Results: Thirty-three patients were evaluable for toxicity. Grade 3 or 4 neutropenia occurred in 7 patients (21%), esophagitis in 7 patients (21%), digestive toxicities in 4 patients (12%). There was a trend of lower severe toxicities when amifostine was administrated. Of the 31 patients evaluable for response, 4 patients achieved a complete response (CR=13%), 15 patients achieved a partial response (PR= 48%) for an overall response rate (RR) of 61% (confidence interval 44% - 78% at 0.05). Nine patients had stable disease (SD=29%), and 3 patients had progressive disease (PD=10%). As pointed out in the Kaplan Meier's survival curve, the 1-year survival rate was 38%, the median survival (mS) was 11 months, at a median follow up of 9 months.

Conclusions: Preliminary analyses indicate that concurrent Navelbine and Cisplatin (2 cycles) with radiotherapy followed by 2 more cycles of the same drugs given as consolidation chemotherapy for advanced stage III NSCLC is feasible and well tolerated and has a positive effect on the response rate and survival.

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Mitogen-activated protein kinase (MAPK) and Akt as predictive factors for response to ZD 1839 therapy in non-small cell lung cancer (NSCLC) patients

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Background: Predictive factors for response to Tyrosine-Kinase Inhibitors (TKIs) are unknown. ZD 1839 is an oral active, selective Epidermal Growth Factor Receptor (EGFR) TKI, active in 10% of pretreated NSCLC patients. The impressive responses obtained in a so far undefined subgroup of NSCLC patients suggest that, in some patients, the EGFR pathway is crucial for malignant cells survival. EGFR activation leads to cell proliferation via Mitogen-Activated Protein Kinase (MAPK) and blocks apoptosis by phosphorilation of the anti-apoptosis protein (AKT). It is possible that only patients with both MAPK-AKT phosphorilation can benefit from ZD1839 therapy. This trial has been designed to test the hypothesis that clinical benefit (PR+NC lasting at least 6 months) is significantly better in patients with AKT-MAPK activation.

Treatment: Patients with locally advanced or metastatic NSCLC, not suitable for chemotherapy, were treated with ZD 1839 at daily dose of 250 mg until disease progression. At study entry histological specimens were collected, and MAPK/AKT were evaluated by immunohistochemistry.

Patients: Ninety-four patients fulfilled the inclusion criteria and entered onto the trial. Main patient characteristics were: median age 64 years (range 33-83), male/female ratio 59/35, stage IIIA/IIIB/IV 2/14/78, PS 0/1/2 38/46/10. Histology was: 49 adenocarcinoma, 10 bronchiolar-alveolar carcinoma, 19 squamous-cell, 16 undifferentiated. Previous chemotherapy-lines: 0/1/2/3+: 8/39/36/11. Twenty-nine patients were not pretreated with platinum (8 received ZD1839 as first line, 15 after gemcitabine and 6 after gemcitabine and vinorelbine failure). Seventy-five patients were pretreated with platinum and taxanes.

Results: At the time of this analysis only data on clinical activity are available. Response has been evaluated in 78 patients: we observed 12 PR (15.4%), 15 NC lasting at least 6 months (19.2%), 7 NC lasting at least 2 months but less than 6 months (8.9%) and 44 PD (56.5%). MAPK and AKT determination is ongoing

Conclusions: These data confirm the activity of ZD1839 in NSCLC. Data from all 94 patients and evaluation of ZD1839 activity and MAPK-AKT expression will be available for the meeting

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Phase 2 study of first line chemotherapy using CT-2103 (XYOTAX) in patients with non-small-cell lung cancer who are >69 years of age or who have performance status (PS) = 2

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Background: CT-2103 (XYOTAX™) is a tumor-targeted taxane designed to concentrate selectively in tumors. CT-2103 exposes normal organs to conjugated paclitaxel, which is non-toxic in vitro, thus minimizing overall toxicity. CT-2103 showed enhanced efficacy compared to paclitaxel/Cremophor in syngeneic and xenogeneic in vivo tumor models including lung tumors. Conjugation of paclitaxel to poly-L-glutamate enhances aqueous solubility and eliminates the need for Cremophor, resulting in a convenient 10-min infusion.

Material and methods: Chemotherapy naive patients with non-small-cell lung cancer (NSCLC) who are >69 years of age or with ECOG PS = 2 are eligible for this open-label, multicenter study. Patients receive a conjugated paclitaxel dose of 175 mg/m2 CT-2103 as a 10-minute IV infusion every 21 days for up to 6 cycles. Safety was assessed using NCI CTC (v 2). Efficacy assessments were done after every second cycle using RECIST.

