rate and decreased vascularisation. In this Phase I trial we have explored the toxicity and pharmacokinetics (PK) of this compound, and attempted to assess its impact on the vascular permeability of solid tumours using Magnevist® enhanced MRI. Escalating doses of SU5416 were administered to sequential cohorts of three patients twice weekly for four weeks per cycle to a maximum of three cycles. To date 11 pts (8 F:3 M), median age 47 (R 25–74) have received 22 cycles of SU5416 at the following doses: 48 mg/m^2 (3), 65 (3), 85 (3), 110 (2). No dose limiting toxicity has been observed. Mild local venous irritation and phlebitis were common (10/11 pts). Despite premedication, hypersensitivity reactions (attributed to the diluent Cremophor™) requiring additional steroid administration have been observed in 4 pts but treatment was continued in all. Other toxicities were mild to moderate and appeared dose related: fatigue (4/11), headache (4/11) and emesis (4/11). No haematologic or metabolic toxicity has been observed. PK of the parent drug in the first 9 patients showed that clearance was rapid (mean 74.3 l/hr, SD 29.5 l/hr) and there was a trend towards an increase in drug clearance with repeated administration. No responses have been seen yet, however 4 pts have had disease stabilisation. At the doses reached no impact on vascular permeability has been visualised by contrast enhanced MRI performed one hour after infusion of SU 5416 and further studies will be performed at 4 hours. Accrual is ongoing.

1135 ORAL

Phase I trials with ET-743, a marine derived (MD) anticancer agent

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ET-743 is a novel MD compound, minor groove binder-selective for G rich sequences, that is completing the phase I evaluation. Five different infusion times (drug given every 3 weeks) have been tested and mature data in 171 patients (pt)/424 cycles are now available

	1 h iv	3 h iv	24 h iv	D × 5	72 h iv
No. Pt	40	19	52	41	19
MTD* 1100	1800	1800	1900	1200	
RD	1000	NA	1500	1650	NA

* = mcg/m^2; NA = not available yet; MTD = maximal tolerable dose; RD = recomended dose.

The dose limiting toxicities are hematological tox and fatigue. As expected from the preclinical tox, drag induced changes in the liver function test have been consistently reported. ET-743 induced transaminitis has an early onset, peaks by day 3–4 post drug administration, a median time to baseline values (AST/ALT) = 10 days and lacks a cumulative effect. Clear evidence of activity has been seen in patients with advanced resistant sarcomas, breast, melanoma and mesothelioma. PKs of ET-743 fit with a bicompartimental model. AUC values achieved in patients are within the range of the figures obtained at curative doses in nude mice bearing tumors. Early phase II studies incorporating 1500 mcg/m^2 iv-24 hours infusion/3 weeks are underway.

1136 ORAL

NCIC CTG IND 113: Two phase I dose escalation pharmacokinetic (PK) studies of BAY 12-9566 (BAY) in combination with either doxorubicin (DOX) or modulated 5-fluorouracil (FU)

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Rationale: BAY 12-9566 is a non-peptidic selective inhibitor of MMPs 2 and 9.

Methods: Two parallel dose escalation studies with a cross-over design were conducted. In cycle (C) one, patients (pts) received chemotherapy (CT) alone and in C2 CT plus BAY. BAY was to be given in a fixed dose of 800 mg bid; FU starting dose was 350 mg/m^2 daily × 5 with a fixed dose of leucovorin 20 mg/m^2 (arm A); DOX starting dose was 50 mg/m^2 (arm B). Dose limiting toxicity (DLT) included grade 3/4 toxicity.

