

**Results:** Increase in doxorubicin intracellular accumulation as well as doxorubicin binding to DNA under genistein action was detected in most tumor samples investigated.

**Conclusions:** 1) Functional activity of MRP is an index of most NSCLC. 2) Taking into account high frequency of MRP gene or protein expression and high functional activity of MRP revealed in most lung tumors we answer the question proposed above: polymerase chain reaction, immunoblotting and immunohistochemistry analysis should be admitted as adequate methods to determine MRP-phenotype for multidrug resistance prediction in NSCLC patients. Supported by Russian Foundation for Basic Research (No. 01-04-49213)

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POSTER

### Correlation between tumor necrosis factor-alpha and D-dimer levels in non-small cell lung cancer patients

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**Background:** Recent studies have shown that activation of fibrinolysis occurs in non-small cell lung cancer (NSCLC), although the origin of this activation could not be related to consistent changes in plasminogen activator and inhibitor levels. Neutralization of endogenous tumor necrosis factor-alpha (TNF) in endotoxemia completely prevents fibrinolysis, suggesting a direct role of this cytokine in the activation pathway of the fibrinolytic system. Increased serum TNF levels can be found in lung cancer. Thus the present study was designed to investigate whether a correlation exists between TNF and coagulation (thrombin-antithrombin III, TAT) or fibrinolysis (D-dimer) activation in patients with NSCLC.

**Methods:** 130 patients with NSCLC (n=65, 53 males, mean age 65±8) or chronic obstructive pulmonary disease (COPD)(n=65, 51 males, mean age 67±9), treated at our Institutions, were enrolled. As control group 65 healthy donors (51 males, mean age 61±14) were studied. NSCLC was histologically diagnosed as adenocarcinoma (n=32) or squamous cancer (n=33), and staged according to the TNM classification: Stage I 29%, Stage II 9%, Stage III 36%, and Stage IV 26%. Plasma TNF (R&D) and TAT (Dade-Behring) levels were determined by ELISA kits. D-dimer levels were measured by an automated analyzer (Roche).

**Results:** The results obtained showed that median D-dimer levels were higher in NSCLC patients (2.95 ug/ml) compared either to COPD patients (1.07 ug/ml, p<0.0001) or controls (0.34 ug/ml, p<0.0001). Positive TNF levels (>10 pg/ml) were found in 26% of NSCLC compared to 3% of COPD and 4% of controls (p<0.0001). Median TAT levels were elevated in both NSCLC (6.9 ug/L) and COPD (5.7 ug/L) patients compared to controls (1.8 ug/L, p<0.001). Correlation analysis showed that D-dimer strongly correlated with TNF (rho=0.35, p<0.005), but not TAT levels, in NSCLC patients. Thus, to further analyze the relationship between D-dimer and clinical and laboratory variables of NSCLC, a multiple regression analysis including age, sex, stage, diagnosis, D-dimer, TAT and TNF levels was performed. Final model by stepwise analysis showed that TNF levels (regression coefficient= 0.38, p<0.03) were independently related to VEGF, but only in the subset of patients with adenocarcinoma.

**Conclusions:** These results suggest that increased levels of TNF might be responsible for an activation of fibrinolysis in patients with lung adenocarcinoma. Partially supported by Grant PF Ministero della Sanità.

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POSTER

### A full Navelbine Oral (NVB oral) treatment in combination with Cisplatin (P) followed by NVB oral single agent as consolidation therapy in advanced non small-cell lung cancer (NSCLC)

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**Background:** The combination of alternating NVB iv/oral with P has demonstrated similar activity as a reference regimen NVB iv + P in the treatment of advanced NSCLC (Jassem et al, Ann Oncol 2002). A multinational phase II trial was performed to investigate a new schedule of a full NVB oral treatment in combination with P followed by consolidation therapy with NVB oral as single agent in advanced NSCLC. Patients and methods: chemo-naïve stage III/IV NSCLC patients (pts) were eligible to be treated with 4 cycles on a 3 weekly schedule combining P: 80 mg/m<sup>2</sup> on d1 with NVB oral: 60 mg/m<sup>2</sup> on d1 & d8 for the first cycle with dose escalation of NVB oral at 80 mg/m<sup>2</sup> on d1 & d8 for the following cycles in absence of grade 3-4 neutropenia. Pts with objective response (OR) or stable disease (SD) received consolidation therapy with weekly NVB oral.

**Results:** between 04/01 and 04/02, fifty six pts were included (M/F 40/16), median age was 60 years (40-70), median KPS 90% (80%-100%), squamous (43%)/adenocarcinoma (45%), stage IV (70%), IIIB (22%). Fifty-five pts were evaluable for safety and 49 pts for efficacy. A total of 180 cycles of combination therapy were administered with a median of 4 cycles (1-5), the RDI was 86% for NVB oral and 96% for P. As consolidation therapy, 25 pts received a total of 281 administrations of NVB oral with a median of 9 (6-24). Thirteen pts achieved partial response (OR: 26.5%) and 22 pts (44.9%) had stable disease. Median progression free survival and overall survival were 3.8 and 10 months respectively. The main grade 3-4 toxicities (NCI-CTC) were neutropenia 34.5% pts, nausea 5.4% pts, vomiting 8.9% pts, fatigue 12.5% pts, one pt experienced grade 3 neuropathy while another one had grade 3 constipation and two pts developed neutropenic infection.

