CHEST TUMORS

2250 PHASE II STUDY OF PAZOPANIB (GW786034) GIVEN PREOPERATIVELY IN STAGE I-II NON-SMALL CELL LUNG CANCER (NSCLC): A PROOF-OF-CONCEPT STUDY

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Pazopanib is an oral angiogenesis inhibitor targeting VEGFR, PDGFR and c-kit. The objective of this single-arm trial was to determine the clinical/biological activity and safety of pazopanib given preoperatively in early stage NSCLC patients (pts). After biopsy and before surgery, pts received pazopanib 800 mg QD for 2.6 weeks followed by a 7-day washout period prior to surgery. The primary endpoint was tumour volume change assessed by high resolution CT (HRCT) images performed before and after pazopanib treatment. Secondary endpoints included RECIST response and safety. The frequency of centrally reviewed scans was blinded. Analysis of pre- and post-treatment plasma samples allowed correlation of cytokines/angiogenic factors (C/AFs) with tumour volume change. Levels of 52 C/AFs were measured by suspension bead arrays at baseline and at the time of therapy withdrawal. In six pts the proteomic profile did not change. The reasons of withdrawal were for progression (3), withdrawal (2) and death (1).

Results: Twenty out of 75 VeriStrat+ pts (27%) switched from VeriStrat+ to VeriStrat- profile at the moment of treatment withdrawal, due to progression, toxicity, discontinuation for any case, were analyzed by MALDI ToF MS. Mass spectra were acquired in linear mode using a Voyager DE-PRO mass spectrometer. Seventy-five spectra have been collected from seven positions in order to generate an average of 500 spectra for each specimen. Samples were randomly spotted on 3 different targets and 3 spectra were collected for each sample.

Conclusion: The EGFR tyrosine-kinase inhibitor erlotinib significantly prolongs overall survival in patients with advanced NSCLC, relapse > 3 months (mo) after (first-line) platinum-based chemotherapy, normal organ reserve, ECOG PS 0–2, >18 years and signed informed consent. After stratification, pts were randomized to (A) P 500 mg/m2 i.v. q 3 wks or (B) C/AUC 5 and P 500 mg/m2 both q 3 wks. Response was assessed 6 weekly according to RECIST and toxicity 3 weekly according to NCI-CTC criteria. In conclusion, short-term pazopanib treatment showed a favourable tolerability profile. The exploratory analysis found that baseline levels of several C/AFs may have predictive value for pazopanib treatment. Further clinical development in lung cancer is underway.

A RANDOMIZED PHASE II STUDY OF PEMETREXED (P) VERSUS PEMETREXED-CARBOPlatin (PC) AS SECOND LINE TREATMENT FOR PATIENTS (PTS) WITH ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)- NVALT 7

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Background: The role of platinum compounds as part of second line therapies in advanced NSCLC is ill defined. We performed a randomized phase II trial comparing P and PC in pts relapsing after platinum-based chemotherapy.

Methods: Main eligibility criteria: histological or cytological proof of advanced NSCLC, relapse > 3 months (mo) after (first-line) platinum-based chemotherapy, normal organ reserve, ECOG PS 0–2, >18 years and signed informed consent. After stratification, pts were randomized to (A) P 500 mg/m2 i.v. q 3 wks or (B) C/AUC 5 and P 500 mg/m2 both q 3 wks. Response was assessed 6 weekly according to RECIST and toxicity 3 weekly according to NCI-CTC criteria. The primary endpoint was time to progression (TTP). Secondary endpoints: objective response rate (ORR), overall survival (OS), toxicity. The study was designed to detect a 33% decrease in hazard of progression in the combination arm with 80% power (at a = 0.05 two-sided log-rank test).

Results: From October 2005 to May 2007 151 males and 89 females, median (range) age 59 (36-84), ECOG PS 0/1/2 39%/38%/9% were enrolled. With data complete and after a median follow up of 14.7 mo, median TTP for arm A was 2.8 mo and for arm B 4.2 mo (HR = 0.64 [0.49, 0.83], p = 0.05). ORR: 4% in arm A and 9% in arm B. Median OS: 7.6 mo versus 8.0 mo. Toxicities grade 3/4 were 29% in arm A and 44% in Arm B, mainly hematological without clinical sequel. No patient discontinued treatment due to toxicity. One fatal toxicity was encountered in arm A, none in arm B.

Conclusions: PC as second line treatment for relapsed NSCLC resulted in a significant 36% reduction of hazard of progression as compared to P alone. Based on the statistical assumptions of the study, further testing of CP in phase II setting is warranted. The role of platinum combinations in relapsed NSCLC deserves further study.

RESISTANCE TO EGFR TKIS AND SERUM PROTEOMIC PROFILE IN NSCLC PATIENTS

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In previous study, the serum proteomic profiles predictive for overall survival in pts with NSCLC treated with EGFR-TKIs was identified and validated. In the current study we evaluated if serum proteomic profile detected at the time of therapy withdrawal and compared to baseline, modifies in advanced NSCLC patients treated with gefitinib.

Methods: 220 sera from 110 pts collected at baseline and at time of treatment withdrawal, due to progression, toxicity, discontinuation for any case, were analyzed by MALDI ToF MS. Mass spectra were acquired in linear mode using a Voyager DE-PRO mass spectrometer. Seventy-five spectra have been collected from seven positions in order to generate an average of 500 spectra for each specimen. Samples were randomly spotted on 3 different targets and 3 spectra were collected for each sample.

Results: Pts characteristics are already reported in JNCI paper 2007;99:838-47. Thirty two were classified as VeriStrat+ (29%), seventy five pts were classified as VeriStrat+ (68%) at the moment of the beginning of gefitinib and three were classified as undefined (3%). Twenty eight out of 32 (87.5%) pts remained VeriStrat+ at progression. Twenty out of 75 VeriStrat+ pts (22%) switched from VeriStrat+ to VeriStrat- profile at the moment of treatment withdrawal and all of them had progressive disease due to new radiological lesions or progression in all tumor sites. In forty nine out of 75 VeriStrat+ pts (65%) the proteomic profile did not change. The reasons of withdrawal were different, mainly toxicity, minimal local tumor progression or death without radiological progression. In six pts (8%) an undefined profile at withdrawal was detected.

Conclusions: Proteomic profile is predictive for pts outcome and modifies from good to bad at progression in a group of pts treated with EGFR-TKIs. This suggests a possible correlation between serum proteomic profile and resistance to gefitinib.

MERIDEA: EXPLORATORY ANALYSIS OF THE TUMOUR GENE EXPRESSION DATASET FROM MERIT, A PHASE II STUDY IN ADVANCED NSCLC PATIENTS TREATED WITH ERLOTINIB

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1Pharmaceutical, F. Hoffmann-La Roche Ltd, Basel/SWITZERLAND, 2Pulmonary Diseases, Netherlands Cancer Institute, Amsterdam/NETHERLANDS, 3Pulmonary Diseases, Netherlands Cancer Institute, Amsterdam/NETHERLANDS, 4Clinical Oncology, Basel/SWITZERLAND, 5Research, F. Hoffmann-La Roche Ltd, Basel/SWITZERLAND, 6Thoracic Surgery, University of Texas MD Anderson Cancer Center, Texas/LONG ISLAND, 7Thoracic Surgery, New York Hospital, Flushing/UNITED STATES OF AMERICA, 8Scientific Communications, GlaxoSmithKline, Collegeville/UNITED STATES OF AMERICA, 9Medical Oncology Service, Vall d’Hebron Hospitals, Barcelona/SPAIN

Background: The EGFR tyrosine-kinase inhibitor erlotinib significantly prolongs survival in advanced NSCLC patients. Methods to predict patient benefit prior to therapy are not established. The primary objective of the multicentre, open-label phase II MERIT study was to identify candidate genes differentially expressed in patients who had clinical benefit (CB) vs no CB with erlotinib.

Methods: Eligible patients had stage IIIIB/IV NSCLC. ECOG PS 0–2 were 218 years old, had failed ≥2 chemotherapy regimens or refused/were unsuitable for treatment. The role of platinum compounds as part of second line therapies in advanced NSCLC is ill defined. We performed a randomized phase II trial comparing P and PC in pts relapsing after platinum-based chemotherapy.
Chemotherapy). Before erlotinib treatment, all patients had a fresh-frozen biopsy for gene expression profiling. Erlotinib (150mg/day p.o.) was given until progression, death, or unacceptable toxicity. CB was defined as either an objective response or stable disease 21 weeks (according to RECIST). Other markers including EGFR FISH, EGFR IHC and EGFR/ERAS mutation were also evaluated.

Results: 264 patients from 26 centers in 12 countries were recruited. Gene expression profiles from 102 patients were suitable for statistical analyses. The primary analysis of CB vs no CB patients did not identify statistically significant genes after correction for multiple testing, thus (based on power calculation) no ‘highly predictive’ markers were found. However, an initial exploratory analysis identified 3 markers of response: EGFR, PSFH and RAPGEP5 (Tan et al, WCLC 2007). Validation of these findings is ongoing. Further exploratory analyses are being conducted utilising an alternative definition of benefiting patients, ‘gene-set’ analysis based on biological pathway/genomic location, and taking prior chemotherapy response as a covariate, referred to as MERIcGA. Results of these analyses will be presented and discussed.

Conclusions: MERIT is one of the largest multicentre, gene-profiling studies ever performed in NSCLC and the gene profile dataset is a valuable tool to assess the relevance of differential expression of pathway-related single genes or gene sets relative to various clinical endpoints. These analyses help to better understand cancer progression and treatment with targeted therapies.

### ADDITION OF CP-751,871, AN ANTI-IGF-IR ANTIBODY, TO PACLITAXEL AND CARBOPLATIN RESULTS IN HIGH ACTIVITY IN NON-CELL SMALL CELL LUNG CANCER (NSCLC), PARTICULARLY IN THE SQUAMOUS SUBTYPE

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Background: The insulin-like growth factor type 1 receptor (IGF-IR) is specifically expressed by normal epithelial cells and a variety of malignancies, including NSCLC. The biologic activity of the IGF-IR is modulated by the extracellular IGF binding proteins (IGFBPs), of which IGFBP-3 is the most abundant. The IGF-IR is an important paracrine/autocrine growth factor receptor that is involved in the growth and survival of tumor cells. Therefore, IGF-IR is a potential therapeutic target for NSCLC.

Methods: In this phase II study, 23 stages IIIB or IV NSCLC patients with untreated disease were given CP-751,871 (4 mg/kg) i.v. every 21 days, plus PAC (175 mg/m2 on day 1, 85 mg/m2 on day 8 and 175 mg/m2 on day 15) and PL (200 mg/m2 on day 1) every 4 weeks for up to 6 cycles. Tumors were evaluated for response and IGFBP-3 levels were measured. Median number of treatment cycles was 4, with 24.6% of pts progressing until disease progression following chemotherapy discontinuation. Pts progressing on PAC alone. As of January 2008, only 38% of pts on PAC alone had objective responses. Of these 6, 1 pt had complete response (CR), 1 pt had partial response (PR), 4 pts had disease stabilization (SD) and 1 pt had progression of disease. Median survival: 24 months (m) overall; 27 m in responders vs 10 m in non-responders (P<0.001); not reached in females vs 16 m in males (P=0.04); 27 m for pts with exon 19 deletion vs 16 m for pts with L858R mutation (P=0.03). Results of the multivariate analysis are shown in the table.

Conclusions: Customized erlotinib in EGFR-mutant NSCLC p results in longer survival in p with exon 19 deletion, P=0.04, and no brain metastases. The Spanish Lung Cancer Group has initiated the European Randomized Trial of Tarceva vs Chemotherapy (EURTAC) trial for stage IV NSCLC to further clarify the prognostic and predictive relevance of EGFR mutations.

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGCG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.20</td>
<td>0.91-5.36</td>
</tr>
<tr>
<td>≥2</td>
<td>3.74</td>
<td>1.26-11.1</td>
</tr>
<tr>
<td>EGFR mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 19 deletion</td>
<td>1 (ref.)</td>
<td></td>
</tr>
<tr>
<td>Exon 21 L858R mutation</td>
<td>2.12</td>
<td>1.10-4.53</td>
</tr>
<tr>
<td>Brain metastasis</td>
<td>No</td>
<td>2.8</td>
</tr>
</tbody>
</table>
Results: of the interim analysis: 76,747 pts were randomized to cediranib/placebo with the arms well-balanced for important baseline factors. Analysis stratified by baseline stratification factors obtained an estimated HR of 1.5 for PFS. Overall response rates (complete + partial) were 41% (20%) for cediranib/placebo (p=0.006). Hypertension, diarrhea, hand-foot syndrome, anorexia and mucositis were more common with cediranib but neither bleeding nor thromboembolic events were increased. More pts on cediranib required dose reductions (37 vs 4%) or discontinued protocol therapy (29 vs 12%) due to toxicity, and more grade 3+ toxicities (75 vs 47%, p<0.001) and fatal serious adverse events occurred (14 vs 1%, p=0.005). Accrual was halted and the trial unblinded at the recommendation of the data and safety monitoring committee.

Conclusions: The addition of cediranib 30 mg/d of antitumour activity of C-RP, but with increased toxicity. Updated results, including all enrolled patients and overall survival, will be available for presentation.

Table 232PD

<table>
<thead>
<tr>
<th>All regimens (1316 pts)</th>
<th>CB dts (464 pts)</th>
<th>CP dts (316 pts)</th>
<th>Non-platinum dts (13 pts)</th>
<th>Monotherapy (30 pts)</th>
<th>Other (110 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs of special interest*</td>
<td>Events (all grades grade ≥3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>230/43</td>
<td>88/11</td>
<td>108/25</td>
<td>3/0</td>
<td>4/2</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>137/4</td>
<td>71/2</td>
<td>47/2</td>
<td>0/0</td>
<td>5/0</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>12/10</td>
<td>8/7</td>
<td>3/3</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Wound-healing complications</td>
<td>13/1</td>
<td>7/1</td>
<td>4/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Embolism</td>
<td>98/57</td>
<td>38/21</td>
<td>50/29</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>5/3</td>
<td>2/1</td>
<td>2/1</td>
<td>0/0</td>
<td>1/1</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>33/1</td>
<td>185/11</td>
<td>116/10</td>
<td>3/1</td>
<td>2/0</td>
</tr>
<tr>
<td>CNS bleeding</td>
<td>3/3</td>
<td>0/0</td>
<td>2/2</td>
<td>1/1</td>
<td>0/0</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>49/2</td>
<td>33/1</td>
<td>12/1</td>
<td>0/0</td>
<td>0/0</td>
</tr>
</tbody>
</table>

*Pts may have experienced multiple events;
†data missing 1 pt
CONCLUSIONS: Patients with completely resected NSCLC and ERCC1-negative tumors derive a substantial benefit from adjuvant cisplatin-based CT in the analysis of IALT long-term results.

235PD
A NOVEL CLINICAL PROGNOSTIC SCORE INCORPORATING THE NUMBER OF RESECTED MEDIASTINAL NODES TO PREDICT RECURRENT AND SURVIVAL IN NON-SMALL-CELL LUNG CANCER

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Background: The number of resected lymph-nodes has been recently demonstrated to be an important clinical prognostic factor in early-stage breast and colorectal cancer. Here we evaluated the prognostic impact of the number of resected lymph-nodes in a series of NSCLC patients who underwent surgery at the Regina Elena National Cancer Institute.

