adequate marrow, hepatic, and renal function; and EF ≥45%. Patients received paclitaxel 225 mg/m2/3 hr, carboplatin (AUC 6) q 3 weeks, and trastuzumab 4 mg/kg IV day 1, then 2 mg/kg weekly for ≤1 year.

Results: From 8/99 till 5/00, 139 patients were screened: 50 (36%) were HER-2/neu (-); 38 (27%) were HER-2/neu 1+; 31 (22%) 2+; and 13 (9%) 3+; 7 (5%) were indeterminate. 56 patients were enrolled, of whom 52 were eligible (21 [40%] were 1+, 23 [44%] were 2+, and 8 [15%] 3+). The incidence of grade ≥3 (4) neutropenia and thrombocytopenia was 53% (31%) and 13% (2%), respectively. Asymptomatic grade +/<2 reduction in LV ejection fraction occurred in 7%. Other non-heme toxicities, including nausea, fatigue, arthralgias, and peripheral sensory neuropathy, were mild to moderate and matched those expected with carboplatin and paclitaxel alone. At median potential follow-up of 12 months, 18 (35%) patients went on to maintenance H. 18% of 51 evaluable patients responded; 5 (10%) remain on treatment; and 50% of patients remain alive, including 5 of 8 HER-2/neu 3+ patients. Projected median time to progression is 3.2 months, and median survival is 9.8 months.

Conclusion: Combination paclitaxel, carboplatin and trastuzumab is feasible. Toxicity appears no worse than cytotoxic therapy alone. Critical assessment of trastuzumab's role in advanced NSCLC will require phase III trials.

99 ORAL

A phase III randomised trial testing accelerated chemotherapy with GM-CSF or cotrimoxazole in extensive-disease (ED) small-cell lung cancer (SCLS). A study by the European Lung Cancer Working Party

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Purpose: To determine the impact on survival of accelerated chemotherapy.

Methods: ED SCLC patients were randomised between 6 courses of standard chemotherapy EVI (epirubicin 90mg/m*, ifosfamide 5g/m*, and vindesine 3mg/m* on day 1) every 3 weeks (arm A) or accelerated EVI every 2 weeks either with GM-CSF 5 μg/kg day 3 to 13 (arm B) or cotrimoxazole (160mg trimethoprim plus 800mg sulfamethoxazole) (arm C) supports.

Results: 233 eligible patients were randomised. Absolute dose-intensity was higher in arm B ($p<0.001$). Best response rates were respectively for arms A, B, and C, 59%, 76% and 70%. It was significantly higher in arm B in comparison to arm A ($p = 0.04$). No significant survival difference was observed between the 3 arms. The median survival times and 2-year rates were respectively for arms A, B and C, 286 days and 5%, 264 days and 6% and 264 days and 6%. There was no difference in toxicity except for shorter duration of neutropenia and increased severe thrombocytopenia in arm B. Multivariate analysis identified as independent prognostic factors for survival, age, Karnofsky PS and neutrophil count.

Conclusions: Our trial failed to demonstrate, in ED SCLC, a survival benefit of accelerated chemotherapy with GM-CSF or cotrimoxazole supports.

New drugs – Phase I: Pharmacogenetics

100 ORAL

Exisulind and CP461 inhibit cell growth, induce apoptosis, and have synergy with herceptin and taxotere in breast cancer cells

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Purpose: Exisulind (AptosynTM) and CP461 belong to a new class of pro-apoptotic drugs termed selective apoptotic anti-neoplastic drugs (SAANDs). Their pro-apoptotic effects are independent of COX I or COX II inhibition, p53, Bcl-2 or cell cycle arrest. In this study, the anti-proliferative and pro-apoptotic effects of exisulind or CP461 alone and in combination with Herceptin or Taxotere on human breast tumor cells with differential expressions of HER2/neu and estrogen receptor (ER) were measured.

Methods: Cell growth inhibition with a 6 day exposure to the drug using sulforhodamine dye binding and apoptosis induction after 2 day exposure using DNA fragmentation by double antibody ELISA were determined for 8 breast tumor cells (MCF-7, MDA-MB-231, MDA-MB-453, MDA-MB-435S, MDA-MB-436, BT-20, BT474 and SR-BR-3). In combination studies, multiple drug effect/combination index (CI) isobologram analysis was done with CalcuSyn Software version 1.1.1 (Biosoft, Ferguson, MO 63135) based on principles described by Chou and Talalay.