**Conclusion:** this schedule of NVB oral + P provides comparable activity as standard regimen with iv form with a better convenience. The consolidation therapy with NVB oral single agent maintained the therapeutic benefit and improved the patient acceptance and comfort.

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POSTER

### Role of gross tumour volume and dose parameters on outcome and toxicity of patients undergoing concurrent chemo-radiotherapy for locally advanced non-small cell lung cancer

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**Background.** Concurrent chemo-radiotherapy (CRT) is a recommended treatment for locally advanced NSCLC. However, CRT is generally associated with higher frequency of toxicity when compared to radiotherapy alone, and the prognosis still remains poor. The aim of this study was to evaluate the prognostic role of gross tumour volume (GTV) on clinical outcome, regardless of T and N status. In addition, we analysed variables important for the development of lung toxicity.

**Materials and methods.** We analysed retrospectively data from 25 patients (pts) with locally advanced NSCLC treated at our institution between 1999 and 2001. Pts characteristics were as follows: mean age 59.9 years (range 44-76), PS 0-1, stage IIIA/N2 (6 pts) and IIIB (19 pts), M/F ratio = 16/9. Pts received concurrent CRT, according to the following schedule: weekly paclitaxel 100 mg/m<sup>2</sup> plus carboplatin AUC 2 for 3 weeks, followed by weekly paclitaxel 60 mg/m<sup>2</sup> plus carboplatin AUC 2 for 6 weeks with concomitant conventional thoracic radiotherapy, 2 Gy per fraction, 5 fractions per week up to 60 Gy. Dose volume histograms were collected from the 3-D treatment plans. GTVs were recalculated for all pts and correlated with time to progression (TTP) and overall survival (OS). In correlation with the development of radiation pneumonitis (RP) WHO grade 2 or higher, the following variables were examined: GTV, planning target volume, mean lung dose, V20 and V30 (volume of lung receiving more than 20 and 30 Gy respectively). Lung parameters were considered both for two lungs taken as a paired organ, as for each lung separately.

**Results.** Pts were divided into two groups according to GTV: < 100 cc (13 pts) and > 100 cc (12 pts). Kaplan-Meier survival analysis showed significant differences between the groups considering both TTP and OS (Logrank  $p = 0.03$  and  $0.01$  respectively). There were no statistical differences in the two groups regarding age, stage or sex distribution. 9/25 pts (36%) developed RP grade 2 or higher. None of the variables examined correlated significantly to the development of lung toxicity.

**Conclusions.** Our preliminary results indicate that in NSCLC, GTV plays a prognostic role even in pts at the same clinical stage and receiving the same treatment combination of CRT. None of the dose parameters was a predictor of development of RP. In addition, there was no difference regarding mean lung dose among the pts who developed lung toxicity when compared to those who did not.

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POSTER

# Statistical analysis of survival in patients with advanced non-small-cell lung cancer (NSCLC) treated with gefitinib ('Iressa', ZD1839) in an expanded access program (EAP): preliminary results

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**Background:** In patients (pts) with refractory NSCLC for whom no other treatment options are available, there is an unmet clinical need for effective treatments which prolong survival. As part of a global EAP gefitinib ('Iressa', ZD1839), an orally active EGFR-TKI (epidermal growth factor receptor tyrosine kinase inhibitor) has been used to treat pts with NSCLC.

**Methods:** Of those pts eligible for entry, the majority had received and failed chemotherapy for advanced incurable stage III/IV NSCLC; a small minority were chemo-naïve pts for whom no other treatment options were available due to co-morbidity or low performance status. Pts received 250 mg/day gefitinib orally. Data collection was limited as the EAP was not designed to provide efficacy data. Duration of therapy and survival were measured from the start of initial therapy or earliest resupply date (if date of initial therapy was unavailable), to the last resupply date for ongoing pts or date of last dose for withdrawn pts. Periodic follow-up data for surviving pts after withdrawal was not collected and pts were censored for survival at withdrawal until death was reported.

**Results:** As of 28 February 2003, data were available on 18,245 pts; 1,093 pts were excluded (missing start or resupply dates) and follow-up was unavailable for 3,504 pts. The earliest resupply date was used as start of therapy for 76 pts. Results for all evaluable pts (confirmed to have started therapy) and for those who entered 1 or more years prior to analysis are shown.

	All evaluable pts (n=17,152)	Pts entered 1 or more years prior to analysis (n=5,755)
Mean duration of treatment, mths	2.61	4.1
No. pts treated for >6 mths	1564	1169
No. pts treated for >12 mths	378	373
Median survival, mths (CI)	5.1 (4.9-5.3)	5.9 (5.6-6.2)
1-year survival, % (CI)	29 (28-30)	33 (31-34)

These data are comparable to those obtained from pretreated pts with advanced NSCLC who received 250 mg/day gefitinib in 2 large Phase II trials (IDEAL 1 and 2) (Fukuoka et al. JCO 2003; in press; Kris et al. Proc ASCO 2002; 21:292a); mean durations of treatment were 2.8 and 2.5 months, median survival was 7.6 and 6.5 months, and 1-year survival rates were 35 and 27%, respectively.

