included in the study. If less than 4 responses occurred in the first 19 registered patients, the study should be closed. Otherwise, accrual had to be pursue until a minimum of 55 eligible patients.

Results: 64 eligible patients were registered between 08/1998 and 01/2003. At this time, 56 patients have been evaluated. Their principal characteristics were: median age 62 years (41-78), median Karnofsky performance status 90, stage I/II/III/IV 23/1/12/20, histological type (epitheliomatous/sarcomatoïd/mixed) 33/9/3, male/female 48/8. Among 51 assessable patients, we observed 6 partial responses after 3 cycles. The best overall response rate at 6 cycles was 17.6% (9 PR) (IC 95% 7.1%-28.1%). After 3 cycles, grade III/IV leucopenia and thrombopenia were respectively observed in 48.1% and 0% of the patients. Non haematological toxicity was mild with grade II/III nausea and vomiting in 50% of the patients.

Conclusions The preliminary results of our phase II trial demonstrate the potential activity of the combination of cisplatin and epirubicin in malignant mesothelioma, with an objective response rate of 17.6%. Except for leucopenia, this regimen is well supported and compares adequately with other active combinations

781 POSTER

A randomized phase II trial of gemcitabine and either day 1 or day 8 carboplatin for advanced non-small cell lung cancer (NSCLC)

J. Iglesias[1], C. Crombie[2], W.I. Burns[3], C. Karapetis[4], R.M. Lowenthal[5], F. Kirsten[6], J.A. Davidson[7], F. Abell[8], W.H.H. Reece[1], P. DeSouza[1]. *[1] Eli Lilly Australia PTY Limited, NSW, Australia; [2] Nepean Hospital, Medical Oncology, NSW, Australia; [3] St Vincent's Hospital Melbourne, Department: Oncology, VIC, Australia; [4] Flinders Medical Centre, Medical Oncology, SA, Australia; [5] Royal Hobart Hospital, Medical Oncology, TAS, Australia; [6] Bankstown/Lidcombe Hospital, Oncology Unit, NSW, Australia; [7] Fremantle Hospital, Oncology, WA, Australia; [8] The Geelong Hospital, The Andrew Love Cancer Centre, VIC, Australia*

Background: Chemotherapy with platinum-containing regimens has been found to produce an improvement in survival and quality of life in patients with advanced NSCLC. The primary objectives of this study were to determine the toxicity and efficacy of gemcitabine (days 1 *and* 8) and carboplatin (on either day 1 *or* 8; Carb d1 or Carb d8 arms) in patients with advanced NSCLC. Secondary objectives included quality of life, duration of response, time to disease progression and survival.

Methods: This was a multi-center, open-label, randomized Phase II study. Eligible patients had histologically or cytologically proven Stage IIIB or IV NSCLC, with ECOG performance status $\leq$ 2. Gemcitabine (1000 mg/m^2) was given as an intravenous infusion over 30 minutes on days 1 and 8 of a 21-day cycle with carboplatin (AUC 5) given as a 1-hour infusion immediately after the gemcitabine infusion on day 1 or day 8.

Results: Forty patients were enrolled in this study, with 20 patients (pts) in each arm (mean age 62 yr; 17 females, 23 males; 9 pts with Stage IIIB disease, 31 pts with Stage IV disease). Reasons for treatment discontinuation were: therapy completed according to protocol (8 cycles) (7 pts), death due to study disease (2 pts), adverse event (1 pt), lack of efficacy/progressive disease (14 pts), patient decision (1 pt), physician decision (14 pts) and protocol violation (1 pt). There were 4 partial responses in the Carb d1 arm and 6 partial responses in the Carb d8 arm, giving an overall response rate of 25%. There were no statistically significant differences between the two arms for median survival time (40.7 weeks in the Carb d1 arm, 39.1 weeks in the Carb d8 arm), time to progression (28 weeks Carb d1, 29.5 weeks Carb d8), or time to treatment failure (14.6 weeks Carb d1, 17.1 weeks Carb d8), and the one-year survival results were similar (27.8% Carb d1, 33.3% Carb d8). The achieved dose intensities of both gemcitabine and carboplatin were significantly higher in the group that received carboplatin on day 1 than in the day 8 group. Toxicities of note included grade 3/4 neutropenia (15 pts Carb d1, 11 pts Carb d8); grade 3/4 thrombocytopenia (14 pts Carb d1, 7 pts Carb d8); grade 3/4 dyspnea (5 pts Carb d1, 3 pts Carb d8); and febrile neutropenia (1 pt Carb d1). Nine patients in the Carb d1 arm, but only one patient in the Carb d8 arm, required a platelet transfusion. There was no clear difference in quality of life, as assessed by the EORTC QLQ-C30 and QLQ-C13 scales after three and six cycles of treatment.