Methods: A panel of established prognostic factors plus either 1) the number of resected nodes (RN) or 2) the ratio between the number of metastatic nodes and RNs (NR) were correlated with OS, CSS and DFS: using the Cox-regression model, Mantingale Residual Plots (MRP), classification and regression trees (CART), and maximally selected log-rank statistics were performed to find optimal cut-offs. Hazard ratios (HR) were computed.

Results: A data-set of 415 stage I-IIA, surgically resected NSCLC patients was retrieved. At multivariate analysis, both RNs and NRs were independent factors for longer OS, CSS and DFS (p<0.001). CART identified 10 nodes as the optimal cut-off for RNs. Patients with 4 < RNs <10 had a significantly better benefit in both CSS (p=0.02) and DFS (p=0.0005). In node-positive patients, a NR <9 significantly correlated with better OS, CSS and DFS. Stratification into High-, Medium-, and Low-Risk classes, based on High- (HRFs: stage, N-status, age, #RNs) and Intermediate-Risk Factors (IRFs: sex, grading, histology), efficiently predicted outcomes (p<0.0011 for OS, CSS, and DFS).

Conclusions: These results contribute to complete the panel of clinico-pathological prognostic factors for resected NSCLC. A prospective evaluation and comparison with molecular prognostic tools is warranted.

237PD
CUSTOMIZING ADJUVANT CHEMOTHERAPY BASED ON BRCA1 mRNA LEVELS IN RESECTED STAGE II-IIIA NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS (P)

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1Oncology Service, Catalan Institute of Oncology, Hospital Germans Trias i Palau, Badalona, Barcelona; 2SPAIN, 3Oncology Service, Hospital General de Alacant, Alicante; 4SPAIN, 5Oncology Service, Hospital de la Princesa, Madrid; Spain

Background: p with low BRCA1 mRNA levels attained longer survival when treated with cisplatin-based chemotherapy (Taron et al. 2004), while p with high BRCA1 levels attained longer survival when treated with taxanes-based therapy (Quinn et al. 2007). Early NSCLC p whose tumors had high BRCA1 levels had significantly worse survival (Rosell et al. 2007). Upregulated BRCA1 is part of a characteristic gene signature in aggressive lung cancers (Deeb et al. 2007).

Methods: Adjuvant chemotherapy was customized based on BRCA1 mRNA levels in 84/100 completely resected N1 and N2 NSCLC p. 11 p with high BRCA1 levels received doc/cisplatin (doc); 29 p with intermediate BRCA1 levels received doc/cisplatin (cis); 44 p with low BRCA1 levels received cis/gemcitabine (gem).

Results: Median survival has not been reached in p with high or intermediate BRCA1 levels, while it was 25.6 months (m) in p with low levels (p=0.04). In a multivariate analysis for survival in all 84 p, the hazard ratios (HR) were 5.23 for high BRCA1 levels (P=0.007), 3.57 for p with tumor size > 3 cm (P=0.07). In the multivariate analysis of 42 N2 p, the HRs were 0.13 for 18 p receiving postoperative radiotherapy (P=0.04) and 22 for 15 p with intermediate or high BRCA1 levels (P=0.01).

Conclusion: Interim analyses show that single-agent doc has no detrimental effect on survival in comparison with doc/cis. In addition, high BRCA1 mRNA expression could be a poor prognostic marker. The Spanish Lung Cancer Group has opened a phase III study of customized adjuvant chemotherapy based on BRCA1 mRNA levels in which p in the control arm receive doc/cis and those in the experimental arm receive chemotherapy according to their BRCA1 levels.
Background: We conducted a study in metastatic NSCLC where treatment was customized according to EGFR mut status and BRCA1 mRNA levels. Loss of BRCA1 function increases sensitivity to cisplatin and resistance to antitumorubol agents (Quinn et al. Cancer Res 2003). The Abraxas-RAP80 complex can modulate BRCA1 levels of all 3 genes and 11 m in other p. In the multivariate analysis of survival (table), we have reached in p with intermediate levels of all 3 genes; MS is 6 m in p with low or high levels; MS is 9 m in 34 p with intermediate BRCA1 levels and 11 m in 12 p with high BRCA1 levels (P=0.03). For the 60 p in whom Abraxas and RAP80 were analyzed, MS has not been reached in 15 p with EGFR mut. MS has not been reached in 32 p with low BRCA1.

Results: With a median follow-up of 10 months (m) for all 92 p, median survival (MS) has not been reached in 15 p with EGFR mut. MS has not been reached in 32 p with low BRCA1 levels. MS has been reached in p with intermediate levels of all 3 genes; MS is 6 m in p with low or high levels of all 3 genes and 11 m in p in other p. In the multivariate analysis of survival (table), BRCA1 expression emerged as a significant prognostic marker (hazard ratio [HR] for HR = 0.71; 95% CI, 0.58-0.88; P = 0.004). Conclusions: Low levels of BRCA1 indicate a favourable outcome to chemotherapy, and BRCA1 may be both a prognostic and predictive biomarker. The Spanish Lung Cancer Group has initiated the BRCA1 Expression Customization (BREC), a phase III randomized trial, to further elucidate the role of BRCA1.

Background: By (Avastin®), an anti-VEGF monoclonal antibody, prolongs progression-free and overall survival in advanced NSCLC pts. Infrquent BV-related serious adverse events (SAE) such as pulmonary hemorrhage (PH), and potential serious adverse events (AE) such as PH, dehydration, leucopenia, rectal, thoracic, 3/4 bleeding, arterial thromboembolic event, 1% ea; PH, <1%.

Results: As of Jan '08, 361 pts >65 yrs (median 70) and 955 pts as of 2/14/08, 996 evaluable NSCLC pts are enrolled. Median F/U is 6.1 mos; 84% of pts have 21 quarterly update. Key demographics are shown in the table. The majority of pts (79%) received first dose at 15 mg/kg/q3wks. BR radiographic features (n=550): central tumor, 33%; cavitation, 19%; SAEs to overall: 6%; grade 3/4 bleeding, arterial thromboembolic event, 1% ea; PH, <1%.

Conclusions: ARIES includes pts underrepresented in E4599 including pts with EGFR PS-2, brain metastasis, therapeutic AC at BL, and older pts, and will expand on current understanding of BV treatment for advanced NSCLC. Based on preliminary data, rates of PH and other targeted BV-related SAEs are low, despite inclusion of pts excluded from RCTs. Central tumors and BL cavitation were commonly identified. Updated safety data, treatment patterns and demographics will be presented at the meeting for >1200 pts.

Background: In advanced NSCLC, smoking status is a potential predictive factor of survival. Smoking status is a potential predictive factor of survival. Smoking status is a potential predictive factor of survival.

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Conclusions: Pts >65 yrs do not appear to be more likely to experience an AE of special interest than pts 56-65 yrs when treated with first-line 1L-based therapy. Previously observed higher risk of thromboembolic events in elderly cannot be confirmed in the currently analysed population. No unexpected safety signals, suggesting acceptable tolerability of therapy up to progression in elderly pts.

Table 1. Incidence of AEs of special interest for patients >65 and 56-65 yrs old

<table>
<thead>
<tr>
<th>Events (all grades)</th>
<th>&gt;65 yrs old (361 pts)</th>
<th>56-65 yrs old (955 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs of special interest*</td>
<td>244/42</td>
<td>61/100</td>
</tr>
<tr>
<td>Hypertension</td>
<td>75/12</td>
<td>153/91</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>51/2</td>
<td>86/2</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>4/3</td>
<td>8/7</td>
</tr>
<tr>
<td>Wound healing complications</td>
<td>5/0</td>
<td>6/1</td>
</tr>
<tr>
<td>Embolism</td>
<td>20/13</td>
<td>78/44</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3/2</td>
<td>2/1</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>85/9</td>
<td>266/14</td>
</tr>
<tr>
<td>CNS Malignancy</td>
<td>2/1</td>
<td>1/15</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>6/0</td>
<td>43/2</td>
</tr>
</tbody>
</table>

*Patients may have experienced multiple events; *All thromboembolic events; Evidence of CNS metastasis
with G4 thrombocytopenia and G3 fatigue. 18 pts having completed 3 cycles of treatment have been evaluated for most common grade 3/4 non-hematological toxicities included fatigue (3 p gr. 3) and 1 out of 4 additional partial R during follow-up was confirmed. Pharmacokinetics on the 1W confirmed a dose-proportional increase of drug exposure and its reproducibility between administrations with low intra-pt variability and without accumulation.

Conclusion: NVBo with this original schedule of 3 times a week concomitantly with RT for 6 w is well tolerated. The RD as single chemotherapy agent is 50 mg D1,3 and 5. Additional evaluation of dose-escalation is planned in combination with CDDP.

244P BEVACIZUMAB (AVASTIN®) IN COMBINATION WITH CISPLATIN AND DOCETAXEL AS FIRST LINE TREATMENT OF PATIENTS (p) WITH ADVANCED OR METASTATIC, NON-SQUAMOUS, NON- SMALL-CELL LUNG CANCER (NSCLC)

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Background: Bevacizumab (B) has been shown to add significant benefit to p with advanced non-squamous NSCLC when combined with carboplatin and paclitaxel (FDA-approved indication) or with cisplatin and gemcitabine (EMEA-approved).

Methods: In this single-stage phase II trial, p received D (75 mg/m2), C (75 mg/m2), and B (15 mg/kg iv) on day 1 every 3 weeks for up to 6 cycles, followed by B 15 mg/kg every 3 weeks until disease progression. Eligibility criteria included chemotherapy-naive stage IIIIB or IV incurable NSCLC of non-squamous histology, PS 0-1, no brain metastases, no history of hematopoietic, stable cardiac condition and no full dose anticoagulation. The primary endpoint was progression-free survival, with secondary endpoints of TTP, RR, OS and safety.

Results: 32 pts have been enrolled of a planned sample size of 47. Baseline characteristics were 34% females, median age 57.8 years old, PS 0: 41%/57%; adenocarcinoma/large cell carcinoma: 78%/9% (4 p with unclassified histology); stage IIIB/IV: 9%/88%. By the time of this analysis, 25 p had received at least one treatment cycle of B (range: 1-8) and they have been included in the safety evaluation. Hematotoxicities: 6 p experienced grade 3/4 neutropenia (3 febrile neutropenia); 1 p grade 4 leucopenia. The most common grade 3/4 non-hematological toxicities included fatigue (3 p gr. 3), alopecia (1 p gr. 4), mucositis (2 p gr. 3), diarrhea (1 p gr. 4), proctitis (1 p gr. 4) and fibrinolysis (1 p gr. 3). One patient died due to hemoptysis (R) having completed 3 cycles of treatment have been evaluated for tumor response by RECIST: 9 PR (81.8%), 1 SD (9.1%) and 1 PD.

Conclusions: This interim analysis shows that the combination of Bevacizumab, D and C is safe and well tolerated, with a trend of promising activity. Enrollment continues and updated results will be presented.

244P CONCOMITANT RADIOTHERAPY (RT) WITH A FRACTIONATED DOSE OF ORAL VINOREBINE(NVB)/CISPLATIN (CDPP) AND CISPLATIN (CDPP) AFTER INDUCTION CHEMOTHERAPY (CT) IN LOCALIZED ADVANCED NON SMALL CELL LUNG CANCER(NSCLC), FIRST RESULTS OF A PHASE II STUDY

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Background: Induction CT followed by concurrent RT-CT with Vinorebine (NVB)+ CDDP is recommended as a validated treatment of LA NSCLC. The oral formulation of NVB could simplifies the administration of CT before and during RT. A phase II trial was initiated to assess a new schedule: iv and oral NVB (NVBO) + CDDP as induction followed by a fractionated administration of NVBO + CDDP during RT.

Methods and materials: Patients (pts) with histologically proven stage IIIA and IIIB non-operable one intent for RT were treated with iv NVB 25 mg/m² and CDDP 80 mg/m² D1 and NVBO 60mg/m² D1 every 3 weeks for 2 induction cycles. Pts presenting a non progressive disease (PD) received a fixed dose of 20 mg NVBO at D1,D3 and D5 + CDDP 80 mg/m² D1 every 3 weeks for 2 more cycles during the RT (66 Gy 5 fractions of 1.8 Gy per week). The recruitment target is 60 pts.

Results: Between February 06 and December 07, 53 pts were enrolled and 27 were reviewed at the 1st expert panel meeting: stage IIIA (19%) and stage IIIB (85%); 52 % squamous cell; 9% adenoarcinoma; median age 65 years (range 46-73 years) and 25% more than KPS 90% (range 80-100%). 25 pts were evaluable for response after 2 cycles of induction, 40 % PR was reported. 38 of 25 pts received CT-RT. Assessment performed 1 month after the end of the concomitant treatment revealed 60% RR (56% in IIT) with 58 % PR, disease control (OR + SD) 84 %. 7 pts did not continue CT-RT due to PD (3 pts); adverse events (3 pts): heart failure G 3 pt, pericardial effusion 1 pt, radiation dermatitis G2 1 pt; 1 pt with PR underwent surgery. Tolerance was excellent: neutropenia G3-4 in 7 pts without febrile neutropeina; anorexia-neuphasgite G3 in 1 pt. No case of pulmonary fibrosis was reported.

Conclusions: This new schedule obtains a clinical benefit in 84% of pts with 60% of RR, which is very promising. Well-tolerance point, this fractionation of NVBO + CDDP allows complete treatment in 72 % of pts. Further follow-up is required in order to assess time to progression and survival.

244P BIWEEKLY DOCETAXEL AS FIRST-LINE THERAPY IN PATIENTS WITH ADVANCED NON- SMALL CELL LUNG CANCER (NSCLC) AND PERFORMANCE STATUS (PS) 2, A PHASE II STUDY OF THE GALICIAN LUNG CANCER GROUP

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Background: There is no standard treatment for patients (pts) with advanced NSCLC and PS 2. Docetaxel (D) is active and well tolerated on a biweekly schedule.

Methods: Pts with stage IIIB (with pleural effusion ) or IV incurable NSCLC of non-squamous histology, PS 0-1, no brain metastases, no history of hematopoietic, stable cardiac condition and no full dose anticoagulation. The primary endpoint was progression-free survival, with secondary endpoints of TTP, RR, OS and safety.

Results: 32 pts have been enrolled of a planned sample size of 47. Baseline characteristics were 34% females, median age 57.8 years old, PS 0: 41%/57%; adenocarcinoma/large cell carcinoma: 78%/9% (4 p with unclassified histology); stage IIIB/IV: 9%/88%. By the time of this analysis, 25 p had received at least one treatment cycle of B (range: 1-8) and they have been included in the safety evaluation. Hematotoxicities: 6 p experienced grade 3/4 neutropenia (3 febrile neutropenia); 1 p grade 4 leucopenia. The most common grade 3/4 non-hematological toxicities included fatigue (3 p gr. 3), alopecia (1 p gr. 4), mucositis (2 p gr. 3), diarrhea (1 p gr. 4), proctitis (1 p gr. 4) and fibrinolysis (1 p gr. 3). One patient died due to hemoptysis (R) having completed 3 cycles of treatment have been evaluated for tumor response by RECIST: 9 PR (81.8%), 1 SD (9.1%) and 1 PD.