Results: 23 patients (pts) have been accrued: median age was 60 yrs (44–78); 12 pts were female; performance status was 0 (5 pts), 1 (13 pts), or 2 (5 pts). Tumor type included colon (6 pts), ovary (4 pts), NSCLC (3 pts), renal (2 pts); 14 pts had had prior CT and 11 prior radiation; common sites of disease included: lung (15 pts); nodes (11 pts); liver (11 pts). Arm A: 12 pts have been accrued to 2 dose levels (DL); at DL-1 (FU 350 mg/m^2 plus BAY 800 mg bid po) thrombocytopenia was dose limiting, although PK in C2 was similar to C1; in DL-2 pts were treated with FU 350 mg/m^2 plus BAY 400 mg bid po without DLT; dose escalation continues in DL-3 (FU 400 mg/m^2 plus BAY 400 mg bid po). Arm B: 11 pts were accrued to 3 DLs. DL-2 (DOX 60 mg/m^2 plus BAY 800 mg bid po) was well tolerated although PK revealed a 30–40% increase in DOX levels in C2 compared to C1. At DL-3 (DOX 70 mg/m^2 plus BAY 800 mg bid po) DLT attributable to DOX was seen; toxicity was similar in C2 and C1 with no evidence of an interaction.

Conclusions: There appears to be evidence of a pharmacodynamic (thrombocytopenia) though not a PK interaction with BAY and FU, although with reduction of BAY to 400 mg bid po the combination was tolerated. Dose escalation in Arm A continues. Despite modest evidence of a PK interaction in Arm B, full dose BAY (800 mg bid po) can be safely administered with DOX 60 mg/m^2 and is recommended as the dose for further study.

1137 ORAL

Phase I dose escalation, pharmacokinetic (pk) study of a novel vascular endothelial growth factor (VEGF) receptor inhibitor, PTK787/ZK 222584 (PTK/ZK)

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PTK/ZK is a novel, low molecular weight, orally bioavailable compound that is a potent inhibitor of VEGF receptor tyrosine kinases. In vitro, it inhibits VEGF-mediated signal transduction and endothelial cell functional responses. After oral dosing in rodent models, it inhibits VEGF-mediated angiogenesis, tumor vascularization, and tumor growth. Preliminary data from a Phase I trial in advanced cancer patients are available. Cohorts of 3 patients were treated at dose levels of 150, 300, 500 and 750 mg once daily for 28 days. Dose escalation is continuing. Patients have been treated for up to 4 cycles without dose interruption or delay. No dose limiting toxicity, hematologic or hepatic toxicity was observed. Pk and surrogate marker samples were obtained at multiple times on days 1, 15 and 28 for each dose level. Current data indicate PTK/ZK is rapidly absorbed, with a Tmax of 1.1–2.0 hours, an average terminal half life (t1/2) of 4.5 hours and has no evidence of accumulation following once daily dosing. The average AUC values decreased slightly from day 1 to day 15 at all dose levels. The mean AUC (0-infinity) was proportional to the administered dose for all dose levels studied. PTK/ZK is well tolerated with a favorable pk profile and can be administered on a continuous basis. This novel compound has therapeutic potential for the treatment of solid tumors and other diseases where angiogenesis plays an important role.

1138 ORAL

Phase I dose finding study with irinotecan (CPT-11) in cancer patients (pts) with hepatic dysfynction

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Biotransformation pathway of CPT-11, and especially enzymes which convert CPT-11 into its active metabolite SN-38, are mainly located in liver. Thus, hepatic dysfunction could alter CPT-11 pharmacokinetic (PK) and may increase the risk of toxicity. This study was designed to determine the maximal tolerated dose and to investigate the PK of CPT-11 in pts with liver dysfunction. Pts groups (gr) were based on the initial total bilirubin level (Tbili): gr A (≤1.0 Normal Limit-NL) and B (>1.0 to ≤1.5 NL) with 350 mg/m^2 starting dose given every 3 weeks. In gr C (>1.5 to ≤3.0 NL), 3 dose levels were planned: 175-240-350 mg/m^2. Transaminase level was ≤20 NL in all gr. Doses were adjusted in pts who experienced Tbili modifications or dose-limiting toxicity (DLT). Blood was sampled up to 24 h post infusion for PK evaluation. Twenty-two pts were treated (M/F: 15/7, median age: 53, PS 0–2): 7 pts-26 cycles (cy), 4 pts-14 cy, 6 pts-16 cy and 5 pts-20 cy so far in gr A, B, C at 175 and C at 240 mg/m^2, respectively. DLTs observed at 1st cy: 1/7 pts-gr A (grade 4 febrile neutropenia-FNG4), 1/4 pts-gr B (FNG4), 1/6 pts-gr C (FNG4) at 175 mg/m^2 and 3/5 pts-gr C (grade 4 diarrhea-thrombocytopenia, FNG4) at 240 mg/m^2. Preliminary PK parameters, obtained by