Results: Twenty-eight patients have been treated. The median age was 76 (range, 49-88). Seven patients (26%) were PS=2; 4 of these were also > 70 years. Of the 25 patients evaluable for response, 18 (72%) achieved disease control; partial response, 2 patients (8%) or stable disease, 16 patients (64%). Fourteen patients (50%) completed 4 or more cycles of therapy. In PS = 2 patients median overall survival (OS) is 5.4 months. In PS = 0 or 1 patients, median OS is 7.8 months. Grade 4 drug-related neuropathy occurred in 2 patients. No other clinically significant drug-related grade 4 adverse events occurred. Grade 3 toxicities were limited to generalized weakness/fatigue (4 patients), neuropathy (3), and febrile neutropenia (1). Neuropathy and weakness/fatigue were seen in patients with concomitant progressive disease and significant disease-related comorbidities.

Conclusions: CT-2103 has demonstrated activity and was well tolerated in elderly and PS = 2 patients with NSCLC. Based on these encouraging results, enrollment in this study will continue with treatment at a higher dose of 235 mg/m2 in patients with PS=2 only. Two randomized phase 3 studies using CT-2103 as a single agent and in combination with carboplatin (Stellar 3 and 4) have been initiated in PS = 2 patients.

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Phase I trial of Cisplatin, Etoposide and CPT-11 triplet in patients with advanced stage SCLC. A Hellenic Cooperative Oncology Group study.

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Background: The unsatisfactory survival figures of extensive stage SCLC prompted us to develop a novel triplet by combining CPT-11, a most promising camptothecin derivative with the Etoposide-Cisplatin doublet which is considered standard therapeutic regimen for this type of cancer. This trial aimed to investigate the feasibility and toxicity and to define the optimal recommended dose (ORD) for phase II evaluation of the study regimen (CEC). Reporting of antitumor activity was a secondary endpoint.

Material and Methods. This was a multicenter dose finding study of single shot CPT-11 combined with cisplatin 20 mg/m^2 plus etoposide 75 mg/m^2 both given intravenously for 3 days. Eligible patients had advanced stage SCLC and normal liver and kidney functions. CPT-11 was escalated by steps of 40 mg/m^2 staring from 60 mg/m^2. Maximum Tolerated Dose (MTD) was defined the dose level where 2/6 patients at minimum developed dose limiting toxicity (DLT). The Common Toxicity Criteria v2 were used for toxicity assessment and the RECIST criteria for response evaluation. By design, at least 12 patients should be treated at mid-step between the MTD and the previous dose level, randomised to receive CPT-11 on day1 or day3 to better define the ORD and timing for CPT-11 administration.

Results. From March 2001 to December 2002, 37 registered patients received 199 treatment courses (median per patient cycles 6) at 4 dose levels of CPT-11: 60 mg/m2 (7 pts), 100 (5 pts), 140 (9 pts) and 120 (16 pts). Demographics: 35 male, median PS 1 and age 66. The MTD for this regimen was achieved at CPT-11 dose 140 mg/m^2. At the MTD 4/6 patients experienced DLT: 3 pts developed febrile neutropenia and one patient grade 3 diarrhea. Median time to nadir neutrophil counts was day 16 (range 13-19). The ORD was 120 mg/m^2 for CPT-11 combined with 20 mg/m^2 Cisplatin and 75 mg/m^2 Etoposide over 3 days and recycled every 3 weeks. Toxicity at ORD was acceptable: 3/16 cases had short-lived neutropenia and 3/16 diarrhea grade 2-3. There was no difference in toxicity between the two time-schedules of CPT-11 administration. Other toxicities reported were mild asthenia, vomiting and neurotoxicity. Among 30 evaluable for response patients a 73% objective response rate was documented with complete response observed in 5/6 cases with brain metastases. Median duration of response was 8 months.

Conclusions: Cisplatin, Etoposide and CPT-11 triplet is a well tolerated regimen with evidence of exceptional activity in patients with advanced SCLC. It thus warrants further clinical exploration in phase II.

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Early recognition of local relapse of lung cancer by follow-up of tumor marker CYFRA 21-1 level

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Background: Lung carcinoma is a polygenic disease. Early recognition of lung cancer in an early stage of disease as well as relapse provides an appropriate treatment. Tumor marker CYFRA 21-1 is a prognostic and predictive factor in non-small cell lung cancer (NSCLC) that contributes to earlier treatment. The aim is to contribute to earlier recognition of relapse of primary lung cancer by continous follow-up of patients with purpose of increase of efficiency of the clinical diagnostics.

Material and Methods: The study includes 882 patients with diagnosed lung cancer who were controled for therapy efficiency. Serum CYFRA 21-1 has been measured by ECLIA method before therapy and twelve times after the therapy through the period of 60 months. Measurements were performed along with the clinical methods in order to compare the results.

Results: The sensitivity of CYFRA 21-1 before therapy was 78,88% in 516 squamous cell carcinoma (SQC) patients and 70,77% in 366 adenocarcinoma (AD) patients, which contributed to diagnosis of NSCLC and justified the use of CYFRA 21-1 in clinical praxis. The sensitivity was 96,74% in SQC patients with relapse and 91,56% in AD patients with relapse.The sensitivity raises from stage IA to IIIA in both SQC and AD. The efficiency of therapy was evaluated using the first two measurements after applied therapy. Both median and Wilcoxon test proved significant differences between stages of disease in both histological types (p

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CT-guided stereotactic radiation therapy for stage I non-small cell lung cancers.