Conclusions: This interim analysis shows that the combination of Bevacizumab, D and C is safe and well tolerated, with a trend of promising activity. Enrollment continues and updated results will be presented.
received a second-line chemotherapy with Docetaxel 75 mg/m² d1 and Gemcitabine 1000 mg/m² d1-8 every three weeks (DG) until progression. Primary endpoints were the 6-months overall survival (OS) in the DG-pts; secondary endpoints were progression free survival (PFS), tolerability and quality of life (QoL) with EORTC QLQ-C30 questionnaire.

Results: After two cycles of DG, 12 pts (31.2%) had PR, 15 pts (39%) were stable and 11 pts (28.6%) had PD. These 11 pts were in early progression after two CD-cycles and performed DG as a second-line therapy. At the CT scan evaluation, after two cycles of DG, 1 pt achieved CR, 4 SD and 6 PD. The non-DG pts continued performing DG. The 6-month-OS was 41.6%. The median PFS, since the DG regimen switch, was 6 weeks (CI 95%: 3-9). Patients who continued with DG (n=27) obtained a 1-year-OS of 69.8%, a 1 yr PFS of 23.7% and a median PFS of 9 months (CI 95%: 6.1-11). Two patients of the DC-ARM received a surgical resection after six cycles of CD and downstaging to IB (UICC 2002) occurred in one patient. The most common adverse events (AE) were alopecia (9%), nausea/vomiting (75%), neutropenia (49%), anemia (10%), and diarrhoea (10%). No significant differences in AEs were observed, except for alopecia and nausea/vomiting, which occurred more frequently with CDDP-Docetaxel, but the differences were not statistically significant.

Conclusions: The combination of gemcitabine and docetaxel is well tolerated in patients with advanced NSCLC who have failed prior taxane platinum chemotherapy and improves pts palliative outcomes without compromising quality of life.

Background: The optimal way of adding anti-EGFR antibodies to chemotherapy in the first-line treatment of advanced NSCLC was unknown. Two parallel randomised phase 2 trials, with different primary end-points (CALC1-E and CALC1-PS2) were performed to choose a common or a sequential strategy of G + C for phase 3 trials.

Methods: Stage IV or IIB (with supraclavicular nodes or pleural effusion) NSCLC pts, aged 70+ yrs, were randomized to CALC1-E: GEM (1200 mg/m² d1 & 8 q 21) max 6 cycles, and/or TS-1 (1000 mg/m² d1-14) + GEM (1000 mg/m² d1-8) q 21. The combined therapy was followed, after progression or 6 cycles, by C as above (CALC1-E). Pts were randomised to combination (G, 1200 mg/m² d1 & 8 q 21 max 6 cycles, plus C, 400 mg/m² d1 then 250 mg/m² weekly until progression) or sequential (G as above + C) strategy. A selection design was applied; 58 elderly and 42 PS2 pts were required.

Results: 100 pts were randomised from Nov 05 to Mar 07 (CALC1-E: 29 pts per arm; CALC1-PS2: 22 pts with combination, 20 with sequential). In sequential arms, 16 (34%) and 12 (60%) pts were not able to receive G after C and G in CALC1-E and CALC1-PS2, respectively. Overall survival rates (95% CI) at 1 year for combination and sequential arms were 41% (27-64) and 31% (18-53) in CALC1-E and 27% (14-54) and 35% (19-66) in CALC1-PS2. In combination arms, overall survival rates (95% CI) at 1 year for pts without and with skin toxicity (grades 1-2) were 20% (6-69) and 53% (34-81) in CALC1-E and 12% (2-78) and 36% (18-72) in CALC1-PS2 respectively. Toxicity was similar across all treatment groups. Skin reactions were more frequent with the combination. There were 5 early deaths possibly related to treatment: 2 in each arm in CALC1-E and 1 in the Seq arm in CALC1-PS2.

Conclusions: No striking differences in efficacy were observed in both CALC1-E and CALC1-PS2 studies. The combination strategy warrants further phase 3 trials, while the result is not feasible to test the efficacy of gemcitabine followed by cetuximab. ClinicalTrials.gov ID: NCT00303746. Partially supported by Merck: Pharma SpA, Italy.

This study was conducted in order to evaluate the efficacy and safety and to compare dosing schedules of gemcitabine combined with TS-1 in chemo-naive NSCLC patients (pts).

Methods: Pts with chemo-naive stage IIIb/IV NSCLC, an ECOG-PS of 0 or 1, and normal renal, liver, and bone marrow functions were randomized into one of 2 treatment arms. Oral TS-1 was administered daily from day 1 to 14, and Gem was given on days 1 and 8 (Arm A) or days 8 and 15 (Arm B). This cycle was repeated every 21 days.

Results: A total of 80 pts were entered and 79 pts, treated in this trial. Randomization was well balanced across patient characteristics except for cell type (adenocarcinoma: squamous cell carcinoma = 37/4 (Arm A), 27/0 (Arm B)). Grade 3/4 hematological toxicities were neutropenia (54%), febrile neutropenia (9%), thrombocytopenia (11%) and anemia (4%). The hematological toxicities did not differ very much between the two arms. Grade 3 pneumonitis was observed in 2 pts (3%). The response rate was 23.1% (95% confidence interval [CI]=11.1-39.9%) in Arm A and 30.6% (95% CI=16.3-46.1%) in Arm B. Median time-to-progression (TTP) in Arm A was 4.1 months (95% CI=2.8-5.5) and Arm B, 5.4 months (95% CI=3.8-6.5) (p=0.75). Median survival time in Arm A was 15.7 months (95% CI=6.8-23.3) and Arm B, 22.4 months (95% CI=11.5-unknown) (p=0.32).

Conclusions: The combination of Gem and TS-1 was determined to be feasible and effective for advanced NSCLC, and these results, particularly the favorable MST of Arm B, warrant further investigation of the Arm B dosing schedule for this combination for NSCLC.
pleural effusion or stage IV, were eligible if they had a performance status of 0 to 2, were 75 years or younger, and had adequate organ function. Patients were treated every 4 weeks with nedaplatin (80 mg/m² on day 1) and weekly palcitaxel (90 mg/m² on days 1, 8, 15, and 21) on our phase II trial. From March 2003 through February 2008, 44 patients (29 men and 15 women; median age, 66 years; age range, 42 to 75 years) were enrolled. The most common histologic type was adenocarcinoma. The overall response rate was 50% (95% CI, 34.6% to 65.4%). The median survival time was 14 months (range, 1 to 36 months). The median time to progression was 4 months (range, 1 to 18 months). Grade 3 to 4 hematologic toxicities included neutropenia in 39.9% of patients, thrombocytopenia in 2.4%, and anemia in 22.0%. Although the most frequent nonhematologic toxicity was hepatic dysfuncion, all cases were only mildly to moderatey severe. No patients had grade 3 or 4 nausea and vomiting, neurotoxicity, arthalgia, or hypersensitivity reaction. Although one patient had grade 3 pulmonary toxicity due to drug-induced pneumonia, this patient recovered after receiving steroid therapy. This combination chemotherapy is active and well-tolerated treatment for advanced NSCLC.

**25SP**

**TRIPLET COMBINATION CHEMOTHERAPY OF CISPLATIN, GEMCITABINE AND VINORELINSE AT LOWER DOSES MAINTAINS A SUFFICIENT EFFECT WHILE AVOIDING TOXICITY IN NON- SMALL CELL LUNG CANCER PATIENTS. RESULTS OF A LONG-TERM FOLLOW-UP DATA**

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Background: Although triplet combination chemotherapy using cisplatin (P), gemcitabine (G) and vinorelbine (V) has been employed in NSCLC treatment with favourable toxicity profile compared to the i.v. form. The GLCG conducted a phase II study to demonstrate the efficacy and safety of NOVGEM regimen in elderly patients with advanced NSCLC. The primary objective was response rate (RR). Secondary objectives included time to progression (TTP) overall survival (OS) and toxicity. Methods: Between July 2005 and January 2008, 45 NOVGEM-naive pts aged >70 years, histologically confirmed NSCLC, stage III/IV, ECOG 0-1, measurable lesions according to RECIST criteria and adequate bone marrow, renal and hepatic function were included. The NOVGEM regimen consisted of pemetrexed 1000 mg/m² i.v., followed by NOV 600 mg/m² days 1 and 8 every 3 weeks, for a maximum of 6 cycles.

Results: To date, 45 pts were included and 180 cycles were administrated. Male / Female 41/4; median age 77 years (range 70-86), all ECOG 1, 29 squamous cell carcinoma, 12 adenocarcinomas and 4 large cell. Median number of cycles was 4. A partial response was obtained in 44 pts with an overall response rate of 95% (95% CI:43-67%). The median survival time was 22 months and the 3-year survival rate was 22%. The predominant toxicity was hematologic: grade 3/4 neutropenia in 30/32 (76%) and grade 3/4 thrombocytopenia in 30/1 (39%) pts. The frequency of grade 3/4 non-hematologic toxicity was low (<3%). Forty pts (88%) completed more than 4 cycles. The median dose intensity (mg/m²wk) was P (17.85), G (35.84%) and V (8.80%).

Conclusions: The triplet chemotherapy administered at a lower dose demonstrated a sufficient cure with acceptable degree of toxicity. This regimen can be also considered to be one of experimental regimens for induction treatment.

**25SP**

**A RANDOMISED PHASE III STUDY OF ADJUVANT CHEMOTHERAPY IN PET SELECTED PATIENTS WITH COMPLETELY SELECTED NON-SMALL CELL LUNG CANCER (NSCLC): NAVTAL VIII**

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Rationale: The use of cisplatin-based adjuvant (ad) chemotherapy (chemo) in patients (pts) with resected NSCLC improves survival. Not all pts benefit from chemo, but how to select pts for treatment is not clear. In this study we select pts by FDG-PET in a good and bad prognosis group using FDG avidity as measured by the standardized uptake value (SUV) Several studies have suggested that treatment with low-molecular weight heparin (LMWH) improves survival in cancer pts. The hypothesis is that pts with a good prognosis will not benefit from ad chemo and that LMWH will improve survival in pts with a worse prognosis. This is a randomised phase III study from the Dutch society of pulmonologists (NAVtal). All PET scans are calibrated and a standard protocol was developed to estimate the SUVmax. As previously shown, the SUVmax value of 1.0 will be used as cut-off value. Inclusion started 11/07. Tumour and blood samples will be collected prospectively. NAVtal 8: pts with a low SUVmax will be randomised to 4 cycles of cisplatin-based chemo or observation in a non- interference design. The median OS in 31, and can be entered in the study in 4 years (y). The follow up will continue for 5 y, at the end of which a total of 150 events will be observed allowing the comparison (alpha=0.05 one-sided-log-rank test.) of the curves by treatment arm with 80% power to test the non-

inferiority of no chemo to ad chemo. NAVTal 18: Pts with a high SUVmax will be randomised to 4 cycles of pemetrexed and cisplatin or without nadroparin for 16 weeks (2 weeks therapeutic dose in 14 weeks half-therapeutic dose). The primary end-point is RFS. 600 pts will be entered in the study in 3 y. The follow up will continue for 2.5 y, at the end of which a total of 243 events would be observed allowing the comparison (alpha=0.05 two-sided-log-rank test.) of the curves by treatment arm with 80% power to detect a true difference of 6% versus 70% at 3 y, or HR=0.70. Eligibility criteria: NSCLC stage Ib-IIIA, R0 resection, no metastatic disease, no other malignancy, no indication for anticoagulant treatment or high risk of bleeding (8b).

Conclusion: This study investigates better selection of pts for ad chemo.
Results: 663 pts were randomized. Rates of grade 3/4 toxicities for PEM were <5%, with the exception of fatigue (8.4%). Of all CTCAE toxicities, only anemia was statistically higher for PEM (4.5% vs. 1.4%, p<0.04). Safety profile within histology groups was generally consistent with the overall population. Resource utilization was summarized in the table. Rates of antibiotic (24.7% vs 19.4%) and antiepileptic (30.8% vs 30.6%) use were not statistically different between arms. Resource utilization overall and by non-squamous histology, comparison between arms

<table>
<thead>
<tr>
<th>All: PEM (N=441) vs Placebo (N=222)</th>
<th>Non-squamous: PEM (n=326) vs Placebo (n=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusions</td>
<td>9.5 vs 3.2% (p&lt;0.01)</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>5.9 vs 1.8% (p=0.02)</td>
</tr>
<tr>
<td>G-CSF</td>
<td>2.9 vs 3.6% (p=0.64)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>15.4 vs 14.0% (p=0.65)</td>
</tr>
</tbody>
</table>

Conclusions: Rates of resource utilization for management of AEs with PEM maintenance therapy for NSCLC were low, corresponding to low rates of AEs. With the exception of transfusions and erythropoietin, rates of resource use were comparable between PEM maintenance therapy and placebo. Consistent results were seen in histology groups.

**25SP** IMPACT OF CHEMOTHERAPY ON THE OUTCOME OF TREATMENT WITH PEMETREXED IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER: A RETROSPECTIVE ANALYSIS OF A PHASE II TRIAL

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Background: A prior study of pemetrexed (Pem) in NSCLC indicated a relationship between first-line therapy and outcome of second-line therapy. We therefore investigated the impact of induction therapy on the outcome of PEM maintenance therapy in NSCLC, in this phase III study.

Methods: After 4 cycles of platinum-based induction therapy, 663 pts were randomized (2:1 ratio) to receive PEM (500 mg/m2, d1) plus BSC or Placebo plus BSC in 21-day cycles until disease progression. Effects of the platinum and non-platinum component and tumor response to induction therapy on progression-free survival (PFS) in our study were initially evaluated using a Cox multivariate model. Treatment interactions for platinum and non-platinum interactions were evaluated in separate Cox models for the subgroups defined by type of induction therapy, Kaplan-Meier estimation and Cox multivariate models were used for PFS analyses and Fisher’s exact test for disease control (CR, PR, or SD) rates.

Results: Pt characteristics were well balanced between arms. The platinum and non-platinum component and tumor response to induction therapy were not statistically significant prognostic factors for PFS. Interactions were not statistically significant for platinum (p=0.211) or non-platinum (p=0.07) treatment. PFS for PEM did not differ based on the type of induction therapy (see table). The disease control rate was 48.1% for pemetrexed versus 27.4% for placebo (p=0.0001) for patients who had responded to induction therapy and 54.9% versus 40.0% (p=0.0155) for patients who had no response.

Conclusions: Consistent with findings in the overall study population, CP is better tolerated, easier to administer, and has a better toxicity profile than CG in elderly advanced NSCLC pts, suggesting it may be a preferred treatment option in this population.

**25SP** ECONOMIC ANALYSIS OF ERLOTINIB, DOCETAXEL, PEMETREXED AND BEST SUPPORTIVE CARE AS 2ND LINE TREATMENT OF NON-SMALL-CELL LUNG CANCER

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Objective: Evaluate costs and benefits of erlotinib in second line treatment of advanced or metastatic non-small cell lung cancer (NSCLC) comparatively to docetaxel, pemetrexed and best supportive care.

