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.