tologically confirmed NSCLC inoperable were evaluable for analysis. 249 (Group A) were randomized to receive P 200 mg/m^2 in 3 h infusion, day 1 plus C AUC = 6, day 1 and 252 (Group B) to receive P 200 mg/m^2 in 3 h infusion, day 1, plus G 1 gm/m^2 days 1, 8. In both groups the treatment was given every 3 weeks with standard premedication and antiemetics without growth factors Eligibility criteria included WHO performance status 0–2, documented inoperable stage IIIA, IIIB, IV, stable brain metastasis, no prior chemotherapy and adequate renal and hepatic function. Baseline demographics and tumor characteristics were well-matched in both groups. Dose intensity of P was 94% and 89% in groups A and B respectively whereas for G 89%.

Results: Response rate for pts in group A was 28% (2%CR, 26%PR) (95%CI 21–36) whereas in group B 35% (5%CR, 30%PR) (95%CI 29–44) P = 0.12. Median TTP was 6.1 months (95%CI 5.2–7.0) for group A and 5.8 months (95%CI 5.1–6.5) for group B (P = 0.35). The median survival time was 10.3 months (95% CI 8.8–11.8) in group A and 9.8 months (95% CI 8.0–11.7) in group B (P = 0.36). The 1-year survival was 40.5% and 41.5% for groups A and B whereas the 2-year survival was 17.4% and 16.4% respectively The best prognostic factor for response was PS: 0–1 (P = 0.004) whereas for median and 1-year survival: stage (P = 0.001), PS (P < 0.0001) and response (P < 0.0001). No toxic deaths were seen. G 3/4 neutropenia was seen in 15% in both groups, thrombocytopenia G 3/4 2% in group A and 1% in group B and anemia G 3/4 5% and 2% in groups A and B respectively. Neurotoxicity G 3 was noticed in 8% and 6% in groups A and B respectively

Conclusion: These final results indicate that both combinations are effective, equally active with comparable toxicity. At least, in this study, the non-platinum combination is neither more active nor less toxic in NSCLC.

95 ORAL

Fractionated thoracic radiotherapy gives better symptom relief in patients with non-small cell lung cancer

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Aims: To determine whether fractionated thoracic radiotherapy offers better symptom relief, quality of life or survival than single fraction treatment in patients with advanced non-small cell lung cancer.

Methods: Patients were randomised to 30 Gy in 10 daily fractions (F) to the chest or a 10 Gy single fraction (S). The principal endpoint was physician-assessed symptom score for cough, chest pain, dyspnoea, haemoptysis and dysphagia. Subsidiary endpoints were survival and quality of life. Symptom scores were compared using the Wilcoxon signed rank test.

Results: 148 patients were randomised into groups matched for age, gender, histology, performance status and initial total symptom score (TSS). Patients randomised to F had lower TSS at 1 month review (p = 0.014) or at 1 and 3 month review (p = 0.001). This group also had better scores at either review for dyspnoea (p = 0.010), chest pain (p = 0.014) and cough (p = 0.029). Overall, TSS improved following TRT in 28/60 assessable patients with S and 40/57 with F (χ^2 = 6.64, df = 1, p = 0.01). Median survival was 23 weeks with S and 28 weeks with F (p = 0.197). Patients treated with S had higher anxiety scores than patients with F (1 month p = 0.01, 1 or 3 months p = 0.003).

Conclusions: Fractionated TRT offered better symptom relief and reduced anxiety compared to single fraction palliation, but did not increase survival.