Methods: Cost-minimization and cost-utility analysis were performed for a time horizon of 2 years, according to a Markov model with 3 health states ("progression free survival", "progression" and "death") and monthly cycles. Survival and time to progression were obtained from clinical trials. Base-case analysis includes second-line patients with advanced or metastatic NSCLC. Quality Adjusted Life Years (QALYs) were obtained from a study in U.K. Resources were estimated by a Portuguese expert panel. Portuguese National Health System (NHS) perspective was applied. Costs were calculated
Annals of Oncology

Inter- and intra-observer variability in assessing eligibility for bevacizumab (BVZ) in advanced non-small cell lung cancer (NSCLC) patients (pts) with centrally located tumors

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Background: BVZ combined with platinum-based therapy is registered for first-line treatment of non-squamous NSCLC. Pts with centrally located tumors close to blood vessels were stated ineligible for BVZ treatment following safety data of the AVF0757 study. The goal of this study was to assess the consistency in evaluating eligibility of pts with central tumors for BVZ treatment.

Methods: The study group was composed of 150 NSCLC pts with centrally located tumors (30 pts received BVZ - clinical trial). Eligibility for BVZ was assessed by chest CT-scan. Eligibility was assessed independently by 7 radiologists and 7 oncologists/chest physicians using CT images reviewed on workstations. Discrepancies were discussed and consensus criteria proposed. Inter- and intra-observer variations on 50 randomly extracted pts were estimated through statistical modeling.

Results: Discordance in (in)eligibility was found for 82 pts (55%; with only one discrepancy in 31 pts, 20%). Agreement was reached in 68 cases (45%: n=39pts, yes=9pts). Analysis of variations showed significant differences among physicians independently of their specialty (p<0.05). Central involvement by tumor (not by lymph node), contact >180° with proximal artery, parietal involvement of main bronchus or trachea, were proposed as criteria for BVZ ineligibility, while tumors with a 360° contact with a segmental artery or a pulmonary vein (outside pericardium), with atelectasis or with necrosis/integration were proposed as needing additional imaging (multiplanar reconstruction) and multidisciplinary team discussion before stating BVZ ineligibility. Among the 30 pts treated with BVZ, 11 (33%) would have been excluded from BVZ treatment by at least one physician, while none presented with haemoptysis. The full results of the inter- and intra-observer variations will be presented at the meeting.

Conclusion: The consistency in evaluating eligibility of pts with central tumors for BVZ treatment is weak. The study group suggested more stringent criteria to help physicians in taking the best treatment choice that need however to be prospectively validated.

Table 261P

<table>
<thead>
<tr>
<th>Group 1 – male C/FS, SqCC</th>
<th>Group 2 – male NS, SqCC</th>
<th>Group 3 – male C/FS, non-squamous</th>
<th>Group 4 – male NS, non-squamous</th>
<th>Group 5 – female C/FS, SqCC</th>
<th>Group 6 – female NS, non-squamous</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCR, %</td>
<td>Survival data</td>
<td>DFS, mths</td>
<td>1-year survival, % OS, mos</td>
<td>n/m, data not yet mature</td>
<td>69 (1&lt;+4+65) n=973</td>
</tr>
<tr>
<td>n=1,205</td>
<td>12.4</td>
<td>10.1</td>
<td>22.1</td>
<td>31.9</td>
<td>n=101</td>
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<tr>
<td>26.4</td>
<td>6.04</td>
<td>n/m</td>
<td>n/m</td>
<td>n/m</td>
<td>n/m</td>
</tr>
</tbody>
</table>

Subgroup analyses of efficacy in the global trust study of erlotinib in non-small-cell lung cancer (NSCLC)

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Objective: TRUST is a global, non-randomised, open-label study of erlotinib (Tarceva®) monotherapy in >7,500 unselected patients (pts) across 52 countries. Interim analyses of efficacy are reported, relative to specific clinical characteristics.

Methods: Oral erlotinib 150mg/d was given to pts with stage IIIB/IV NSCLC who had received at least one line of chemo-/radiotherapy or were unsuitable for such therapy. Treatment continued until progression or unacceptable toxicity.

Conclusion: There were no differences in gender, smoking status, performance status, type of mutation or response to erlotinib (70%) between 23 p with BAC and 142 with adenocarcinoma or large-cell carcinoma. However, the pattern of metastases was different: 91% of p with BAC and 65% of p with other histologies had lung metastases (P<0.01). No brain metastases were identified in p with BAC, in contrast to 17.6% of p with other histologies (P<0.001) (Table). Time to progression for 23 p with BAC was not reached, while it was 11 months for 142 p with other histologies. Median survival was 27 and 18 months, respectively.

Conclusion: The trend towards better time to progression and survival without differences in response rate could be due to the different patterns of metastases. In addition, the presence of brain metastases has been identified as an independent prognostic marker of survival in p treated with erlotinib.

Background: EGFR mutations have been identified as a cause of non-small-cell lung cancer, particularly in adenocarcinoma and BAC. The activating mutations confer dramatic sensitivity to gefitinib and erlotinib. A. Cardenali1, R. Borgoño2, M. Provencio3, J.L. Gonzalez-Larriba4, N. Rosell5

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Background: EGFR mutations have been identified as a cause of non-small-cell lung cancer, particularly in adenocarcinoma and BAC. The activating mutations confer dramatic sensitivity to gefitinib and erlotinib.

Methods: In a prospective trial, 165 p with EGFR mutations (exon 19 D746-750 deletion and exon 21 L858R mutation) were treated with erlotinib. 23 were BACs.

Results: There were no differences in gender, smoking status, performance status, type of mutation or response to erlotinib (70%) between 23 p with BAC and 142 with adenocarcinoma or large-cell carcinoma. However, the pattern of metastases was different: 91% of p with BAC and 65% of p with other histologies had lung metastases (P<0.01). No brain metastases were identified in p with BAC, in contrast to 17.6% of p with other histologies (P<0.001) (Table). Time to progression for 23 p with BAC was not reached, while it was 11 months for 142 p with other histologies. Median survival was 27 and 18 months, respectively.

Conclusion: The trend towards better time to progression and survival without differences in response rate could be due to the different patterns of metastases. In addition, the presence of brain metastases has been identified as an independent prognostic marker of survival in p treated with erlotinib.

According to official Portuguese databases and actualized to 2008. Only direct health costs were applied. Annual discount rate of 5% (costs and utilities). Sensitivity analysis included different subpopulations, a time horizon of 3 years and a probabilistic analysis.

Results: After 2 years, the cost per patient was lower with erlotinib (€26,428) than with docetaxel (€28,160) or pemetrexed (€32,334) and higher than with best supportive care (€15,752). QALYs per patients were higher with erlotinib (0.24) than docetaxel (0.22), pemetrexed (0.23) or best supportive care (0.18). Erlotinib was “dominant” in the cost-utility analysis, with lower cost and higher efficacy, versus docetaxel and versus pemetrexed. The sensitivity analysis confirmed the robustness of the base-case analysis results. If 1,000 patients with advanced or metastatic NSCLC were treated with erlotinib, the annual saving for NHS (substitution rates: 5%-6%) would range between €135,911 – €1,740,840 (docetaxel replacement) and €280,937 € – €3,652,181 (pemetrexed replacement).

Conclusions: The use of erlotinib instead of docetaxel or pemetrexed could contribute with savings for the NHS, in the treatment of advanced or metastatic NSCLC, patients, with a gain in terms of QALYs.
Results: At cut-off for these analyses (27 Feb 2008), data were available for 5,434 pts in six subgroups. Efficacy analyses were conducted based on histology (squamous-cell carcinoma [SqCC] vs non-squamous), gender, and smoking status (current/former smokers [GFS] vs never smokers [NS]). Disease control rate (DCR) was assessed for OS and PFS. Response rate, PFS, and overall survival are reported in the tables below. OS are currently mature for groups 1 and 3 only; median OS was 6.04 mos and 5.58 mos, respectively. In this study, there was no significant difference between male and female GFS with SQCC, PFS with NSCB, and OS in NS with non-squamous tumours was superior to that in other pts (8.0 mos vs 12.0 mos; p<0.0001).

Conclusions: These analyses demonstrate that a wide range of pt subgroups derive a clinical benefit from erlotinib therapy, thus confirming the results of the phase III BR.21 study. Some subgroups may achieve a greater survival benefit when receiving erlotinib, but the predictive and prognostic values could not be distinguished in this non-placebo-controlled study. Based on these data, pts should not be excluded from receiving erlotinib as second- or third-line treatment because of their clinical characteristics.

GLOBAL EFFICACY AND SAFETY RESULTS FROM THE TRUST STUDY: ERLOTINIB MONOTHERAPY IN >7000 PATIENTS (PTS) WITH NON- SMALL CELL LUNG CANCER (NSCLC)

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Objective: The open-label TRUST study was initiated firstly to allow access to erlotinib for a global population of pts with refractory NSCLC and secondly to further elucidate the safety and clinical benefits of erlotinib in this population.

Methods: This non-randomised study enrolled stage IIIb/IV NSCLC pts who had either previously failed or were unsuitable for chemotherapy/radiotherapy. Treatment consisted of erlotinib (150mg/d.p.o.) monotherapy until disease progression or unacceptable toxicity.

Results: Interim results (cut-off date of 27 February 2008) are presented for 6,809 of 7,043 pts enrolled in the TRUST study. At baseline, the study population was typical of advanced NSCLC studies: median age 63 yrs (range 19-96); male/female 61%/39%; Caucasian/Asian/other 73%/20%/7%; stage IIIB/IV 22%/78%; adenocarcinoma/eosophageal/squamous-cell carcinoma 55%/24%/21%. Best responses related to erlotinib were SD in 3,110 pts (56%). Median PFS according to RECIST was 14.3 wks (95% CI 13.6–15.0; n=6,807). The 1-year survival rate was 38.6%. Overall survival data is >25% and SD in 3,110 pts (56%). Median PFS according to RECIST was 14.3 wks (95% CI 13.6–15.0; n=6,807). The 1-year survival rate was 38.6%. Overall survival data is >25% and SD in 3,110 pts (56%). Median PFS according to RECIST was 14.3 wks (95% CI 13.6–15.0; n=6,807). The 1-year survival rate was 38.6%.

Conclusions: Combination of erlotinib and RT seems to be an active treatment for this population. The addition of erlotinib does not appear to increase in-field toxicities, being a feasible and well-tolerated option for pts with unresectable stage I-IIIA NSCLC.

ERLOTINIB AS SECOND-LINE THERAPY IN PATIENTS (PTS) WITH ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) AND GOOD PERFORMANCE STATUS: INTERIM ANALYSES FROM THE TRUST STUDY

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Objective: TRUST is an open-label study of erlotinib in unselected pts with advanced NSCLC. Pts who have either failed prior therapy or are unsuitable for receive chemo-/radiotherapy. The current analysis evaluated the efficacy of erlotinib in the subgroup of patients with good performance status and one prior line of therapy.

Methods: Pts received erlotinib 150mg/d.p.o. until disease progression or unacceptable toxicity.

Results: This interim analysis includes 3,338 pts (2,575 of whom were PS 0/1) who received erlotinib as second-line therapy (as of the cut-off date of 27 Feb 2008). At baseline, the study population was typical of that of other advanced NSCLC studies: median age 62 yrs (range: 19-92); male/female 60%/40%; Caucasian/Asian/other 70%/22%/8%; stage IIIb/IV 23%/77%; adenocarcinoma/squamous-cell/other histology 56%/23%/21%. In the overall 2nd-line population, best response was CR in 27 pts (1%), PR in 373 pts (13%) and SD in 1,501 pts (54%). For the 2,780 pts for whom data were available, the disease control rates (CDR) were 49%. Best responses were: CR in 47 pts (1%), PR in 672 pts (12%), and SD in 3,110 pts (56%). Median PFS according to RECIST was 14.3 wks (95% CI 13.6–15.0; n=6,807). The 1-year survival rate was 38.6%. Overall survival data is >25% and SD in 3,110 pts (56%). Median PFS according to RECIST was 14.3 wks (95% CI 13.6–15.0; n=6,807). The 1-year survival rate was 38.6%.

Conclusions: In pts with advanced NSCLC who either failed or were unsuitable for chemotherapy/radiotherapy, 2nd-line erlotinib monotherapy achieved favourable clinical outcomes, comparable to those previously seen in the pivotal phase III BR.21 study. Better PS (0/1) and/or presence of rash was associated with superior outcomes. The combined efficacy and favourable tolerability profile of erlotinib suggest this agent could play a major role in 2nd-line therapy for NSCLC.

FEASIBILITY AND TOLERABILITY OF THE ADDITION OF ERLOTINIB TO 3D THORACIC RADIOTHERAPY (RT) IN PATIENTS (P) WITH UNRESECTABLE NSCLC: A PROSPECTIVE RANDOMIZED PHASE II STUDY

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Background: RT is the standard treatment for p with unresectable or locally advanced NSCLC. Considering the high frequency of tumour recurrence it is necessary to improve the outcome of the RT by integrating regimens of chemoradiotherapy and targeted therapies into current radiotherapy strategies. Erlotinib is an EGFR TKI that has shown activity in recurrent/metastatic NSCLC. This study aims to evaluate the feasibility of the addition of erlotinib to RT in p with unresectable NSCLC.

METHODS: Pts with unresectable stage I-IIIA NSCLC not suitable to receive chemotherapy, EGFR TKI or RT alone, or not responding to chemoradiotherapy were recruited in this open-label, multicentre, prospective, randomized phase II study. P pts included in arm A received 3D thoracic RT (66 Gy in 33 fractions during 6 weeks). Pts assigned to arm B were treated with 3D thoracic RT (66 Gy in 33 fractions during 6 weeks) and concurrent oral erlotinib. Response rate was assessed at 6 weeks, the time of evaluation of the planned 5th cycle of RT. Follow-up continued for 6 months. The primary objective is the evaluation of grade 3-4 toxicities and secondary endpoints are OS, time to treatment failure, OS and RR. A total of 40 pts have been randomized from March 06. Data from 23 pts have been included in each arm. Baseline characteristics were similar between both arms. Esophagitis was observed in 4% (40%) in arm A and 3% (23%) in arm B (no grade 3-4). Pneumonitis occurred in 5% (50%) in arm A (no grade 3-4 observed) and in 1% (8%) in arm B, being grade 3. Pneumonitis was observed in 2% (20%) in arm A (grade 3) and 1% (8%) in arm B (grade 3-4 observed). Main toxicities related to erlotinib were skin rash (61.5%) and diarrhoea (23%) being all cases mild to moderate. 15 pts were evaluable for tumour response. Response rate in arm A was 55.3% and 83% in arm B. Disease progression is documented in 22.2% of pts in arm A and 16.7% of pts in arm B.

Conclusions: Combination of erlotinib and RT seems to be an active treatment for this population. The addition of erlotinib does not appear to increase in-field toxicities, being a feasible and well-tolerated option for pts with unresectable stage I-IIIA NSCLC. Data on survival will be presented.
Conclusions: EGFR mutations, EGFR IHC+ status and EGFR FISH+ status seem to be associated with better clinical outcomes on erlotinib. High response rates were also observed in EGFR mut+ pts.

Efficacy of erlotinib in >4,000 patients (pts) with advanced non-small-cell lung cancer (NSCLC): analysis of the European subpopulation of the TRUST study

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Objective: The open-label, non-randomised phase IV TRUST study was initiated to allow unselected pts with advanced NSCLC to receive erlotinib (Tarceva®) and to assess the efficacy and safety of this agent in a large, global population. An interim analysis of the European subpopulation is presented.

Methods: Eligible pts with stage IIIB/IV NSCLC had either failed or were unsuitable to receive chemo-radiation therapy. Erlotinib 150mg/day was given orally until disease progression or unacceptable toxicity.