a model-independent analysis from 13 pts-15 cy, showed a high increase in systemic exposure to CPT-11 (≈ 80–100%) and SN-38 (≈ 180–300%) in pts with liver dysfunction, even for slight hyperbilirubinemia as observed in gr B and could explain DLTs observed in gr C at 240 mg/m^2 as well as in gr B. Intermediate dose level for gr C (200 mg/m^2) and a new gr of pts with Tbili >3.0 NL with 100 rag/m^2 starting dose are now investigated (1 pt already included in each gr). Updated clinical and PK results will be presented.

1139 ORAL

Phase I and pharmacokinetic (PK) study of troxacitabine (b-L-dioxolan-cytidine;BCH-4556) on a daily × 5 day every 4-week schedule

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Purpose: Troxacitabine, the first of a new class of dioxolane analogs, has broad activity against solid tumors in preclinical studies. Troxacitabine is resistant to cytidine deaminase. The objectives of this study are to define the toxicities and MTD for troxacitabine given as a 30 min infusion daily × 5 days

Methods: 30 patients have received 76 courses. At 1.2 mg/m^2/day, delayed marrow recovery required a change in dosing interval to every 4 weeks. At 1.5 mg/m^2/day, DLT consisting of grade 4 neutropenia + fever was observed in 2 heavily pretreated patients (heavily pretreated = >6 prior cx of alkylators; Xrt to pelvis or >25% marrow; >2 cycles mitomycin C), Dose escalation was then stratified for both minimally and heavily pretreated pts. Heavily pretreated and minimally pretreated pts are currently accruing at the 1.2 and 1.8 mg/m^2/d dose levels, respectively. A patient with metastatic melanoma had a PR.

The PKs appear linear and fit a 3-compartment model. The fractionary urinary excretion (0–24 hr) of parent compound is 66 ± 22% and clearance is slow (mean clearance, 129 ± 44 ml/min/m^2).

Conclusion: The recommended doses for heavily and minimally pretreated pts are projected to be 1.2 and 1.5–1.8 mg/m^2/day, respectively. The PK profiles of troxacitabine are clearly distinctive relative to other nucleoside analogs.

1140 ORAL

NCIC CTG IND 103: A Phase I and pharmacokinetic (PK) study of the novel L-nucleoside analog troxacitabine (BCH-4556) given every 21 days

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Aims: Troxacitabine is a dioxolane L-nucleoside analog with broad cytotoxic activity in preclinical models. This study sought to define the safety and PK profile of troxacitabine given as a single 30-minute infusion every 3 weeks.

Methods: Starting dose was 0.025 mg/m^2. Doses were doubled until grade 1 or 2 toxicity seen; thereafter a modified Fibonacci schema was used up to the maximum tolerated dose (MTD) at dose level (DL) 13 (12.5 mg/m^2).