Conclusion: The two gemcitabine-carboplatin schedules were of similar, moderate efficacy in treating patients with advanced NSCLC, however, fewer patients in the arm that received carboplatin on day 8 experienced grade 3/4 neutropenia and thrombocytopenia and required platelet transfusions.

782 POSTER

CPT-11- Gemcitabine as second line chemotherapy in small cell lung cancer (SCLC). A multicentric phase II trial.

M. Domine[1], M. Provencio[2], R. Garcia Gomez[3], J.L. Gonzalez Larriba[4], D. Isla[5], J. Terrasa[6], J. Andrade[7], I. Maestu[8], L.G. Estevez[9], F. Lobo[10]. *[1] Fundacion Jimenez Diaz. Clinica de la Concepcion., Oncology, Madrid, Spain; [2] Clinica Puerta Hierro, Oncology, Madrid; [3] Hospital Gregorio Marañon, Oncology, Madrid; [4] Hospital Clinico San Carlos, Oncology, Madrid; [5] Hospital Clinico Universitario Lozano Blesa, Oncology, Madrid; [6] Hospital Son Dureta, Oncology, Mallorca; [7] Hospital Virgen de la Salud, Oncology, Toledo; [8], Hospital Virgen de los Lirios, Oncology, Alcoy; [9] Fundacion Jimenez Diaz. Clinica de la Concepcion., Oncology, Madrid; [10] Fundacion Jimenez Diaz. Clinica de la Concepcion., Oncology, Madrid*

Background: CPT-11 and Gemcitabine have shown activity in SCLC even in pretreated patients (pts). We conducted a prospective phase II study to determine the activity of this combination as second line treatment in pts with SCLC.

Patients and methods: Pts were eligible if they had measurable or evaluable disease, performance status (ECOG) 0-2 and adequate hepatic, renal and bone marrow function. CPT-11 dose was 150 mg/m^2 (90-minute IV infusion) day 1, and Gemcitabine dose was 1500 mg/m^2 (30-minute IV infusion) day 1. Cycles were administered every 2 weeks.

Results: 47 pts were enrolled, 38 male and 9 female. Median age was 64 years (range 42- 78); 91.5% had PS 0 or 1. Twenty-seven pts had sensitive disease and twenty refractory disease (defined as progression within 3 months of starting first-line treatment). A total of 306 courses have been administered (median 6 per patient, range 1 -12).

To date all the pts were evaluable for toxicity and 39 for efficacy. Response rate (RR) was 31% (95% C.I: 17 47.6%), 1 patient with sensitive disease achieved a complete response (2.5%). 33% of pts showed stable disease (SD) and 36% progression (PD). The RR in refractory disease was 22.2%(95% C.I: 6.4 47.7%), SD 38.9% and PD 38.9%. In sensitive disease RR was 38% (95 C.I: 18 61.6%), SD 28.6% and PD 33.3%. Median duration of response was 3 months, median time to progression 6 months (95% C.I: 4.5 7.4 m) and median survival 9.3 months (95% C.I: 5.8 12.8 m).

Toxicity was very mild without grade 3- 4 hematological toxicity. Non-hematological toxicity was also mild, grade 3-4 toxicity including was observed in <1% of cycles (Nausea/ vomiting, asthenia, renal, hepatic or diarrhea). 3 pts developed skin toxicity grade 1-2, and 5 alopecia grade 1 3.

Conclusions: This combination is active as second line treatment of SCLC, showing an encouraging median survival. The profile of toxicity is very mild. Further development of this combination is warranted.

783 POSTER

New EGFR variants around the EGFRvIII region in non-small cell lung cancers(NSCLC)

M. Sugita, F.R. Hirsch, W.A. Franklin. *University of Colorado Cancer Center, Pathology, Denver, USA*

Epidermal growth factor receptor (EGFR) is a 170kDa transmembrane glycoprotein and is overexpressed in various human malignancies including NSCLC. While it is a potential target for prevention and therapy, EGFR is also expressed by normal lung. An RNA variant (EGFRvIII) has been described in a number of tumors including NSCLC in which there is an 801bp deletion (exon 2 to 7). This variant has been reported in tumors but has been absent from normal lungs and cell lines. Its absence from normal lung suggests that it may be used as a biomarker or chemotherapeutic target. However, there are few clinical reports on EGFRvIII in lung cancers to date. One immunohistochemical study has found EGFRvIII in 16% of non-small cell lung cancers. While EGFRvIII has been detected by RT-PCR and sequenced in gliomas, prostate cancers, and breast cancers, no similar studies have been carried out in lung cancers so far.