Results: At data cut-off in Feb 2008, data were available for 4,002 of the 4,112 eligible pts enrolled in TRUST. Pts had a median age of 68y (range 19–91) and 99% were Caucasian. Other baseline characteristics (%): male/female 64/36; ECOG PS 0/1/2/3 25/50/25/5; never-smoker/ex- or current-smoker 22/7/8; <10 pack-years; adenocarcinoma/squamous-cell/other 56/27/17; Caucasian/Asian/other 71/29/1. Erlotinib 150mg/day was administered as a single oral dose. Median duration of treatment was 6 months. Median survival was 13.1 months. Complete response (CR) and partial response (PR) occurred in 14% and 19% of pts respectively. A total of 52% of pts achieved stable disease (SD). Disease control rate (DCR; CR+PR+SD) = 73%

Conclusions: These results indicate that erlotinib is well tolerated and effective in first-line NSCLC, with a CR+PR+SD of 75% in all evaluable pts, suggesting a value for this agent in earlier lines of therapy. Dose increases for pts with a history of smoking could potentially enhance the efficacy of erlotinib in these pts.

First-line erlotinib in elderly patients (pts) with advanced non-small-cell lung cancer (NSCLC)


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Objective: The prognosis for elderly pts with advanced NSCLC is relatively poor, partly due to comorbidities that limit treatment options, while poor performance status often means that aggressive treatments are contraindicated. Erlotinib (Tarceva®) is approved for 2nd-line therapy of NSCLC and, given its favourable tolerability, is a useful option for elderly pts. To date, however, experience with erlotinib in chemotherapy elderly pts is limited.

Methods: The open-label, open-trial TRUST study investigated erlotinib in >7,400 pts with stage IIIB/IV NSCLC who had either failed or were unsuitable for standard chemotherapy/radiation therapy. This report focuses on pts >70y who received erlotinib (150mg/day) as 1st-line therapy.

Results: By February 2008, interim analysis data were available for 478 eligible pts (>70y; received at least one dose of 1st-line erlotinib). Median age was 78y (range 73–94). Other baseline characteristics (%): female 54/45; never-smoker/current or former smoker/no data 32/5/18; stage IIIB/IV 5/20; adenocarcinoma/BAC/squamous-cell/other 51/31/11/1; Caucasian/Asiant/other 75/15/9; PS 0/1/2 3/14/6. Response rate (RECIST) = 75% (p = 0.0013). Median duration of treatment was 6 months. Median survival was 13.1 months. Complete response (CR) and partial response (PR) occurred in 4% and 3% of pts respectively. A total of 90% of pts achieved stable disease (SD). Disease control rate (CR+PR+SD) = 75%. Progression-free survival (PFS) = 19.7 wks (n = 477; 95% CI: 15.9–21.9). Overall survival will be reported.

Conclusions: Erlotinib achieved encouraging outcomes as 1st-line therapy for elderly pts with NSCLC. PFS compared favourably with the 14 wks recently reported for pemetrexed+ gemcitabine in chemotherapy >70y (Grilli et al, J Thorac Oncol).
A PHASE I, DOSE-ESCALATION STUDY TO DETERMINE THE MAXIMUM TOLERATED DOSE OF ERLOTINIB WHEN COMBINED WITH PERTUZUMAB IN PREVIOUSLY TREATED NON- small-cell lung cancer patients

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Background: Erlotinib (E) is an effective small molecule inhibitor of HER1 (EGFR) tyrosine kinase and is registered for the treatment of relapsed NSCLC. However, despite inhibition of its enzyme activity, HER1 may still be activated by the formation of heterodimers with HER2, which is also expressed in NSCLC. Therefore, blocking the formation of HER1:HER2 heterodimers would provide a more complete inhibition of HER signaling in such tumors. The humanized monoclonal antibody pertuzumab (P) binds to the extracellular domain of HER2 and is known as the first in a new class of HER2 dimerization inhibitors. Preclinical studies in NSCLC models suggest that combining P and E may improve antitumor efficacy (Iressa, etc. Clin Can Res 11 (14), 2005).

Methods: This is a Phase I, dose-escalating study. Consenting NSCLC pts with EOCOG performance status of 0 or 1, progression after chemotherapy and adequate cardiac reserve were recruited in 2 cohorts. Tumour specimens were available from all patients for evaluating biomarkers potentially associated with response. The 1st cohort received full dose of P (840 mg iv, as a loading dose, followed by 420 mg iv every 3 weeks) plus E at a daily oral dose of 100 mg. If the maximum tolerated dose (MTD) was not reached, a 2nd cohort was to be recruited (these pts were to receive the full dose of P plus E at the full dose of 150 mg orally daily). Dose-limiting toxicity (DLT) was initially defined as any adverse event (AE) grade 3; an incidence of DLT in 2 out of 6 pts was defined as MTD. Based on experience with the 1st cohort, the protocol was modified to exclude rash as a DLT (rashes encountered were manageable and responded to interruption or reduction of E). Subsequently a 2nd cohort (9 pts) has been recruited.

Results: In the 1st cohort tolerability was good, the common AEs being diarrhea in 3 pts (50%), which was generally mild and self-limiting, and rash, which was reported by all 6 pts (100%). Rash was severe (grade 3) in 3 pts but responded to either dose reduction of E or treatment withdrawal. In the 2nd cohort, the combination has been well tolerated with no DLTs reported to date.

Conclusions: For Phase II evaluation, full dose of E (150 mg orally daily) with a daily dose of P is recommended.

AN OPEN LABEL NON-RANDOMIZED PHASE II TRIAL OF ERLOTINIB FOLLOWING CONCURRENT CHEMORADIOTherapy As MAINTENANCE THERAPY In PATIENTs (P) With Stage III non-small cell lung cancer (NSCLC), A GALICIAN Lung cancer GROUP study


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Background: Based on recent studies, concurrent chemo-radiotherapy could be considered the standard treatment of stage III NSCLC p without malignant effusions. Erlotinib is an oral EGFR TKI, that has shown activity in recurrent and metastatic NSCLC. This phase II study aims to assess the activity and toxicity of the addition of erlotinib as a maintenance therapy in stage III NSCLC p after a standard concurrent chemo-radiotherapy regimen.

Methods: P with stage IIA-IIIB (without malignant effusions) medically inoperable or unresectable NSCLC who had received concurrent chemo-radiotherapy and had no sign of progression disease after that treatment, performance status (PS) 0-2, adequate bone marrow, hepatic and renal function, measurable disease by RECIST criteria, and written informed consent were enrolled into this prospective open label one arm phase II study. P were treated with Erlotinib 150 mg/day po for 6 months as maintenance therapy after standard concurrent chemo-radiotherapy. Primary endpoint of the study is the percentage of p without evidence of disease progression after 6 months Erlotinib treatment.

Results: A total of 36 p have been recruited from March 2006. Data from 21 p are available. All p were caucasian, men 90%, median age 64 years (range 18-87), 81% never smokers 95%, PS 0-1,000, histology adenocarcinoma 14,3%, squamous cell carcinoma 81%, other histologies 4.7% and stage IIIB 76.2%. 18 p have been evaluable for response, 16,7% reached complete response, 11.1% partial response, 11,1% stable disease and 11,1% progression disease. 16 p have ended treatment with Erlotinib, from which 8 patients have been treated during the 6 expected months, 3 stopped Erlotinib due to adverse events (only 1 grade 3 rash), 2 presented progression disease and withdrew the informed consent.

Conclusions: Erlotinib as maintenance therapy after standard concurrent chemo-radiotherapy treatment in stage III NSCLC p seems to be efficient and does not appear to increase toxicities. Data on survival will be presented.

ERLOTINIB AND BEXAROTENE FOR PREVIOUSLY TREATED ADVANCED NON-SMALL CELL LUNG CANCER WHO HAD FAILED GEFITINIB

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We previously reported a phase I trial of erlotinib and the ruxinoid, bexarotene, in patients with advanced aerodigestive tract cancers showing minimal toxicities and preliminary evidence of clinical activity. Combining erlotinib with bexarotene also induced at least additive suppression of growth and cycin D1 expression in human bronchial epithelial cells and in some lung cancer cell lines. A phase II trial of erlotinib and bexarotene was conducted in patients with stage IV NSCLC. Primary objective was radiographic response rate. Secondary objectives were survival, time to progression, toxicities, and correlation of early metabolic response by PET at 8-12 days and 2 months. Dosing was erlotinib 150 mg and bexarotene 400 mg/day daily orally. Forty-two patients were enrolled including 52% women and 62% with adenocarcinoma, median age 67 (46-77) years, 12% were current smokers, 17 % were never smokers. Median number of prior therapies was 2 (range 0-5), 21% had prior anti-EGFR therapy. Common toxicities were hyperglycemia and skin rash. Grade 3 pulmonary hemorrhage (1), rash/mouth sores (1), cough (1), hyperhomocysteinemia syndrome (1), and abdominal pain (1) led to treatment discontinuation. There were 2 objective partial responses, 7 patients had stable disease including one patient with prior gefitinib (35 weeks on study). Median time to progression was 7 weeks, median overall survival was 21 weeks (intent-to-treat). Decreased metabolic activity on PET imaging at 10 days was associated with radiographic response at 2 months. Correlation between the severity of hyperglycemia and clinical outcome will be presented.

The effect of this combined regimen on the levels of EGFR and/or cyclin D1 expression between the severity of hypertriglyceridemia and clinical outcome will be presented. Overall survival was 21 weeks (intent-to-treat). Decreased metabolic activity on PET imaging at 10 days was associated with radiographic response at 2 months. Correlation between the severity of hyperglycemia and clinical outcome will be presented.

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DESCRIPTION OF PATIENTS WITH ERLOTINIB-RELATED SKIN EFFECTS IN FRANCE.

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Introduction: The PRECEDE study (PRIX En Charge des Effets Dermatologiques sous Eroltinib) reported on the prevalence of Erlotinib-related skin effects (ERSE) and that there is no current consensus on its management in France. We present here a descriptive analysis of the patients who developed ERSE in the PRECEDE study.

Methods: Data were retrospectively collected from the medical files of lung cancer patients treated with Erlotinib in 7 cancer centers from January 2005 to December 2007. Gender, age, weight, height, serum creatinine, hemoglobinemia, hematocrit, lung cancer stage, bone and visceral metastasis were collected. Renal function was estimated using the Cockcroft-Gault and aMDRD formulae.

Results: 234 patients were included among whom 152 (65.0%) presented with ERSE. In 131 patients (85.8%), ERSE improved or resolved, either spontaneously (46/131, 35.1%) or under treatment (85/131, 64.9%). The demographic, biological and clinical characteristics of patients with ERSE and patients without are reported in the table. No statistic differences were found between patients with ERSE and patients without, except when comparing the means of hemoglobinemia and hematocrit (p<0.05).

Conclusion: This interim analysis of unselected Israeli pts in TRUST confirms the favourable safety profile and efficacy of erlotinib in the real-life setting. The results indicate that most pts (79%) can receive the recommended dose of 150mg/day. Erlotinib achieved a DCR of 37%, with over one-third of patients surviving beyond 1 year.

PHASE II STUDY OF ERLOTINIB AS A FIRST-LINE THERAPY FOR NON-SMALL-CELL LUNG CANCER PATIENTS ACCORDING TO THEIR CLINICAL PREDICTORS

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Background: Many studies of EGFR TKIs suggest positive and negative predictors for response and survival. We conducted the study to evaluate the efficacy of erlotinib as a first-line therapy for patients with non-small cell lung cancer (NSCLC) according to their clinical predictors.

Methods: The eligible patients who had histologically confirmed NSCLC were categorized as follows: those with squamous cell carcinoma (SQCC), ever-smokers with adenocarcinoma (ADC) and never-smokers with ADC. Additional inclusion criteria were as follows: stage IIIIB or IV, ECOG PS 0-2, adequate organ functions, and measurable lesions. No prior chemotherapy or targeted therapy was allowed. Treatment consisted of erlotinib 100mg to 150 mg orally given once daily till disease progression, unacceptable toxicity or patient’s refusal. Objective tumor responses were assessed one month after the commencement of erlotinib and then every two months.

Results: Between 10/2006 and 12/2007, 7 patients with SQCC, 13 ever-smokers with ADC and 45 never-smokers with ADC participated in the study. The response rate for never-smokers with ADC was 66.7%, while those for smokers with ADC and those with SQCC were 23.0% and 0.0%, respectively. The frequently observed toxicity was rash and diarrhea but manageable. The response rate for 11 patients with mutant-type EGFR was 81.8% while that of 12 patients with wild-type EGFR was 16.7%. Retrospective analysis showed that in 2(18.2%) of 11 with mutant-type EGFR we found EGFR gene mutation in serum. However, out of a total of 32 examined, only 3 cases (9.4%) showed positive serum EGFR mutation. Survival outcomes and results of further biologic study will be presented at the meeting.

Conclusions: Erlotinib can be used in first-line setting in never-smoking patients with adenocarcinoma of the lung or patients with activating somatic mutation of EGFR gene. To use erlotinib based on molecular predictor(s), the ease and accurate method identifying those predictors should be developed.

REFERENCES OF PATIENTS WITH ERLOTINIB IN NON-SMALL-CELL LUNG CANCER (NSCLC) IN ISRAEL: INTERIM ANALYSIS FROM THE TRUST STUDY

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Background: In a large placebo-controlled trial (BR.21), erlotinib significantly prolonged survival, delayed symptom progression and improved quality of life of patients (pts) with relapsed NSCLC [Shepherd et al. 2008; Bejot et al. 2007]. The global TRUST study investigated use of open-label erlotinib in >6000 pts with stage III/IV NSCLC failing or unsuitable for standard chemotherapy/radiation therapy. This report describes results for pts enrolled in TRUST in Israel.

Methods: Eligible patients received oral erlotinib (150mg/day) until disease progression or unacceptable toxicity. The NCI CTCA v3.0 was used for evaluation of toxicities. Dose reductions were allowed. Pts were monitored monthly.
Methods: Heavily pretreated (almost with two lines of chemotherapy) advanced NSCLC patients, who had previously obtained a partial response (PR) or a prolonged stable disease (SD) with G, were treated with E after progression of disease (PD) to gefitinib. Patients accrual was stopped early because of the unavailability of G after the closure of the sponsor following the results of INEL study.

Results: Eighty-one pts with advanced NSCLC were included in analysis: 74.1% males, median age 64 years (range 37-87); ECOG performance status (PS) 0-1 (76.5%) and 2 (10.3%), Eighty-one pts with advanced NSCLC were included in analysis: 74.1% males, median age 64 years (range 37-87); ECOG performance status (PS) 0-1 (76.5%), respectively. The median time to progression (TTP) and overall survival with E were 5.75 and 12 months, respectively. At an exploratory analysis those patients who obtained PR or SD with E had a longer TTP to previous G (21 and 16 months, respectively) than those who progressed with E treatment (18.5 months).

Conclusion: E seems to be a potential therapeutic option for the treatment of selected advanced NSCLC patients after the failure of G. Further studies are warranted to evaluate the molecular mechanisms behind this evidence and to clarify how to select patients for one or more treatment with EGFR TKIs.