Results: 42 patients (pts) who had had no more than 2 prior chemotherapy (CT) regimens and with acceptable organ and marrow function were entered to 13 DL,s and received 120 cycles of troxacitabine. Median age was 52 yrs (34–75 yrs); 31 pts were male; performance status was 0 (13 pts), 1 (22 pts), or 2 (7 pts); the most common tumor types were renal cell (11 pts), colon (4 pts), rectal (3 pts) and head and neck (3 pts); the most common sites of disease were lung (24 pts), nodes (23 pts) and liver (12 pts); 25 pts had had prior CT and 21 pts prior radiation therapy. 20 pts were treated at 3.2 mg/m^2 without dose limiting toxicity (DLT); 3 pts received 8 mg/m^2 (1 DLT – gr 3 rash); 6 pts received 6.4 mg/m^2 (1 DLT – neutropenia); 3 pts received 8 mg/m^2; 7 pts received 10 mg/m^2 (2 DLT,s- rash); and 3 pts received 12.5 mg/m^2 (2 DLT,s – neutropenia). Hand-foot syndrome was reported in 2 pts. Rash was ameliorated by the introduction of prophylactic steroids in DL12. The most common toxicities reported were rash (43%), fatigue (29%), nausea (19%), grade 3/4 granulocytopenia (19%) and dry skin (14%). 1 pt with renal cell carcinoma achieved a confirmed partial response, and 13 patients had stable disease with median duration of 4.4 months (range 2.2–11.9 mths). PK,s were linear and at 10 mg/m^2 AUC was 1886 ng*h/ml; Cmax 882 ng/ml; clearance 159 mL/min, and T1/2 12 hrs.

Conclusions: The MTD of troxacitabine when given in this schedule is 12.5 mg/m^2 and the recommended doses for further study 10 mg/m^2. The DLT is granulocytopenia when prophylactic steroids are used.

1141 ORAL

Phase I studies with antimetabolites (A-M): Should dose escalation be driven by considerations other than body surface area (BSA)?

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Aim: The clinical development of A-Ms often seems confounded by the occurrence of dose limiting toxicities (DLT) at doses well below those ultimately recommended (RD) for further study, necessitating frequent expansion of dose levels and usually a change to more conservative dose escalation. This not only slows development but exposes more patients to ineffective doses of the drug, and raises questions about current methodology of including a single patient per dose level. Christian et al described results from the NCI phase I database showing first DLT occurred at 80% of the maximum tolerated dose (MTD).

Methods: Starting dose, number of dose levels, dose at first DLT, MTD and RD was extracted from the NCI-Canada phase I trial database, and from a literature survey of phase I studies published between 1991–1998. Combination phase I studies were excluded.

Results: 11 trials with A-M and 18 with other cytotoxic agents were reviewed. The median dose at first DLT/MTD was 44% ± 0.21 for A-Ms and 76% ± 0.20 for other cytotoxic agents ($p < 0.05$). Patients included in phase I trials are strictly controlled for adequate liver, renal and bone marrow function and dose is guided by BSA. Not controlled are gender, lean body mass, age, subclinical differences in renal or liver function, prior exposure to chemotherapy agents (usually), nutritional status nor pharmacodynamic aspects for e.g. intracellular polyglutamation.

Conclusions: For A-Ms toxicity appears to be incompletely predicted by dose alone. DLT may occur in certain patients at doses well below RD. Current phase I design may not be ideal for development of this class of compound.

1142 POSTER DISCUSSION

Phase I study 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 (DLTs), and the pharmacokinetics of BMS-184476 given weekly on day (d) 1, 8 and 15 by a 1-hour infusion in patients (pts) with advanced malignancies. Courses (crs) 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 pre-defined 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. All pts but 2 had received prior chemotherapy (median 2, range 1–5 regimens). Dosing/toxicity data is available for 22 patients. No drug-related severe toxicity was reported at 7, 14 and 28 mg/m^2 in 1, 2 and 8 pts respectively. At 40 mg/m^2, 1/14 pt developed a DLT (Grade (Gr) III diarrhea) and GrIII neutropenia with fever. At 50 mg/m^2, no DLT were observed in 4 pts. At 60 mg/m^2, 1/1 pt developed a GrIV febrile neutropenia and GrIII diarrhea (DLT). Additional non-hematological drug-related toxicities reported include GrII diarrhea (6 pts), GrII asthenia (6 pts), GrII nausea/vomiting (6 pts), GrII arthralgia/myalgia (5 pts), GrII anorexia (4 pts), GrII peripheral neuropathy (2 pts), and GrII mucositis (2 pts). No hypersensitivity reaction was reported. Activity has been documented in patients with breast cancer, NSCLC and colon cancer. MTD has not been reached and the study is enrolling patients at 60 mg/m^2.