Results: Exisulind and CP461 showed growth inhibition (IC50, 32 ~248 μM, 0.5~0.9μM, respectively) and apoptosis (EC50, 200~500 μM; 0.5~7.2 μM, respectively) in all eight cell lines independent of HER-2/neu and ER expression. Both exisulind and CP461 showed a synergistic effect with Herceptin in cell growth inhibiton and apoptosis induction specific for HER-2/neu over-expressing breast cells [CI = 0.27±0.09, P=0.02 (exisulind + Herceptin); CI = 0.26±0.17, P=0.03 (CP461 + Herceptin) in MDA-MB-453]. Synergistic or additive interaction with Taxotere was observed for both agents [CI =0.68±0.16, P=0.05 (MDA-MB-435S); 0.80±0.25, P=0.06 (BT-474) for CP461+Taxotere; ~0.63±0.23, P=0.03 (MDA-MB-453); 1.19±0.38, P=0.08 (MDA-MB-435S) for exisulind+Taxotere] and was independent of HER-2/neu status.

Conclusion: Exisulind and CP-461 demonstrate synergistic cytotoxicity in combination with Herceptin and/or taxanes against human breast cancer cells. The mechanism of drug interaction involves induction of apoptosis. Such combinations merit further clinical testing in breast cancer.

101 ORAL

A phase I study of T900607 given once every three weeks in patients with advanced refractory cancer. A National Cancer Institute of Canada-Clinical Trials Group Study (NCIC CTG-IND 130)

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T900607 is a novel tubulin-active agent which disrupts microtubule polymerization by a unique mechanism of action. T900607 may be active in tumours with acquired resistance to vinca alkaloids or taxanes. In April 2000 the NCIC-CTG initiated a phase I trial of T900607 given on a three weekly schedule in patients with advanced solid tumours who had incurable disease to establish the maximum tolerated dose (MTD), recommended phase II dose (RD), toxicity and pharmacokinetics. Sixteen patients have been enrolled in six doses levels to date. No dose limiting toxicities have been seen in the first five dose levels. At the first five dose levels, related toxicities were mild with grade 1 nausea in 3 patients, grade 1 neuropathy in 3 and grade 2 fatigue, fever, vomiting and injection site reaction each seen in one patient. No grade 4 toxicity has been seen and the only grade 3 toxicity is tumour pain in three patients that is possibly related. Hematological toxicity has included one grade 4 anemia at the first five doses and mild granulocytopenia. At the sixth dose level of 270mg/m2 grade 4 thrombocytopenia has been seen and that dose level is currently being expanded. No significant biochemical toxicity has been seen at the lower dose levels but one patient at the 6th level had a transient rise in troponin levels, not associated with any other evidence of cardiac damage. As one other patient in another current phase I trial of T900607 has also experienced a rise in this enzyme, additional troponin assessments will be conducted to determine if this drug has an associated cardiotoxicity. The trial is continuing to accrue patients with careful troponin and hematological assessments to define MTD. A full report of this trial including response rates, MTD determination and pharmacokinetics will be presented in October 2001.

102 ORAL

ZD1839 ('Iressa'), an orally-active, selective, epidermal growth factor receptor tyrosine kinase inhibitor (egfr-tki), is well tolerated in combination with gemcitabine and cisplatin, in patients with advanced solid tumours: preliminary tolerability, efficacy and pharmacokinetic results

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Aims: To assess the tolerability of ZD1839 ('Iressa') given continuously in combination with gemcitabine and cisplatin, and to determine whether the pharmacokinetic profiles of these three drugs are altered by concurrent administration.

Methods: ZD1839 was given as a single, oral, daily dose from day 2 onwards, at one of two dose levels (250 or 500 mg). Gemcitabine (1250 mg/m2) was administered as a 30-min infusion on days 1 and 8, and cisplatin (80 mg/m2) as a 2-h infusion on day 1, after gemcitabine. Cycles were repeated every 3 weeks for a maximum of 6 cycles, or until disease progression, toxicity or patient (pt) refusal. Recruitment of 6-12 pts was planned at each ZD1839 dose level. Pharmacokinetic analyses were done during cycles 1 and 2.