SOMATIC K-RAS MUTATIONS PREDICT RESISTANCE TO GEFITINIB AND ERLOTINIB IN NSCLC: A META-ANALYSIS FROM A COMPREHENSIVE EGFR SOMATIC MUTATION DATABASE

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Background: Somatic mutations of KRAS (KRAS-m) have been evaluated as a predictive factor of response to tyrosine kinase inhibitors (TKIs). Similarly, the presence of somatic mutations of the k-RAS oncogene (s-RAS-m; codons 12 & 13) has been classified as a ‘de novo’ resistance mechanism. Mutual exclusivity of these mutations allows for clear patient stratification once their predictive powers have been adequately investigated. We investigated the negative predictive power of s-RAS-m in NSCLC treated with anti-EGFR TKIs.

Methods: A computerized search of MEDLINE (01/01/03-31/08/03) was performed to identify articles pertaining to s-RAS-m, both s-RAS-m in TKI treated NSCLC. Using the EAP EGFR-D (www.somaticmutations-EGFR.org) we identified studies reporting on the association between mutations and response to anti-EGFR TKIs. Eligible studies: single agent TKI of unselected advanced NSCLC.

Statistics: Between-study heterogeneity (I2 statistic); positive and negative likelihood ratios (+LR and -LR) were pooled using random effects models.

Results: From 162 identified studies, 10 (512 patients; 77 with somatic mutations) were considered eligible. No evidence of between-study inconsistency (I2=0%) was evident. The presence of any k-RAS mutation was significantly correlated with lack of response (resistance) to TKIs in NSCLC: +LR = 3.07; 95% CI, 1.99-4.70 and -LR = 0.81; 95% CI, 0.51-1.26. Similarly, the presence of somatic mutations of the k-RAS oncogene (s-RAS-m; codons 12 & 13) has been classified as a ‘de novo’ resistance mechanism. Mutually exclusive association was observed between the two molecular mechanisms.

Conclusions: This analysis provides empirical evidence that s-RAS-m are negative predictors of response (‘de novo’ resistance) to single agent anti-EGFR TKI’s in advanced NSCLC. Coupled with data showing that mutually exclusive s-EGFR-m predict response of s-RAS-m, these results support the removal of stratification using these 2 molecular markers. In conclusion, the negative predictive power of s-RAS-m may lead to improvements in patient care. Further studies investigating patient stratification based on molecular profiling will be necessary for this class of agents.
Annals of Oncology

Results: Out of 265 studies reporting on EGFR mutation or amplification in NSCLC, 14 (98 patients) of 54 s-EGFR-Ampl1 and 41 studies (1,964 patients 641 s-EGFR-m) were considered eligible. No evidence of extreme between-study inconsistency was evident (I²=75% for all comparisons). s-EGFR-m (OR=4.99; 95% CI, 3.30-7.77 and LR=0.34; 95% CI, 0.28-0.41) and g-EGFR-Ampl (LR=1.84; 95% CI, 1.50-2.17 and LR=0.66; 95% CI, 0.50-0.88) were both predictive of response to EGFR-TKIs, with s-EGFR-m appearing to be a better predictive marker. Neither patient ethnicity nor the method of analysis for g-EGFR-Ampl influenced this result. Similarly, for s-EGFR-m, neither ethnicity nor study TKI (cetuximab versus gefitinib) altered the association.

Conclusions: This analysis provides large-scale empirical evidence that s-EGFR-Amp and s-EGFR-m are predictive of response to TKIs in advanced NSCLC. Overall, s-EGFR-m appear to be a better predictive marker. We encourage a consortium effort to develop the potential for clinical validation of this association.

282P MYC AND EIF3H CO-AMPLIFICATION SIGNIFICANTLY IMPROVES RESPONSE AND SURVIVAL OF NON-SMALL CELL LUNG CANCER PATIENTS (NCSLC) TREATED WITH GEFITINIB

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Background: Human chromosome 8 often suffers genetic damage in lung cancer, including amplification of the MYC oncogene at 8q24.21. The gene for eukaryotic translation initiation factor 3, subunit H (EIF3H), also located within 8q24, is amplified in cancer, but data on EIF3H in lung cancer are lacking. MYC is a negative prognostic factor and MYC amplification seems to increase sensitivity to trastuzumab (Herceptin®), a monoclonal antibody against HER2, a member of the EGFR family. In this study we investigated if EIF3H was amplified, and whether MYC and/or EIF3H genomic gain affected response to EGFR tyrosine kinase inhibitors in NSCLC.

Methods: Metastatic NSCLC patients (N=92) treated with gefitinib were assessed for MYC and genes by FISH, using a custom-designed 3-color DNA probe set.

Results: Amplification of MYC (ratio MYC/CEP8 > 2), was observed in 10 cases (18.5%) and MYC was co-amplified in all. MYC amplification without co-amplification of EIF3H was observed in 2 cases (3.3%). Response to gefitinib therapy was higher in MYC amplified than in non-amplified patients (25% versus 14%, p=0.04) and in EIF3H amplified versus non-amplified (30% versus 14%, p=0.03). In order to investigate whether this trend for higher response was due to chance or reflected a significant biological difference, a Receiver Operating Characteristic (ROC) analysis was conducted to identify the cut-off for MYC and EIF3H copy number that best distinguished sensitive and resistant patient populations. MYC-FISH positive patients (mean 22.79) had significantly higher response rate (RR: 31% versus p=0.003), significantly longer time to progression (TTP: 4.4 versus 2.6 months, p=0.01) and OS (17.8 versus 6.4 months, p=0.01) than MYC-FISH negative patients (mean <2.79). EIF3H-FISH positive patients (mean 22.75) had significantly higher RR (32% versus p=0.003), significantly longer TTP (4.4 versus 2.7 months, p=0.01) and OS (17.8 versus 6.4 months, p=0.01) than EIF3H-FISH negative patients (mean <2.75).

Conclusions: MYC and EIF3H are frequently co-amplified in NSCLC and increase sensitivity to gefitinib therapy. Prospective validation of these findings is warranted.

283P MOLECULAR PROFILING OF THE EPIDERMAL GROWTH FACTOR RECEPTOR PATHWAY IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS (PTS)

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Background: Molecular alterations along the EGFR pathway have been proposed to be the major determinant of clinical outcome in response to EGFR tyrosine kinase inhibitors (TKIs) in NSCLC. However, their potential impact on resistance mechanisms (CHT) and their optimal use for the prospective identification of TKI-sensitive pts is currently under debate. Advanced NSCLC pts (n=188) were screened for EGFR and KRAS gene mutations, EGFR gene copy number and protein expression, HER-2 and phosphorylated AKT (pAKT) expression. Correlation between molecular alterations and clinical outcome (OS, PFS, and DFS) were explored retrospectively for I-line CHT (n=141) and prospectively for EGFR TKI (gefitinib or erlotinib, n=98) treatment. Multiple correspondence analysis demonstrated that high KRAS mutation and KRAS gene amplification, EGFR gene copy number and protein expression, HER-2 and pAKT expression were the only independent predictors of response to I-line CHT, whereas pAKT and HER-2 expression were the only independent predictors of PFS and OS. Upon progression pts were prospectively assigned to TKI treatment according to one of the following groups: 1) mutated EGFR (n=12); 2) highly polysomic or amplified (n=18); 3) EGFR and/or pAKT positive (n=41); 4) AdR and no smoking history (n=13). Disease control rate was highest in groups 1 and 4 (>50%) and lowest in group 3 (<20%) (p=0.02, respectively). The impact of sex, smoking history, EGFR/KRAS mutation, and pAKT on survival outcomes in response to TKI was confirmed by multivariate analysis performed in the intention-to-treat population (n=98). EGFR pathway alterations significantly impact on outcome following 1-line CHT for advanced NSCLC. Selection of patients based on either EGFR mutation or clinical characteristics seems to be the most effective way to optimize TKI treatment.
EGFR/KRAS-GERMLINE MUTATION ANALYSES IN ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH GEFITINIB/ERLOTINIB

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Background: Approximately 10% of NSCLC respond positively to treatment with tyrosine kinase inhibitors (TKIs) gefitinib/erlotinib. Molecular analyses identified specific somatic mutations, such as deletion within exon 19 and aminodic substitution at codon 858 of exon 21, in the kinase domain of EGF, in about 80% of responsive patients. On the contrary, a specific somatic mutation in exon 20 of EGFR (T790M), and KRAS mutations in exon 2 were reported to be important predictors of resistance to TKIs. A few data about EGFR/KRAS-germline mutations, in advanced NSCLC patients treated with TKIs, have been reported.

Patients and methods: EGFR and KRAS sequencing analysis of DNA from peripheral blood mononuclear cells of a cohort of 38 advanced NSCLC patients treated with TKIs was performed. Patient characteristics: 22 male and 16 women; stage IIIIB and 33 stage IV; 14 PS 0, 18 PS1; median age 69 years (range 44-86); 10 adenocarcinoma; 18 bronchioloalveolar carcinoma; 6 squamous, 6 NSCLC, 5 undifferentiated carcinoma; 19 never smokers, 19/previous/current smokers; Seven pts (18.4%) had a PR to TKIs, 12 pts a SD longer than 6 months, 3 pts a SD shorter than 6 months, 16 pts a PD.

Results:No KRAS mutations were identified whereas 2 out of 38 pts were carriers of T790M-EGFR mutation in exon 20. Two these patients were sisters, never smokers, affected by undifferentiated carcinoma and responders to TKIs; in 1 of these patients there were sufficient tumour tissue to demonstrate a somatic mutation in exon 19.

Conclusion: These observations confirm previous reports about the association of EGFR T790M germline mutation and the susceptibility to NSCLC, and suggest that EGFR somatic activating mutations, that confer sensitivity to TKIs, may occur in germline mutated patients and that a linkage between resistant and activating mutations in EGFR could be supposed.

NEW SENSITIVE METHODS TO DETECT EGFR GENE MUTATIONS IN LUNG CANCER SPECIMENS, STRUCTURE-SPECIFIC FLAP ENDONUCLEASE BASED METHOD; COMPARISON WITH DIRECT SEQUENCING

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Background: Somatic mutations in the tyrosine kinase (TK) domain of the EGFR gene are associated with clinical response to TK inhibitors in patients with non-small cell lung cancer (NSCLC). A sensitive assay to detect such mutations using small clinical specimens is really needed.

Methods: Known EGFR mutations (exon 19 to 21) were analyzed with PCR-Invader method (Mutation Research 2005: 103-110); briefly the method uses structure-specific flap endonuclease to cleave three-dimensional complex formed by allele-specific oligonucleotide to target DNA containing mutations. DNA from archived specimens (paraffin-embedded or pleural effusions) was obtained by PCR (n=11), transbronchial lung biopsy (TBLB) (n=9), lymph node biopsy (n=5), and thoracocentesis (n=2). In cases with gefitinib treatment, relationship between the responses and EGFR gene mutations were evaluated.

Results: In total, 27 samples from 20 NSCLC patients were investigated (more than two different specimens from six patients). In 55% of patients (11/20) and 56% of samples (11/19), EGFR gene mutations (exon 19 del, exon 21 del, cases L858R in four cases, L861Q in one case) were identified with PCR-Invader method. In the samples obtained from the same patients at different sites and different time, EGFR mutations were coincident (EGFR mutations were found in all the 7 samples from 3 patients, but none of 6 samples from 3 cases). Nine patients with EGFR mutations were treated with gefitinib. Median progression free survival was eight months and response rate (RR) was 78% (2/2). These EGFR mutation negative patients were treated with gefitinib, but failed within 2 to 4 weeks with 0% RR. Direct sequencing could only detected EGFR mutations in 30% (6/20) of patients and in 22% (6/27) of samples. None of the known mutations were missed by PCR invader method.

Conclusions: PCR-Invader method effectively detected EGFR mutations with clinical lung cancer specimens compared with direct sequencing. Because this method can utilize archived small paraffin specimens, it can be easily applicable in the clinical settings.

DIFFERENCE IN SKIN TOXICITY INCIDENCE BETWEEN ERLOTINIB (E) AND GEFITINIB (G) IN THE TREATMENT OF ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: Cutaneous toxicities are common and reversible adverse effects of EGFR tyrosine kinase inhibitors (TKI). In the two large randomized trials of E (Shepherd F et al, NEJM 2005) and G (Thatcher N et al, Lancet 2005) vs. placebo in pretreated NSCLC patients (pts), the incidence of skin rash toxicity reported for the two drugs was different: skin rash toxicity of all grades (gr) was observed in 76 and 37%, while gr 3-4 in 9 and 2% of pts treated with E and G, respectively. Aim of this study was to assess the incidence of the most common toxicities in a cohort of NSCLC pts treated with E or G in the same time span and evaluated by the same medical staff at our Institute. Patients and Methods: Overall, 47 pts with advanced NSCLC treated with oral EGFR TKI between May 2005 and July 2006 were included: 16 pts received E, 16 gr 15 pts were treated with G followed by L at progression. E was administered at 150 mg daily in the open-label TRUST study. Patients not eligible for the TRUST study were given G (250 mg daily) in a compassionate-use program. Toxicity was graded according to the Common Toxicity Criteria version 3.0.

Results: Cutaneous toxicities (gr 3-4) for E vs G included: acneiform rash (64 vs 25%, 13 vs 0%), rash/desquamation (83 vs 19%, 12 vs 0%), pruritus (38 vs 16%, 6 vs 0%), dry skin (48 vs 32%, 3 vs 0%), nail changes (15 vs 6%, 3 vs 0%), diarrhea (54 vs 19%). When pts were treated with E followed by G, worse grade toxicities (all gr, gr 3-4) were: acneiform rash (93 vs 20%, 27 vs 0%), rash/desquamation (100 vs 20%, 20 vs 0%), pruritus (41 vs 13%, 7 vs 0%), dry skin (34 vs 27%, 7 vs 0%), nail changes (27 vs 7%, 0 vs 0%), diarrhea (gr 1-2, 53 vs 7%). Ten (32%) pts treated with E received antibiotics instead of best supportive care alone.
Annals of Oncology

therapy for skin toxicity vs 1 (3%) pt treated with G. Response rate was similar for both drugs: 0% partial response (PR) and 26% stable disease (SD) for E vs 10% PR and 29% SD for G treatment.

Conclusions: Our data confirm the observation that there are less cutaneous adverse effects with G compared to E. This finding is also confirmed in patients treated with G at progression after E. Such a difference may be related with the higher biological dose of E compared to G.

**288P**
PREDICTORS OF Gefitinib ANTITUMOR ACTIVITY AND SURVIVAL BENEFIT IN EAST ASIAN CHEMOTHERAPY naive patients with adenocarcinoma or bronchioloalveolar carcinoma.

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Background: Rapid and dramatic response is observed in a subset of East Asian patients treated with gefitinib in clinical practice. Although a strong correlation between response and epidermal growth factor receptor gene mutation was reported. A faster and more economic method to select appropriate patients by clinicopathologic or laboratory predictors is needed.

Methods: Between Nov 2002 and Jun 2007, medical charts of 203 patients with advanced or recurrent non-small cell lung cancer treated with gefitinib monotherapy at 4 major medical centers in Taiwan were retrospectively reviewed. Tumor response, survival, clinicopathologic and laboratory data were collected. Multivariate analyses were performed to identify factors that independently predict for response and survival to gefitinib.