**Conclusion:** An ad-hoc retrospective analysis has found that gefitinib provides unprecedented, clinically meaningful and durable antitumor activity in a group of pts with incurable NSCLC for whom no other treatment options are available. 'Iressa' is a trademark of the AstraZeneca group of companies

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POSTER

# The role of Her-2/neu expression on the survival of patients with non-small cell lung cancer (NSCLC). A systematic review of the literature with meta-analysis.

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**Background:** Neu prognostic value for survival in patients with lung cancer remains controversial. We performed a systematic review of the literature to clarify its impact.

**Material and methods:** Studies related to the assessment of neu in lung cancer patients were identified after an extensive review of the literature by an electronic search, completed by the references found in the selected articles. A team of nine investigators performed a methodological evaluation of each trial by using the European Lung Cancer Working Party scale, as previously described (Eur Respir J 2001; 18: 705). A study was called positive or negative if neu was respectively a significant favourable or unfavourable prognostic factor for survival (significant studies). Otherwise, a study was considered as non-significant. Combined hazard ratio (HR) for survival was obtained by the Peto method.

**Results:** Thirty studies were eligible: 24 dealt with NSCLC, 5 with adenocarcinoma and 1 with small cell carcinoma. Thirty-one % of the 4582 patients were positive for neu, without difference according to disease extent or histological type. According to neu expression, 13 studies were "negative", 1 "positive" and 16 not significant. The median quality score for the pooled trials was 57.6% (range: 37.4% to 82.6%). Significant studies had a statistically significant better quality score than non-significant studies (61.2% vs 52.6%,  $p = 0.03$ ). Respectively 86% and 56% of the significant and non-significant studies were evaluable for the meta-analysis. This suggested a potential bias favouring significant studies, when aggregating survival results. We calculated a HR by a random-effect method, including 20 studies assessing the role of neu in NSCLC (test of heterogeneity  $p = 0.001$ ). The HR was 1.55 (95% CI: 1.29-1.86), meaning that tumours without neu expression had a better prognosis. When we compared the studies with a quality score above and below the median quality score, we found respectively HR = 1.59 (95% CI: 1.23-2.04) and 1.50 (95% CI: 1.13-2.00).

**Conclusion:** Overexpression of neu might be a factor of poor prognosis for survival in NSCLC. Nevertheless, the potential bias in favour of the significant studies that we observed justified further prospective large size confirmatory study

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POSTER

# A phase II randomized study comparing docetaxel/cisplatin induction therapy followed by thoracic radiotherapy with or without weekly docetaxel in unresectable stage IIIA-IIIb non-small cell lung cancer

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A phase II randomized study comparing docetaxel/cisplatin induction therapy followed by thoracic radiotherapy with or without weekly docetaxel in unresectable stage IIIA/IIIB non-small cell lung cancer

**Background:** This study evaluated the efficacy and safety of induction chemotherapy (docetaxel/cisplatin) followed by either concomitant docetaxel-based chemotherapy plus radiotherapy or radiotherapy alone in locally advanced NSCLC.

**Material and methods:** 108 chemoradiotherapy-naïve patients with unresectable Stage IIIA or IIIB NSCLC, and WHO performance status  $\leq 1$ , received 2 cycles of induction chemotherapy (docetaxel 85 mg/m<sup>2</sup> d1 + cisplatin 40 mg/m<sup>2</sup> d1, 2 q3w). In cases of complete response, partial response or no change following 2 cycles of induction chemotherapy, patients were randomized to either thoracic radiotherapy (2 Gy for 5 d/w, total 60 Gy) with weekly docetaxel (20 mg/m<sup>2</sup>) [Group A] or radiotherapy alone (total 60 Gy) [Group B] q6w.

**Results:** An overall response rate (ORR) of 44% [95% CI: 34.252.9] was achieved after induction chemotherapy, with disease control reported in 86% of patients (PR 44%, SD 42%, progressive disease [PD] 12%, early death 2% [lung haemorrhage, sudden death]). Although NCI-CTC-defined grade 3-4 neutropenia occurred in 46% of patients, febrile neutropenia occurred in only 4%. Characteristics of the 89 patients randomized to local therapy were well balanced between the treatment arms. In the 89 treated patients (n=43 [A], n=46 [B]), a higher ORR of 58% was achieved for Group A (CR 5%, PR 53%, SD 7%, PD 26%) versus 48% for Group B (CR 2%, PR 46%, SD 9%, PD 35%). Despite a high incidence of grade 3-4 lymphocytopenia in the chemoradiotherapy arm (80% in Group A and 20% in Group B), infection only occurred in 5% of patients in Group A. Grade 3-4 neutropenia was low in both groups with no patient receiving radiotherapy plus docetaxel experiencing this toxicity; 2% of patients experienced grade 3 neutropenia in Group B. Since the cutoff date of 1 March 2002, 70%