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

T. Berghmans, J.P. Sculier, J. Lecomte, O. Van Cutsem, J.J. Lafitte, M. Paesmans, G. Koumakis, M.C. Florin, V. Ninane, J. Klastersky. [1] *Institut Jules Bordet, Internal Medicine, Bruxelles, Belgium*

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

M. Pegram[1], L. Liu[2], M. Lloyd[2], R. Pamukcu[2], D. Slamon[1], W.J. Thompson[2]. [1] *University of California Los Angeles, Hematology/ Oncology, Los Angeles, USA;* [2] *Cell Pathways, Inc., Horsham, PA, USA*

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)

K.A. Gelmon[1], K. Belanger[2], C. Britton[1], D. Soulières[2], S. Janke[3], J. Dionne, J. Powers, L.K. Seymour, J. McNally. [1] *British Columbia Cancer Agency, Medical Oncology, Vancouver, Canada;* [2] *CHUM Notre-Dame, Medical Oncology, Montreal, Canada;* [3] *British Columbia Cancer Agency, Clinical Nursing, Vancouver, Canada*

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

G. Giaccone[1], J.L. Gonzales-Larriba[2], E.F. Smit[1], A.T. van Oosterom[3], M. Martins[3], G.J. Peters[1], W.J.F. van der Vijgh[1], R. Smith[4], A. Fandi[4], S. Averbuch[5]. [1] *Free University Medical Center, Amsterdam, The Netherlands;* [2] *Hospital Clinico San Carlos, Madrid, Spain;* [3] *University Hospital Gasthuisberg, Leuven, Belgium;* [4] *AstraZeneca, Macclesfield, UK;* [5] *AstraZeneca, Wilmington, USA*

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.