Results: At analysis, 152 out of 203 patients (74.9%) had expired, and the median follow-up duration was 13.2 months (range 10.6-18.9). 80 patients were male (44.3%). 161 patients (79.3%) had adenocarcinoma or bronchioloalveolar carcinoma, and 39 patients (9.9%) had squamous carcinoma. 132 patients (65%) were never smokers. 153 patients (75.4%) had ECOG performance status 0, 64 patients (31.8%) had ECOG performance status 1. Median age of all 162 patients (male:93; female:69) was 62(13-78) years. The most common grade 3/4 adverse events were neutropenia (73.3%) and anorexia (13.3%). 107 patients had stable disease. The estimated overall survival was 10.7-16.7 (median 16.0) months. Expression of EGFR, p-STAT3, p53 and VEGFR-1 were detected in 70.6%, 30.2%, 34.7% and 46.6%, respectively. Mutant p53 staining was significantly correlated with longer survival (p=0.019) and ECOG performance status (p=0.001). None of the laboratory parameters (WBC, LDL, AST and ALT) was associated with response or survival.

Conclusion: Higher response rate and longer survival to gefitinib was observed in chemonefactors patients with adenocarcinoma or bronchioloalveolar carcinoma.

**288P**
Clinical Impact of expression of EGFR, phospho-STAT3, p53 and VEGFR-1 in resected Adenocarcinoma of Lung using microarrays.

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Purpose: Epidermal Growth Factor Receptor (EGFR) is frequently overexpressed in non-small cell lung cancer (NSCLC). Signal transducer and activator of transcription 3 (STAT3) is a key downstream pathway of EGFR and plays a major role in tumorigenesis. We evaluated clinical significance of pSTAT3, EGFR, p53, and vascular endothelial growth factor receptor (VEGFR) expression in patients with completely resected adenocarcinoma of lung.

Patients and methods: Expression of EGFR, phospho-STAT3, p53 and VEGFR-1 was evaluated by immunohistochemical staining of tissue microarrays from 162 cases of curatively resected adenocarcinoma of lung with clinical characteristics. The relationships among these proteins were evaluated and the correlation between these biomarkers and various clinicopathological factors were determined.

Results: Median age of all 162 patients (male: 93; female: 69) was 62 (13-78) years. Median disease free survival (DFS) was 37.1 months and overall survival (OS) was 67.1 months. Expression of EGFR, p-STAT3, p53 and VEGFR-1 were detected in 70.6%, 30.2%, 34.7% and 46.6%, respectively. Mutant p53 staining was significantly correlated with VEGFR-1 (P<0.001). EGFR expression was significantly associated with pSTAT3 and VEGFR-1, respectively (P=0.0001, P=0.026). EGFR expression was significantly associated with poor OS (P=0.02); 75 months vs 59 months). Interestingly, never smoking patients were associated with low expression levels of p53, EGFR, and VEGFR-1. Age, smoking, stage, p53 and pSTAT3 staining were identified as independent prognostic factors by Cox-regression test.

Conclusion: These findings suggest that p53 staining was significantly correlated with VEGFR-1, and these molecules might play major roles in NSCLC in terms of clinical relevance in collaboration with p53, pSTAT3 and VEGFR-1. Further studies in relation to the detailed mechanism among the proteins are to follow.
Results: RD was 18.4% (7/38 patients; complete response/partial response/stable disease/progressive disease = 0/7/25/6). Median PFS was 141 days (95% CI: 119-189 days). Major toxicities equal to or more than grade 3 assessed by CTCAE v3.0 were neutropenia (19/38, 50.5%), mucositis (4/38, 10.5%), and anorexia (4/38, 10.5%).

Conclusions: S-1/Dox seemed to be effective and feasible for NSCLC in a second or third line regimen. A phase III trial should be performed to compare S-1/Dox with Doc alone in such patients.

**293P** PHASE I/II STUDY OF S-1 PLUS CARBOPLATIN (CBDCA) IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: S-1 is an oral anticancer agent composed of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate. The objective of this study was to determine the maximum tolerable dose (MTD), the toxicity profile, the recommended dose (RD), setting of dose-limiting toxicity (DLT) as part of phase I, and to evaluate the efficacy and safety as part of phase II.

Patients and methods: Eligibility criteria were unsatisifiable NSCLC; no prior chemotherapy or radiation therapy; 20-75 years old; performance status (ECOG) 0-1; adequate main organs function and written informed consent. S-1 was given orally on day 1-14, and CBDCA was infused intravenously on day 1, repeated every 3 weeks. The treatment was continued until disease progression. The Gefitinib dose was 250 mg twice daily for patients refractory to or relapsed after gefitinib, one or more prior chemotherapy regimens, or if the patient has experienced progressive disease after treatment with gefitinib.

Methods: Eligibility criteria included histologically confirmed NSCLC, age 20-74 years, refractory or relapsed after gefitinib, one or more prior chemotherapy regimens, ECOG performance status (PS) 0-2, adequate organ function and informed consent. Pts were treated with CPT-11 on days 1 and 15, and daily gefitinib from day 2 every 4 weeks. The treatment was continued until disease progression. The Gefitinib dose was fixed at 250 mg. The starting dose of CPT-11 was 80 mg/m², and then was escalated in different steps at 25 mg/m² increments up to 150 mg/m².

Results: 25 pts were enrolled. Male/female =14/11; Median age = 60 (45-74); Histology, adenocarcinoma = 15/2. Median PFS = 18/2 months. The objective response rate of gefitinib alone at dose level 4 was 72.0% and 28.0%. For 10 pts at level 5, the DCR and RR were 80% and 60%.

Conclusion: In phase I-II study, the combination of CPT-11 and gefitinib appeared effective and well tolerated in patients with NSCLC that had progressed following prior treatment with gefitinib.

**294P** THE EFFECT OF ALL-TRANS RETINOIC ACID WITH CHEMOTHERAPY BASED ON PaclITAXEL AND CisPLATIN AS FIRST LINE TREATMENT OF PATIENTS WITH STAGE IIIIB WITH PLEURAL EFFUSION AND STAGE IV NON-SMALL CELL LUNG CANCER: A RANDOMIZED, DOUBLE BLIND, PHASE II TRIAL

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Background: Retinoic acid (RA) regulates genes related with cellular proliferation through the retinoic acid receptors RXRs and RARs; specifically all trans retinoic acid acts through its receptor RAR beta. Phase I and II studies suggest that RA could have a synergic effect combined with cytotoxic chemotherapy in head and neck cancer, particularly paclitaxel and cisplatin. We conducted a phase II randomized double blind clinical trial to determine the effect of all trans retinoic acid in addition to the combination of paclitaxel and cisplatin in patients with advanced non-small cell lung cancer (NSCLC).

Methods: Between April 2005 and October 2007 patients with NSCLC were included to receive chemotherapy based on combined Paclitaxel 175 mg/m² and cisplatin 80mg/m² (PC) every 21 days for a maximum of 6 cycles. Patients were randomized to receive all-trans retinoic acid 20 mg/day (RA/PC) or placebo (P/PC) 1 week before treatment and after completing 2 cycles. Prior and after two cycles of chemotherapy, imaging studies were performed.

Results: There were no differences among general characteristics of the patients (age, gender, performance status, stage [IIIB vs IV], histological type) between groups. The median follow-up of the patients was 8.4 ± 0.07 months. Response rate for RA/PC was 52.7% (95% CI, 46.2% to 59.2%) and for P/PC of 17.5% (95% CI, 13.7 to 21.3% p< 0.001). The logistic regression analysis adjusted to age and gender showed a greater response rate for the RA/PC group (p<0.001). Median global survival was 21.29 ± 2.8 months vs 12.7 ± 1.7 months (p = 0.014) for RA/PC and P/PC, respectively. The multivariate analysis of survival adjusted to age and performance status showed significant differences in favor of the RA/PC group (p<0.043). No significant differences in toxicity were found between groups except for hypertension/cardiomegaly, 25% vs 5% in RA/PC (p = 0.001).

Conclusions: All-trans retinoic acid has an additive effect in the response rate of patients treated with PC in metastatic NSCLC. A phase III clinical trial should be performed to confirm these findings.

**295P** IMPACT OF BI 2536, A NOVEL PLK1 INHIBITOR, ON DISEASE PROGRESSION AND QUALITY OF LIFE PARAMETERS IN PATIENTS WITH RELAPSED NON-SMALL-CELL LUNG CANCER: RESULTS OF A RANDOMIZED PHASE II TRIAL


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Background: BI 2536 is a novel highly potent, selective inhibitor of Polo-like kinase 1 (PLK1). Favourable tolerability and antitumor activity was shown in Phase I trials. We investigated efficacy, safety and the effect on quality of life of two dosing schedules of BI 2536 in patients with relapsed advanced or metastatic non-small-cell lung cancer (NSCLC).

Methods: Eligibility criteria included patients with advanced NSCLC who had relapsed after ≥1 prior systemic therapy. Patients were randomized (1:1) to receive BI 2536 2536 mg/m² or 507 mg/m² on days 1-14 of a 21-day cycle. The primary endpoint was progression-free survival (PFS) in the intent-to-treat (ITT) population. Safety and quality of life (QOL) parameters were evaluated in the safety population. Demographic and baseline characteristics were compared using chi-squared tests for categorical variables and t-tests for continuous variables.

Results: A total of 318 patients were enrolled, with 159 in each arm. The median age was 67 years in both groups. The majority of patients had an Eastern Cooperative Oncology Group (ECOG) performance score of 0-1 (77% vs 76%). The median number of prior chemotherapy regimens was 2 in both groups. The most common prior regimens were platinum-based chemotherapy and targeted agents. The median PFS was 3.7 months in the low-dose group and 4.3 months in the high-dose group (HR = 0.82, 95% CI = 0.63-1.06, p = 0.12). The median overall survival (OS) was 12.1 months in the low-dose group and 13.4 months in the high-dose group (HR = 0.85, 95% CI = 0.67-1.08, p = 0.16). The most common adverse events were neutropenia, anemia, and nausea. There were no significant differences in QOL parameters between the two treatment groups.

Conclusions: BI 2536 demonstrated favorable tolerability and antitumor activity in patients with advanced NSCLC. The PFS was non-inferior between the two dose levels, and there were no significant differences in OS or QOL parameters. Further studies are needed to confirm these findings.
Preliminary results show moderate efficacy and acceptable safety of BI 2536 monotherapy in relapsed NSCLC. The effect on quality of life was moderate. The most frequent AEs reported were neutropenia (26%, no CTCAE Grade 4, 2% CTCAE Grade 3) and nausea (26%, no CTCAE Grade 4, 2% CTCAE Grade 3). Febrile neutropenia was reported in one patient.

### Conclusion

The median time to progression (TTP) and overall survival (OS) were 5.1 months (95% CI: 4.6–6.0) and 11.2 months (95% CI: 9.9–13.5), respectively. The most frequently reported grade 3/4 non-hematologic AEs were fatigue/asthenia (24%), diarrhea (9%), and stomatitis (5%). Most frequent grade 3/4 hematologic lab abnormalities were neutropenia (13%) and lymphopenia (21%). In summary, these data suggest that SU 50 mg/day on Schedule 4/2 is tolerable as a maintenance therapy for patients with locally advanced or metastatic NSCLC.

### Study Design

This open-label, multi-center, Phase II study used a Simon 2-stage (St) design to evaluate the efficacy and safety of patupilone in patients (pts) with locally advanced or metastatic NSCLC. The response rates assessed by investigators were 22.5% and 12.8% in stage IIIB or IV and stage IV disease patients, respectively. The most frequently reported grade 3/4 adverse events were neutropenia (20%), anemia (18%), and fatigue (15%). The median TTP and OS were 5.1 months (95% CI: 4.6–6.0) and 11.2 months (95% CI: 9.9–13.5), respectively. The most frequent grade 3/4 non-hematologic AEs were fatigue/asthenia (24%), diarrhea (9%), and stomatitis (5%). The most frequent grade 3/4 hematologic lab abnormalities were neutropenia (13%) and lymphopenia (21%). In summary, these data suggest that SU 50 mg/day on Schedule 4/2 is tolerable as a maintenance therapy for patients with locally advanced or metastatic NSCLC.

### Activity of Patupilone in Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC): A Phase II Study

**Methods:**

Patients with NSCLC stage IIIb/IV and Eastern Cooperative Oncology Group (ECOG) performance status ≤2 who had relapsed after 1st- or 2nd-line therapy were randomized to receive BI 2536 on Day 1 (200 mg) or Days 1–3 (350 mg/3x60 mg) of 21-day treatment courses. Primary endpoint was objective response according to Response Evaluation Criteria in Solid Tumors (RECIST). Secondary efficacy endpoints were progression-free survival (PFS) and OS. Adverse events (AEs) were evaluated using Common Terminology Criteria for AEs (CTCAE).

**Results:**

95 patients were treated. The median OS was 201 days. The most frequently reported AEs were neutropenia (26%, no CTCAE Grade 4, 2% CTCAE Grade 3) and nausea (26%, no CTCAE Grade 4, 2% CTCAE Grade 3). Febrile neutropenia was reported in one patient.

**Conclusion:**

The median time to progression (TTP) and overall survival (OS) were 5.1 months (95% CI: 4.6–6.0) and 11.2 months (95% CI: 9.9–13.5), respectively. The most frequently reported grade 3/4 non-hematologic AEs were fatigue/asthenia (24%), diarrhea (9%), and stomatitis (5%). Most frequent grade 3/4 hematologic lab abnormalities were neutropenia (13%) and lymphopenia (21%). In summary, these data suggest that SU 50 mg/day on Schedule 4/2 is tolerable as a maintenance therapy for patients with locally advanced or metastatic NSCLC.
A PHASE I, OPEN-LABEL STUDY OF VANDETANIB (VAN) IN COMBINATION WITH VINORELBINE/CISPLATIN (VC) OR GEMCITABINE/CISPLATIN (GC) AS 1ST LINE TREATMENT FOR ADVANCED NSCLC


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Background: VAN (ZACTIMATM) is a once-daily oral agent that selectively inhibits VEGFR, EGFR and RET signalling. This study investigated the safety and tolerability of VAN in combination with VC or GC in patients with previously untreated advanced or metastatic (IIIb-IV) NSCLC.

Methods: In the initial cohort of each treatment group, up to 10 patients received once-daily oral VAN (100 mg) with 21-day treatment cycles of VC (25 mg/m² iv day 1 and 8; C, 75 mg/m² iv day 1; and GC (250 mg/m² iv day 1 and 8; C, 75 mg/m² iv day 1). If <2 patients experienced a VAN-related dose-limiting toxicity (DLT), additional cohorts would receive 300 mg + VC or GC.

Results: Seventeen patients (6 male/11 female; mean age 60 years, range 40-72) received VAN 100 mg plus VC (n=9) or GC (n=8). Three DLTs were reported in each group only). There was no apparent PK interaction between VAN and V or G but there was an ~30% increase in exposure to C in the presence of VAN, which may be an interactor of VEGF, VEGFR, EGFR and RET signalling.

Conclusions: VAN 100 mg + VC or GC did not have an acceptable safety profile in previously untreated advanced NSCLC. VAN is in Phase III evaluation in previously treated NSCLC, both as monotherapy and in combination with docetaxel or pemetrexed.