Results: Between November 2000 and February 2001, 18 pts were enrolled (M:F 11:7; median [range] age, 59 [30-71] years; WHO performance status, 0 [4 pts], 1 [11] and 2 [3]). Primary tumours: non-small cell lung cancer (NSCLC) (8 pts), adenocarcinoma of unknown primary (ACUP) (3), oesophageal (3) and other (4). All pts were chemonaive for advanced or metastatic disease. Nine pts were included at each ZD1839 dose level and all pts were assessable for toxicity. Toxicity at the 250 mg dose level comprised: G1 skin rash (3 pts), G1 diarrhoea (3), G3 asthenia (1), G3 thrombocytopenia (1), G3 vomiting (1) and G4 asymptomatic short-lasting (2 days) elevated hepatic transaminases (1). At 500 mg, 4 pts experienced G3 diarrhoea and 1 pt had G4 asymptomatic elevation of hepatic transaminases. Skin rash was observed in 7 pts but was generally mild (G1 [3 pts], G2 [3] and G3 [1]). No other severe toxicity or treatment-related deaths were observed. Fifteen pts are evaluable for efficacy, to date (1 pt withdrew after 1 cycle, 1 pt had only pleural effusion and 1 pt too early). Six pts had PRs (NSCLC [4 pts], ACUP [1] and pancreatic [1]), 7 pts had SD, including 2 pts with MRs (mesothelioma and oesophagus) and 1 pt with an unconfirmed PR (NSCLC); 2 patients progressed. Pharmacokinetic results will be available by September 2001.

Conclusion: p The combination of ZD1839 with gemcitabine and cisplatin is feasible and well tolerated, and appears highly active. A three-arm, multicentre, Phase III trial of the same combination, in patients with advanced NSCLC, has completed accrual with >1000 patients having been enrolled.

'Iressa' is a trade mark of the AstraZeneca group of companies

103 ORAL

A phase I dose escalation pharmacokinetic (PK) study of BAY 38-3441 administered as a short infusion once every three weeks

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Rationale: BAY 38-3441 is a camptothecin glycoconjugate that was designed to stabilize the lactone form of camptothecin in blood, thereby increasing the proportion of the lactone available for uptake by tumor cells.

Methods: BAY 38-3441 was administered as a single 30-minute intravenous infusion once every three weeks (q3wks) to patients with advanced refractory cancer. Patients received 20 (n = 3), 40 (n = 6), 67 (n = 3), 100 (n = 6), 140 (n = 3) and 210 (n = 3) mg/m^2/day q3wks BAY 38-3441. Plasma samples were taken at pre-defined time points for the determination of pharmacokinetic parameters, including C_{max}, AUC, t_{max}, $t_{1/2}$, and CL.

Results: Twenty-four patients (pts) with different solid tumor types have been accrued so far. The median age was 60 yrs (27–71), At 20 mg/m^2 1 pt developed brain metastases 16 days after dosing with BAY 38-3441. At 40 mg/m^2 1 pt with mCRC developed an increase of liver enzymes after the first dosing, but was considered disease-related rather than drug-related. At 67 mg/m^2 no TOX was observed. At 100 mg/m^2 1 pt developed bradycardia, hypotension, and loss of consciousness during drug infusion, and these conditions were considered possibly drug-related. No further TOX was seen. At 140 and 210 mg/m^2 no TOX has been observed so far. The following pharmacokinetic results were obtained.

