demonstrate that the combination of weekly OXA, continuous infusion FU and pelvic radiotherapy is feasible, well tolerated and has promising antitumor activity. The MTD has not been reached up to the dose of 60 mg/m2/week of Oxaliplatin. The study is now accruing patients at this OXA dose combined with FU 225 mg/m2/die.

254 POSTER

A phase I study of ZD0473 and Docetaxel given once every three weeks in patients with advanced refractory cancer. A National Cancer Institute of Canada-Clinical Trials Group Study (NCIC CTG-IND 131)

K.A. Gelmon[1], D. Stewart[1], D. Ayers[1], D. Fry[1], L. Douglas[2], L.W. McIntosh[1], L.K. Seymour[1]. [1]*NCIC Clinical Trials Group, Kingston, Canada;* [2]*AstraZeneca, Mississauga, Canada*

ZD0473 is a new generation platinum compound with significant activity against a wide range of cultured human tumour cell lines and against a panel of human ovarian xenografts, including cisplatin- and carboplatin-resistant cell lines. Phase I and II studies reported activity in several solid tumours. As platinum agents are often combined with taxanes in a number of solid tumours, NCIC-CTG initiated a phase II study in of the combination of ZD0473 and docetaxel in advanced refractory cancers to define the toxicity, maximum tolerated dose (MTD), recommended phase II dose (RD) and pharmacokinetics. 17 patients (pts) have been enrolled on three dose levels (DL). 14 pts are evaluable for toxicity and 7 for response at this time. Eligibility criteria included pts with histologically advanced incurable cancer, performance status (ECOG 0-2), adequate organ function, and informed consent. All pts at DL1 (80 mg/m2 ZD0473 and 60 mg/m2 docetaxel), experienced grade (gr) 4 granulocytopenia; 1 pt was treated with GCSF after 4 days and was considered a possible DLT; the DL was expanded with 4 additional pts: no further DLTs were observed. Four pts were entered at DL2 (80 mg/m2 ZD0473 and 75 mg/m2 docetaxel); toxicities included gr 4 granulocytopenia lasting < 7 days (3 pts). 1 DLT of febrile neutropenia was seen and thus the DL was expanded with 2 more pts but no further DLT was seen. Toxicity data is currently pending for the 3 patients entered at the third DL of ZD0473 100 mg/m2 and docetaxel 75 mg/m2. Other related toxicities included 3 gr 3 infections (1 fatal), 2 gr 3 fatigue, and 1 gr 3 vomiting. Hematological toxicity included four gr 3 anemia, one gr 3 thrombocytopenia, and nine gr 4 granulocytopenia which was associated with febrile neutropenia in only two cases. 8 serious adverse events have been reported, 5 related fever and/or infection; 1 pain control; 1 unrelated bowel obstruction and 1 possibly related GI bleed. DLT is likely to be hematological and MTD is likely to be close to the current dose level. Median number of cycles is 6 at DL 1 and 3 at DL 2. It is too early to definitively assess activity, but this combination appears active and may have future potential in tumours that are responsive to taxane/platinum combination. The updated results of this phase I trial with pharmacokinetics will be reported.

255 POSTER

Pharmacokinetic (PK)/pharmacodynamic (PD) trial of the new generation platinum compound ZD0473 administered as an iv infusion every 21 days

J.P. Stevenson[1], I.A. Blair[1], M. Redlinger[1], W. Sun[1], T. Oe[1], M. Koehler[2], D.W. Roberts[3], M.D. Malone[1], P.J. O'Dwyer[1]. [1]*University of Pennsylvania, Philadelphia, PA;* [2]*AstraZeneca, Wilmington, DE, USA;* [3]*AstraZeneca, Alderley Park, UK*

Aims: ZD0473 is a new generation platinum drug designed to have an extended spectrum of antitumor activity and overcome platinum resistance mechanisms. Initial Phase I studies did not reveal a clear relationship between total plasma ultrafiltrate platinum (analyzed by atomic absorption spectroscopy) and toxicity. We aimed to better define a ZD0473 dose for further Phase II/III evaluation and to study PK/PD relationships.

Methods: In this ongoing multicenter, open-label, dose-escalating Phase I trial, ZD0473 was administered as a 1-h iv infusion q 21 days. The ZD0473 plasma ultrafiltrate concentrations were then determined by a novel stable isotope dilution liquid chromatography/tandem mass spectrometry assay.

Results: All 7 patients (pts) with refractory solid malignancies were minimally pretreated (no more than 1 prior chemotherapy regimen that included an alkylating agent) and had PS 0 or 1. ZD0473 doses were: 120 mg/m^2 (1 pt; 6 cycles), 150 mg/m^2 (1 pt; 5 cycles) and 180 mg/m^2 (5 pts; 2 cycles [median], range 1–4). ZD0473 had a manageable safety profile: pts receiving 120 or 150 mg/m^2 did not have dose-limiting toxicity (DLT). All toxicities were G1 or 2, and the only serious adverse event was G1 fever at 150 mg/m^2. Of pts receiving 180 mg/m^2 ZD0473, 2 experienced DLT (G4 thrombocytopenia or G3 non-hematologic toxicity). Other toxicities at 160 mg/m^2 included anemia (G3, 3 pts: G4, 1 pt) and thrombocytopenia (G3, 1 pt: G4, 3 pts). No adverse events were fatal or led to withdrawal from therapy at any dose tested. An evaluation of the preliminary PK data suggests that exposure in terms of $AUC_{(0-4)}$ and C_{max} increase with dose. The $t_{1/2}$, clearance, volume of distribution (V_{ds}) and mean residence times (MRT) were similar for all pts.