96 ORAL

Postoperative oral administration of UFT for completely resected pathologic stage I non-small cell lung cancer: the West Japan study group for lung cancer surgery (WJSG), the 4th study

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[Purpose] To examine the efficacy of UFT, an oral 5-fluorouracil derivative anti-tumor agent, as a postoperative adjuvant therapy for p-stage I non-small cell lung cancer (NSCLC), because previous prospective studies suggested the efficacy for early-stage NSCCL patients. [Patients and Methods] Patients who underwent complete tumor resection with mediastinal dissection for p-stage I, adenocarcinoma (Ad) or squamous cell carcinoma (Sq) were eligible. A total of 332 patients were randomized to the surgery-alone group (control group) and the treatment group (UFT 400mg/m2 for 1 year after surgery, UFT group) after stratified by the histologic types. [Results] For Ad patients, the 5- and 8-year survival of the UFT group (n=120) were 85.2 and 79.5%, respectively, which seemed better than those of the control group (n=121) (79.2 and 64.0%, respectively) although without statistical significance (p=0.081). For p-stage IA Ad patients, the difference reached statistical significance (p=0.011). For Sq patients, there was no difference in the prognosis between the control group (n=48) and the UFT group (n=43). For all p-stage IA NSCLC patients, the 5- and 8-year survival rates of the UFT group were 85.8 and 79.7%, respectively, significantly better than those of the control group (76.7 and 61.6%, respectively, p=0.027). In contrast, UFT proved not to be effective for p-stage IB NSCLC patients. [Conclusions] Postoperative UFT administration proved to be effective for p-stage IA NSCLC patients, especially for p-stage IA, Ad patients.

97 ORAL

A three-arms phase III randomised trial comparing combinations of platinum derivatives, ifosfamide and/or gemcitabine in stage IV non-small cell lung cancer (NSCLC): an european lung cancer working party study

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Purpose: To determine, in stage IV NSCLC, if the combination of gemcitabine -a new active drug - with ifosfamide (IG) or with the cisplatin-carboplatin association (CCG) will improve survival (primary endpoint) in comparison to a first-generation regimen, cisplatin-carboplatin-ifosfamide (CCI).

Patients and methods: A total of 284 patients without prior chemotherapy and with metastatic NSCLC were randomised. Four were ineligible and 16 not assessable for responses. Cisplatin was given at 60 mg/m2 on day 1, carboplatin AUC 3 on day 1, ifosfamide 4.5 g/m2 on day 1 and gemcitabine lg/m2 on days 1,8 and 15. Courses were repeated every 4 weeks. Response was assessed after 3 courses and chemotherapy was continued in case of response until best response. There were 94 eligible patients in the CCI arm, 92 in CCG and 94 in IG.

Results: Objective response rate was, respectively for CCI, CCG, and IG, 23% (95% CI: 15-32), 29% (95% CI: 20-39) and 25% (95% CI: 16-33) (p = 0.61). Median survival time was respectively 24,34 and 30 weeks (p = 0.20); 1-year survival time 23%, 33% and 35% and 2-year survival time was 11%, 14% and 17% respectively. There was a significant survival advantage in disfavour of CCI in the subgroups of women and of patients older than 60 years. Toxicity was tolerable: severe alopecia was less frequent in the CCG arm, IG was significantly associated with more thrombopenia and CCG with more leucopenia.

Conclusion: The regimens including a new drug (gemcitabine) were associated with a better survival (statistically significant in some subgroups) than a classical first-generation cisplatin containing regimen in the treatment of stage IV NSCLC. The non-platinum combination with gemcitabine was as effective as the platinum regimen with gemcitabine.

98 ORAL

Phase II Eastern Cooperative Oncology Group (ECOG) pilot study of paclitaxel (P), carboplatin (C), and trastuzumab (T) in HER-2/neu (+) advanced non-small cell lung cancer (nsclc): early analysis of e2598

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Background: Multiple NSCLC cell lines and 20% to 50% of pathologic specimens express HER-2/neu, the target of trastuzumab (Tsai JNCI 1993;85:897). HER-2/neu expression has also proven to be an independent, unfavorable prognostic factor in resected patients with pulmonary adenocarcinoma (Cancer Res 1990;50:5184-91). Trastuzumab has demonstrated in vitro synergy with carboplatin and additivity with paclitaxel. ECOG therefore launched a phase II study evaluating combination carboplatin, paclitaxel and trastuzumab in patients with incurable, advanced NSCLC.

Methods: Eligibility stipulated measurable tumor; HER-2/neu positivity (1+ to 3+ by IHC, confirmed by central pathology review); ECOG PS 0-1;

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.