PK parameters of BAY 56-3722 (free base of BAY 38-3441) and Camptothecin (means/SD)

Dose [mg/m^2]	20	40	67	100	140
BAY 56-3722					
C_{max} [mg/L]	1.85/1.47	4.27/1.33	9.38/1.27	7.39/1.36	13.1/1.63
AUC [mg*h/L]	1.50/1.71	4.83/2.20	20.3/2.02	8.52/1.73	16.2/3.03
$t_{1/2}$ [h]	1.10/1.69	2.65/1.44	9.20/2.51	4.31/1.69	10.2/1.28
CL [L/h]	19.2/1.67	13.8/2.16	5.26/1.85	21.4/1.60	13.3/3.16
Camptothecin					
C_{max} [µg/L]	3.39/1.58	16.8/2.50	15.3+	17.7/1.42	28.1/2.05
AUC (0-tn) [µg*h/L]	53.3/2.74	537/2.70	410+	346/2.34	591/3.88
$t_{1/2}$ [h]	22.9/1.33	33.4/1.23	–	26.8/2.74	37.8/1.67

+) median

Conclusion: BAY 38-3441 administered intravenously once every 3 weeks is generally well tolerated up to the 210 mg/m^2 dose level. The PK parameters show large interpatient variation; the MTD has not been reached.

104 ORAL

Pharmacokinetic (PK) and Pharmacodynamic Analysis of Aspirin Administered with Multi-targeted Antifolate (ALIMTA)

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Purpose: ALIMTA (pemetrexed disodium, LY231514) is an antimetabolite, which inhibits three folate dependent enzymes. ALIMTA has a similar structure to methotrexate and both are excreted unchanged in the urine. Salicylates have been shown to impair the renal clearance and enhance the toxicity of methotrexate and thus patients (pts) taking non-steroidal anti-inflammatory drugs have been excluded from ALIMTA trials. Myelosuppression with ALIMTA is most pronounced in pts with folic acid or B12 deficiency.

Methods: Pts with normal renal function (as determined by glomerular filtration rate) were randomized to receive asplrin (ASA) either with the first cycle of ALIMTA (Group 1) or with the second cycle (Group 2). After the first cycle the pt was crossed-over to the alternate treatment. ALIMTA was dosed at 500 mg/m2 day 1 of a 3 week cycle. Vitamin supplementation was mandated: Folic acid, at least 350 µg per day, beginning at least one week prior to the first dose of ALIMTA;1000 µg of intramuscular vitamin B12 one to two weeks prior to first day of treatment then every 9 to 12 weeks. ASA 325 mg was given orally every 6 hours starting 2 days prior to ALIMTA with the 9th dose taken 1 hour prior to infusion. Samples for PK analysis were obtained with the first and second cycles.

Results: 24 pts (15 men and 9 women) with solid tumors, a median number of 2 prior therapies and a median age of 52 years (range: 34 - 71) received at least two cycles. ASA was administered to 12 pts in their first cycle and 12 pts took ASA with their second cycle. Preliminary PK analysis was performed on the first 7 pts in each group and showed that ASA ingestion did not appear to alter the clearance, mean steady state volume of distribution (Vss - L/m2), or area under the curve (AUC - µg/mL*hr). The median nadir neutrophil count for Group 1 after the 1st and 2nd cycles were 2.0 and 1.44 respectively and were 2.85 and 1.81 respectively for Group 2. A paired analysis of each individual pt's nadir neutrophil count from cycles 1 and 2 demonstrates that ASA did not augment the myelosuppression of ALIMTA (p=0.199). There were 3 episodes of grade 3/4 granulocytopenia and all occurred in cycles without ASA. There were no episodes of febrile neutropenia.

Conclusions: ALIMTA administered with folic acid has minimal myelosuppression and is well tolerated even when administered with ASA. Preliminary PK analysis suggest that ASA ingestion does not alter the disposition profile of ALIMTA

105 ORAL

Extended temozolomide (TMZ) dosing schedules permit the administration of higher TMZ dose intensities and inhibit the DNA repair enzyme O6-alkylguanine DNA alkyltransferase (AGAT)

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Purpose: AGAT has been implicated in the development of resistance to alkylating agents such as TMZ. Preclinical studies of prolonged exposure to TMZ have shown progressive depletion of AGAT. Extended TMZ dosing schedules may therefore decrease resistance and enhance cytotoxicity. We have conducted two dose-escalation studies to evaluate extended TMZ dosing.

Methods: Two TMZ dosing schedules were studied: 7-days on/7-days off (7/7) and 21-days on/7-days off (21/7). All patients received escalating doses of TMZ from 50 mg/m2 up to 150 mg/m2 per day; patients on the 7/7 schedule were titrated to a maximum dose of 175 mg/m2 per day.