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SRT is highly effective for brain metastases from NSCLC. As such, we started CT-guided SRT for primary lesions of stage I NSCLC 9 years before. Between 1994 and 1999, initial 50 patients were treated. Of these 21 were medically inoperable and 29 refused surgery. In most patients, SRT was 50-60 Gy in 5-10 fractions for 1-2 weeks. 18 patients also received conventional RT of 40-60 Gy before SRT. A median follow-up period of living patients was over 5 years: range 45-90 months. The 5-year overall survival was 58% in all 50 patients and 72% in 29 patients who refused surgery. No definite adverse effects were observed except for 2 patients with minor bone fracture and 6 with temporary pleural pain. CT-guided SRT was highly safe and effective for stage I NSCLC. Additional studies should be warranted to confirm the efficacy of this new treatment.

810 POSTER

The influence of radiotherapy on lung function in patients with non-small cell lung cancer.

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Background: Radiotherapy may cause irreversible damage of normal lung tissue. However, only little is known about the relation between absorbed dose, irradiated volume and lung function.

Material: In a period from 1995 to 2002 218 patients with non-small cell lung cancer (NSCLC) were treated with curative intended radiotherapy. The distribution of disease-stage was: Twenty-six stage I, 25 stage II, 151 stage III, and 16 patients with recurrent disease after primary surgery. Radiotherapy was given with involved-field technique. Total dose to the planning target volume was 60 to 80 Gy. In 8 patients curative treatment were not accomplished. Lung function parameters in the shape FEV-1 and FVC were performed before treatment and every 3 month in the follow-up period.

Results: The changes in mean FEV-1 and FVC in percent of the initial value in time is demonstrated in the figure. At 48 months the mean FEV-1 was 85% (95% CI: 73-97%) and the mean FVC was 95% (95%CI: 85-105%) of the initial value.

Conclusion: Patients with NSCLC often have a compromised lung function. Curative intended radiotherapy may furthermore result in a moderate decrease in lung function parameters, especially FEV-1. This must be considered in each patient before final treatment decision.

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Adjuvant therapy with gefitinib ('Iressa', ZD1839) following complete resection in Japanese patients with non-small-cell lung cancer: safety report of the first 38 patients recruited

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Objective: A randomized, double-blind, placebo-controlled, Phase III multicenter trial to compare survival between adjuvant therapy with gefitinib 250 mg/day and placebo for patients (pts) with completely resected non-small-cell lung cancer (NSCLC).

Methods: Pts with completely resected NSCLC (IB, IIA, IIB or IIIA), within 4-6 weeks following surgery, were randomized to receive either 250 mg/day gefitinib or matching placebo for 2 years, until recurrence/secondary carcinoma or withdrawal criteria were met. Enrollment began in August 2002, and the planned accrual was 670 pts over 2 years.

Results: As of October 2002, 38 pts had been randomized into this trial*; 18 received gefitinib (M/F, 14/4) and 20 received placebo (M/F, 15/5). The demography of enrolled pts was well balanced between the two arms in terms of sex, performance status, and histology type and disease stage. The most common drug-related adverse events (AEs) were CTC grade 1/2 gastrointestinal and skin disorders, observed in 66.7% and 88.9% of pts who received gefitinib, and 25.0% and 30.0% who received placebo, respectively. Grade 3 drug-related AEs (liver function disorders, pneumonitis, eczema, and neutropenia) were seen in 22.2% of pts in the gefitinib arm and 5.0% in the placebo arm. The drop out rates were quite high in both arms with only 4/18 pts in the gefitinib arm and 12/20 in the placebo arm continuing treatment as of March 2003. Interstitial lung disease (ILD) was reported in 3 pts, 1 pt in the gefitinib arm died (they had taken concomitant medication of other ILD inducing drugs), and 2 pts in the placebo arm. There was no impact on surgery-related complication or wound healing between the two arms.

Conclusion: There were no unexpected AEs seen in an adjuvant setting compared with those reported in Phase II trials (IDEAL 1 and 2) of more advanced NSCLC pts (Fukuoka et al. JCO 2003; in press; Kris et al. Proc ASCO 2002; 21:292a). There was no impact on surgical-related complication when dosing gefitinib within 4-6 weeks after operation. Poor compliance in this trial may indicate that dose/schedule modification may be required in the adjuvant setting in Japan.

*The recruitment was stopped in October 2002 and the trial was finally terminated in March 2003 due to the difficulty in recruiting patients in Japan in the current environment, and poor compliance with dosing schedule.

'Iressa' is a trademark of the AstraZeneca group of companies