Pt	Dose (mg/m^2)	$AUC_{(0-4)}$ (ng/ml.h)	C_{max} (ng/ml)	$t_{1/2}$ (h)	Total clearance (l/h)	V_{ds} (l)	MRT (h)	Thrombo-cytopenia (grade)
1	120	9308	5772	0.90	23.94	29.70	1.01	0
2	150	12981	7228	1.02	20.14	27.46	1.32	1
3	180	19821	12137	1.11	15.16	20.38	1.29	4
4	180	17450	10117	1.23	18.15	26.70	1.38	3
5	180	15781	7655	0.98	21.44	30.33	1.38	3
6	180	19102	10373	1.01	18.67	24.09	1.26	3
7	180	14586	7580	1.11	19.12	26.52	1.33	4

Conclusion: The maximum tolerated dose in minimally pretreated pts was 180 mg/m^2 (2 of 5 pts with DLT). Using the more specific analytical method would enable us to define the PK/PD relationship more accurately. We await further data to determine if this specific assay will permit the description of a PD model for ZD0473 to account for interpt variability.

256 POSTER

Phase I study of MGI 114 (Irofulven) given as either D1, D8 q3 weeks or D1, D15 q4 weeks schedule (sch) as a 30 minute infusion in advanced solid tumors (AST): preliminary results

E. Raymond[1], J. Alexandre[2], E. Brain[3], S. Faivre[1], M. Ould Kaci[4], S. Vignot[3], S. Smith[5], S. Lagree[4], K. Vanderbilt[5], J.L. Misset[2]. [1]*Institut Gustave Roussy, Villejuif, France;* [2]*Hôpital Paul Brousse, Villejuif, France;* [3]*Centre René Huguenin, Saint Cloud, France;* [4]*C.A.C., Kremlin-Bicêtre, France;* [5]*MGI Pharma, Minnesota, USA*

Purpose: Pharmacokinetic (PK) analysis of Irofulven (DNA interacting acylfulvene illudin S analog) given as a 5 min infusion showed a short mean plasma half-life (t1/2 range 4 to 6 min), with substantial interpatient variability (ASCO 2001). Therefore, a steady state should be reached by the end of a 30 min infusion. With preliminary in vitro data showing that increasing cytotoxicity closely correlates with increasing time of exposure over the first hour after administration, a 30 min infusion was implemented to evaluate toxicity, optimize activity and reduce interpatient PK variability.

Methods: Patients (pts) with AST were treated with the same schedules (sch) previously explored with the 5 min infusion duration (B: D1, 8, q3w and C: D1, 15 q4w) using the following dosing levels (DL in [mg/m2/d]). Sch B: DL2 [18], DL3 [21]; Sch C: DL2 [24], DL3 [28]. Maximal tolerated dose was based on standard acute dose limiting toxicity (DLT) criteria and toxicity-related treatment delays in the first 2 cycles. Planned dose intensity (DI) was increased by 2mg/m2/w at successive DL if <50% of = or <6

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

S. Holden[1], S. Eckhardt[1], R. Basser[2], D. Rischin[2], H. Hurwitz[3], R. DeBoer[2], M. Rosenthal[2], H. Swaisland[4], M. McKinley[4], L. Schacter[4]. *[1] University of Colorado Cancer Center, Medical Oncology, Denver, USA; [2] CDCDT, Parkville, Australia; [3] Duke University Medcial Center, Medical Oncology, Durham, USA; [4] AstraZeneca, Alderley Park, UK*

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

L. Seymour[1], L. Siu[1], G. Batist[1], J. Cammisano[1], M. Maclean[1], L. McIntosh[1], O. Petrenciuc[2]. *[1] NCIC Clinical Trials Group, Kingston, Canada; [2] Bayer Inc, Canada*

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

A. Braud, A. Goncalves, D. Genre, G. Gravis, F. Viret, J. Camerlo, M. Cappiello, D. Blaise, D. Maraninchi, P. Viens. *Institut Paoli Calmettes, Medical Oncology, Marseille, France*

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

X. Pivot[1], E. Chamorey[1], E. Guardiola[1], N. Renee[1], D. Mari[1], B. Giroux[2], Z. Mouri[2], M. Schneider[1], G. Milano[1]. *[1] Centre Antoine Lacassagne, Oncopharmacology Unit, Nice, France; [2] Roche Pharmaceuticals, Oncology, Neuilly sur Seine, France*

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.