We examined total RNAs from 18 NSCLC cell lines, 6 benign bronchioepithelial primary culture cells, and 48 non-small cell primary lung tumors by RT-PCR (regular RT-PCR or nested RT-PCR) using several primer pairs spanning EGFRvIII (EGFR exon 1-8). When a truncated EGFR variant was present in PCR reaction mixture, we isolated the truncated product from ethidium bromide stained agarose gels and sequenced the cDNA created from the isolated product.

We were unable to confirm the presence of EGFRvIII in NSCLC cell lines, primary tumors, or normal bronchioepithelial primary culture cells. Wild type EGFR was demonstrated in 78% primary tumors, 94% cell lines, and 83% bronchioepithelial primary culture cells. In addition, we found 10 truncated EGFR variants that did not correspond by sequence analysis to EGFRvIII. These new variants were present at variable copy number. They may not be

specific to tumor, because several were also expressed in normal primary bronchial cell cultures. Three of the 10 new variants were frame shifts and the remainder introduced termination codons. We conclude that wild type EGFR is the most frequently expressed RNA species in NSCLC. In addition, many previously undescribed EGFR variants are present at variable copy number but EGFRvIII is rare if it exists at all. The region spanning EGFR exon 1-8 may be genetically or epigenetically unstable.

784 POSTER

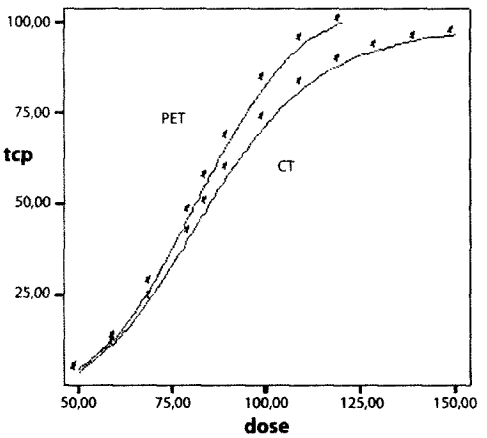
Increased Tumor Control Probability (TCP) and radiation dose escalation by FDG-PET planning of patients with N2/N3 M0 non-small cell lung cancer (NSCLC): A modeling study.

A. van der Wel[1,2], S. Nijsten[2], S. Bentzen[3], M. Hochstenbag[1], U. Bull[4], L. Lutgens[2], R. Wanders[2], B. Wouters[1,2], P. Lambin[1,2], D. De Ruysscher[1,2]. [1] *University Hospital, Maastricht, The Netherlands;* [2] *Maastro, radiotherapy, Maastricht, The Netherlands;* [3] *Gray Cancer Institute, Northwood, United Kingdom;* [4] *University Hospital, Aachen, Germany*

Purpose: To evaluate the feasibility of radiation dose escalation by incorporating FDG-PET scan data in radiotherapy planning of N2/N3 NSCLC and to estimate the resulting gain in local tumor control.

Methods and Materials: 21 consecutive patients with CT stage N2/N3 M0 NSCLC were studied. For each patient two 3D conformal treatment plans were made: one with a *CT* based PTV and one with a *PET-CT* based PTV. Dose and volume parameters predictive for lung and esophagus toxicity were analyzed for comparison between both plans. For each patient, radiation dose escalation for CT versus PET-CT PTV was calculated based on constraints for the lung, the esophagus and the spinal cord. The Tumor Control Probability (TCP) was calculated for each plan. The dose response curves were modeled based on the data of Martel et al. (Lung Cancer 24 (1999) 31-37) and with allowance for the reduction of geographical misses with CT-PET based treatment planning.

Results: Using PET-CT based PTV for treatment planning resulted in an absolute reduction of geographical miss of 14%. This led to a steeper TCP curve and therefore the possibility of achieving local control at lower doses (figure).



All lung and esophageal dose-volume parameters were significantly improved for CT-PET planning, allowing dose escalation. Taking lung, esophageal and spinal cord constraints into account and using *standard* 3D *planning*, there was an increase of TCP using PET-CT planning rather than CT planning (table).

Constraint	tcp-ct (%)	sem	tcp-pet-ct (%)	sem	p*
All	14.16	5.58	22.77	7.13	0.053
Lung	50.37	8.45	58.05	8.82	0.005
Esophagus	25.17	7.16	46.46	10.09	0.005
Myelum	25.36	6.99	37.55	8.55	0.041

Conclusions: Integrating PET scan data in radiotherapy treatment planning of N2/N3 NSCLC patients increased TCP even with standard 3D planning. Moreover, inclusion of PET information facilitated dose escalation in most cases.

785 POSTER

The value of the expression of thyroid transcription factor-1 (TTF-1) in malignant pleural effusion smears for distinguishing primary from metastatic lung carcinomas

P. Athanassiadou[1], M. Gonidi[1], A. Liossi[1], E. Petrakakou[1], A. Bandis[2], P. Athanassiades[2]. [1] *Medical School, The National and Kapodistrian Univ, Pathology Lab, Cytology Dept, Athens, Greece;* [2] *"Alexandra" University Hospital, Clinical Therapeutics, Athens, Greece*

Background: Thyroid transcription factor-1 (TTF-1) is expressed in the epithelium of the lung and is essential for lung morphogenesis. The aim of this study was to evaluate the expression of TTF-1 in pleural effusion for distinguishing between tumours of lung and non-lung origin.

Material: Forty-two (42) effusion smears were studied from patients with malignant diseases (20 lung adenoCa, 8 small cell lung carcinomas, 2 squamous cell carcinomas, 5 ovarian carcinomas and 7 breast carcinomas). An immunocytochemical method was performed with the use of anti TTF-1 antigen.

Results: Positive immunoreactivity of TTF-1 was observed for lung adenocarcinoma (55%) and small cell carcinomas (62.5%). No or very low reaction was observed for all other carcinomas.

Constraint	tcp-ct(%)	sem	tcp-pet-ct (%)	sem	p*
All	14.16	5.58	22.77	7.13	0.053
Lung	50.37	8.45	58.05	8.82	0.005
Esophagus	25.17	7.16	46.46	10.09	0.005
Myelum	25.36	6.99	37.55	8.55	0.041

*2-tailed p-value from paired t-test

Conclusions: TTF-1 is a specific marker for primary lung adeno- and small cell carcinomas. Furthermore is a useful marker for the differential diagnosis between primary and metastatic adenocarcinomas of the lungs.

786 POSTER

Intratumoral homogeneity of gelatinolytic activity in resected lung adenocarcinoma

R. Nakahara[1,2], K. Nagai[3], Y. Nishiwaki[3], A. Ochiai[1]. [1] *National Cancer Center Research Institute East, Pathology division, Chiba, Japan;* [2] *Tochigi Cancer Center, Division of Thoracic diseases, Tochigi, Japan;* [3] *National Cancer Center Hospital East, Division of Thoracic Oncology, Chiba, Japan*

Background: Matrix metalloproteinase-2 (MMP-2) is involved in invasion and metastasis of various malignant tumors. There are only a few reports investigating the relationship between tumor MMP-2 activity and clinicopathological features or intratumoral distribution of MMP-2 activity in lung. The aim of this study is to light up the characteristics of operable lung adenocarcinoma patients with high MMP-2 activity and intratumoral heterogeneity of MMP-2 activity.

Material and methods: A total of 70 consecutive primary lung adenocarcinoma patients operated on at National Cancer Center Hospital East were used in the study. MMP2 activity of each carcinoma tissues and the corresponding normal lung tissues was investigated by gelatin zymograpy and MMP-2 activation ratio (active MMP-2/total MMP-2) was measured. The MMP-2 activation ratio was compared with clinicopathological factors. In 24 cases, MMP-2 activity was examined in both central and peripheral portion of the tumor separately. Localization of gelatinolytic activity on tissue sections was examined by film in situ zymography (FIZ).

Results: Lung adenocarcinoma tissues of male and smokers possessed significantly higher MMP-2 activation rate than those of female and never smokers. In clinicopathological factors, lymph node involvement, vascular invasion, nuclear atypia and scar grade were significantly correlated with high MMP-2 activation rate in carcinoma tissues. MMP-2 activation ratio of central and peripheral area was significantly correlated ($r=0.860$; $p<0.0001$). These data and results from FIZ demonstrated the homogenous activation of MMP-2 regardless of tumor invasive and non-invasive sites.

Conclusions: This study clearly showed that MMP-2 activation is related to invasive phenotypes, but among the tumor with high MMP-2 activity, high MMP-2 activation is observed even in non-invasive area of the tumor.