A PHASE II TRIAL OF SAGOPILONE (ZK-EPO), A NOVEL EPOThILONE, AS SECOND-LINE TREATMENT IN PATIENTS WITH STAGE IIIb-IV NON SMALL CELL LUNG CANCER (NSCLC)

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Sagopilone, a novel epothilone, has demonstrated significant activity in pre-clinical NSCLC tumor models. A Phase II trial of second-line sagopilone therapy in patients (pts) with stage IIIb-IV NSCLC, was undertaken. In the first arm of this study (16 mg/m² q3w, 3-h infusion), confirmed partial responses were observed in 43/8 pts. Sagopilone was well tolerated, with peripheral sensory neuropathy being the most commonly reported toxicity (38% vs. grade 3: 14% vs. grade 4). To further evaluate efficacy, the study was amended to include 2 additional arms (22 mg/m² q3w as 30-min or 3-h infusion). Pts who relapsed after a single previous platinum-based chemotherapy regimen, and had measurable disease (RECIST), were randomized to
receive 22 mg/m² of cisplatin iv 75 mg/m² on Day 3. If the maximum tolerated dose (MTD) was not reached at dose levels 1 or 2, increasing doses of vorinostat with gemcitabine 1250 mg/m² and a platinum agent were infused. Platinum agents and gemcitabine potentiated the activity of cisplatin and gemcitabine. Platinum agents and gemcitabine are standard treatments for advanced non-small-cell lung cancer (NSCLC). We investigated vorinostat combined with gemcitabine and a platinum agent in an ongoing Phase I study in advanced NSCLC.

Methods: Eligible patients were aged ≥18 years with Stage IIIb/IV NSCLC, ECOG performance status (PS) 0-2, and no prior systemic chemotherapy (except adjuvant). Patients were sequentially enrolled on escalating doses of vorinostat using a standard 3+3 design for 56 cycles. Dose levels 1 (2) were vorinostat 300 mg QD for 7 days, then a 14-day rest period plus gemcitabine 1 250 mg/m² on Days 1 and 10, plus cisplatin iv 75 mg/m² on Day 1. If the maximum tolerated dose (MTD) was not reached at dose levels 1 or 2, increasing doses of vorinostat with gemcitabine 1250 mg/m² and cisplatin 75 mg/m² were investigated. If dose levels 1 or 2 exceeded the MTD, carboplatin 3 AUC regimens would be investigated, with escalating combinations of vorinostat 300 or 400 mg and gemcitabine 1000 or 1250 mg/m². At the MTD, the cohort will be expanded to 14 patients. The primary objective is to determine the dose-limiting toxicities and MTD of vorinostat plus gemcitabine and a platinum agent.

Results: Twenty one patients have been enrolled to date (4 at dose level 1; 6 at dose level 2; 5 at dose level 3; 3 at dose level 4; 3 at dose level 5; median [range] age: 56 [37-78] years; males: 14 [67%]). Adverse events (AEs) occurred in 15 patients: 85% of AEs were mild to moderate in severity and 62% were not considered to be treatment related. Eleven patients had serious AEs, and there were 5 fatalities (only one was considered ‘probably’ treatment related; the others were considered ‘definitely not’ related to treatment). There were 5 partial responses (3 confirmed, 2 unconfirmed), 7 stable disease and 1 disease progression (13 patients evaluable for response). We will present the MTD recommended for Phase II trials.

Conclusions: Our preliminary data suggest that vorinostat combined with gemcitabine and cisplatin may be possible without unacceptable toxicity.

EXHALED PENTANE AS A MARKER OF LIPID PEROXIDATION DURING RADIOTHERAPY FOR LUNG CANCER

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Background: Radiotherapy (RT) is known to induce formation of free radicals, which can damage membrane lipids. To examine the lipid peroxidation caused by radiotherapy, we measured exhaled pentane, serum thiorbitaric-acid-reactive substances (TBARS) and conjugated dienes (CD) in lung cancer patients at baseline and during radiotherapy for lung cancer.

Patients, materials and methods: The study population consisted of 11 novel lung cancer patients (7 men, 4 women; mean age 64 years) and 30 healthy controls (19 men, 11 women; mean age 51 years). All patients received radiotherapy as a treatment. The exhaled pentane was determined of patients and controls at baseline before any treatment, and of cancer patients during radiotherapy before RT, and at 30 min and 120 min from the onset of RT on day 1, 4, 5 and on RT day of 30 Gy and 40 Gy, if possible. The pentane was analyzed by gas chromatography. Serum samples were collected of patients before RT on each evaluated collection day.

Results: Lung cancer patients had significantly higher exhaled pentane levels at baseline compared to healthy controls (1.73 ng/L vs 0.83 ng/L). The patients’ controls ratio was 2.08 (95% CI 1.13 to 3.76), p<0.017. The levels of CD decreased significantly during the first week of radiotherapy (p<0.014). There was also a tendency for exhaled pentane and serum TBARS to decrease during the first week radiotherapy. Six patients developed radiologically verified radiation pneumonitis, which seemed to be more common if the baseline pentane levels were above the median. The median overall survival of the patients was 10.7 months, and both exhaled pentane (p=0.083) and serum TBARS (p=0.051) were associated with survival.

Conclusions: Lung cancer seems to be associated with increased lipid peroxidation. The levels of lipid peroxidation markers decreased during radiotherapy, which suggests that patients’ own antioxidative defense mechanisms are activated after ionizing radiation, and can counterfight the lipid peroxidation caused by RT. Our results imply that higher exhaled pentane levels might be associated with occurrence of radiation pneumonitis. Interestingly we also found that exhaled pentane and serum TBARS are prognostic factors of overall survival.

PROGNOSTIC IMPORTANCE OF RESPONSE TO PLATINUM-BASED CHEMOTHERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: In recent years there is a renewed interest for building a clinical model to predict survival in advanced NSCLC patients. We are still in platinum-based chemotherapy era, with conscience that the efficacy of those regimens have reached a plateau. Response to chemotherapy, apart from stage and PS, remains the issue of controversy regarding its influence on survival in advanced NSCLC.

Methods: An individual data from 362 patients (pts) have been reviewed from four prospective phase II and III studies conducted at the Institute for Oncology and Radiology of Serbia 1990-2004, to construct a model, with regard to clinical features and parameters: performance status (PS), disease stage (IBB or IV) and response to therapy (WHO criteria). Forty percent of patients had PS 2/3 (31% PS 2) and 55% of pts had stage IV. Overall response rate was 52% (117/362pts). Univariate survival analysis was performed together with Cox proportional hazard (PH) model to predict hazard of death. Landmark method was used to adjust survival times (3 months).

Results: Univariate survival analysis revealed statistically significant differences among response categories – log rank test, p<0.005 (median survival time was 8 months in responders, 5 months in stable disease category and 2 months in progressive disease patients). Cox PH model for hazard of death showed that stable disease category did not bear statistically significant increase hazard of death compared with responders, HR 1.21 (95%CI 0.47-3.07), p=0.150. Expected, progressive pts carried significantly higher risk of death, HR=2.03 (1.56-2.63), p=0.00099.

Conclusions: In the context of Cox PH model it seems that response rate to platinum-based chemotherapy in advanced NSCLC is not associated with a survival benefit. In population with very advanced disease (40% with poor PS) pretreatment prognostic factors probably play more pronounced role in predicting patient outcome.

PROGNOSTIC MODEL TO PREDICT SURVIVAL IN PATIENTS WITH NON-SMALL CELL LUNG CANCER TREATED WITH GERFITINIB

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Background: This study was to devise a prognostic model for non-small cell lung cancer (NSCLC) patients treated with gefitinib.

Patients and methods: A retrospective analysis was carried out on 358 NSCLC patients, who received gefitinib from February 2002 to December 2005.
Results: In multivariate analysis, poor prognostic factors were smoker (p=0.020; HR: 1.96; 95% CI: 1.05–1.76), EGFR performance status 2 (p=0.001; HR: 2.065; 95% CI: 1.395–2.674), WBC<10,000/µL (p=0.001; HR: 1.658; 95% CI: 1.268-2.168), hemoglobin <10g/dL (p=0.001; HR: 1.797; 95% CI: 1.273-2.536), alkaline phosphatase higher than normal (p=0.028; HR: 1.374; 95% CI: 1.052-1.795), Abnormal serum calcium (p=0.005; HR: 1.693; 95% CI: 1.175-2.440) and metastasis to abdominal organ (p=0.001; HR: 1.818; 95% CI: 1.385-2.587). Of 308 patients evaluable in multivariate analysis, 26 patients (8%) were categorized as good prognosis group (0 risk factor), 138 patients (45%) as intermediate (one to two risk factors), 111 patients (36%) as poor (three to four risk factors) and 33 patients (11%) as very poor (five or more risk factors). Median overall survival (from the time treated with gefitinib) of good, intermediate, poor and very poor prognosis groups were 20.0, 11.6, 3.1 and 1.0 months, respectively. Between all prognosis groups, statistically significant differences of OS were found: Good vs. Intermediate (p=0.001); Intermediate vs. Poor (p=0.001); Poor vs. Very poor (p=0.001).

Conclusion: This prognostic model based on clinical variables might stratify the prognosis of NSCLC patients undergoing gefitinib into different prognostic groups, which may facilitate the risk-adapted therapy.

SOCP

18F-FDG UPTAKE PREDICTS THE PRESENCE OF EGFR MUTATIONS IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER


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Purpose: We launched this retrospective study to evaluate a possible association between the presence of epidermal growth factor receptor (EGFR) mutations and standardized uptake value (SUV), semi-quantitative 18F-fluoro-2-deoxy-glucose (FDG) uptake, at presentation in patients with non-small-cell lung cancer (NSCLC).

Patients and methods: We included 110 patients who underwent EGFR test and positron emission tomography/computed tomography. EGFR mutations of exons 19 and 21 were determined using direct sequencing in the tissues. The maximum SUV by the primary tumor was chosen for further analysis. Receiver operating characteristic analysis was used to obtain the cutoff value of SUV.

Results: We detected EGFR mutations in 25 patients (22%). EGFR mutations were more frequent in never-smokers versus ever-smokers (35% versus 13%; P = 0.005), in adenocarcinomas versus non-adenocarcinomas (36% versus 6%; P < 0.001), and in females versus males (40% versus 13%; P = 0.003). The SUV ranged from 1.3 to 53.8 (median 10.5). Receiver operating characteristic curve analysis suggested that the SUV was a predictor of EGFR mutations (area under curve, 0.74; 95% CI, 0.63–0.84). When a cutoff value was used, patients with low SUVs were likely to have EGFR mutations than those with high SUVs (41% versus 12%; P < 0.001). Controlling for smoking history, sex, and histology, a low SUV remained significant predictors for EGFR mutations (P = 0.035).

Conclusions: Our data suggest that the FDG uptake could predict EGFR mutations and help to discriminate beneficial patients with tyrosine-kinase inhibitors.

SOCP

THE PROGNOSTIC SIGNIFICANCE OF [18F]FLUORODEOXYGLUCOSE UPTAKE BY POSITRON EMISSION TOMOGRAPHY IN ADVANCED NON SMALL CELL LUNG CANCER

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Background: Lung cancer is the leading cause of cancer-related death in Korea. Non small cell lung cancer (NSCLC) comprises 80-85% of lung cancer. Positron emission tomography with [18F]fluorodeoxyglucose (FDG-PET) shows various levels of FDG uptake for patients with NSCLC. The aim of this study was to determine whether the standardized uptake value (SUV) of FDG uptake by PET could be a prognostic factor for advanced NSCLC.

Method: FDG-PET was performed for 59 patients with stage IIIB and IV non small cell lung cancer. The SUV of each patient was calculated for each organ. Overall survival (OS), progression free survival (PFS) were calculated by the Kaplan-Meier method and evaluated with the log-rank test. The prognostic significance was assessed by univariate and multivariate analysis.

Results: A cutoff of 7 for the SUV showed the best discriminative value. In univariate analysis, performance status (p=0.012) and SUV (p=0.013) were the significant predictors of OS. The patients with low SUVs (7) showed significantly better PFS than those with high SUVs (7, p=0.04). A multivariate Cox analysis identified performance status and the SUV as important for the prognosis.

Conclusion: These results suggest that SUV was the significant prognostic factor among the patients with advanced non small cell lung cancer.
**Annals of Oncology**

**Conclusions**: Re-asserting, appropriate patients were referred for consideration of adjuvant chemotherapy. 48% of those offered chemotherapy agreed to receive treatment. Dose intensity was maintained in almost 80% of all patients. This audit suggests that adjuvant chemotherapy is acceptable to the non-trial population.

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**WHY IS ADJUVANT CHEMOTHERAPY IN COMPLETLEY-RESECTED NON-SMALL CELL LUNG CANCER (NSCLC) NOT ADMINISTERED? A PROSPECTIVE ANALYSIS**


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**Introduction**: Adjuvant chemotherapy (ACT) is considered a standard treatment after complete resection of some stage IB and stages IIA/IIB NSCLC. However, only a fraction of them do receive ACT. The purpose of this study is to know how many patients (pts) in regular clinical practice do not receive it and for which reasons only.

**Methods**: Seventy-three pts were prospectively (prior to surgery) consented and enrolled in the study between June 2005 and December 2006 at our institution. All pts had pathologically-proven NSCLC and radiologically resectable stages I to III at the time of restaging. Restarting was done for all pts based on the post-operative pathology. Eligibility criteria for ACT were stage IB to IIIA and complete resection, which were confirmed by consultation with Multidisciplinary Lung Cancer Clinic team.

**Results**: Of 73 pts, median age 70 (40-86), 48 males, 25 females, 27 pts were eligible for ACT, 26 pts had stage IA, and one had incomplete resection. Forty-six pts were eligible for ACT, 21 pts (46%) received platinum-based ACT, but 25 pts (54%) did not for the following reasons: 6 pts refused it, 5 pts had tumor size < 4 cm (stage IB), 4 pts had post-op distant metastases (three pts in brain, one pt in bone), 5 pts had severe comorbidities i.e., emphysema, infections, cardiac, diabetes, 1 pt had poor performance status and 4 pts were previously on chemotherapy for other malignancies. Of 7 pts post pneumonectomy, only one of 6 eligible pts received ACT. Nineteen (76%) of 25 pts eligible for ACT, but who did not receive it, had comorbidities while only 9 (43%) of 21 pts who received ACT had comorbidities (diabetes, hypereension, COPD).

**Conclusion**: Over 50% of our NSCLC pts with indication for ACT did not receive it for different reasons. Many pts had significant comorbidities which prevented ACT. Pts post pneumonectomy had lesser chance to get ACT. Improving early staging and individualized treatments on basis of prognostic tumor markers might further improve selection of pts for ACT.

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**LOW EXPRESSION OF BAX PREDICTS POOR PROGNOSIS IN RESECTED NON-SMALL CELL LUNG CANCER PATIENTS WITH NONSQUAMOUS HISTOLOGY**


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**Background**: The present study evaluated the prognostic significance of apoptosis-related proteins p53, Bax, and gaplen-3 in patients with non-small cell lung cancer (NSCLC) treated with surgical resection.

**Patients and methods**: We investigated the expression of these proteins and their association with clinicopathologic characteristics including disease-free survival (DFS) and overall survival (OS) in 205 NSCLC patients who underwent surgical resection (stage I: 97, II: 46, IIIA: 45, IIIB: 17) using immunohistochemistry. Eighty-eight patients (43%) received adjuvant treatment (chemotherapy: 8, radiotherapy: 24, both: 56).

**Results**: High expressions of Bax, p53, and gaplen-3 were observed in 48 (28%), 81 (40%), and 105 (51%) patients, respectively. Low expression of Bax was significantly associated with male gender, squamous cell histology, and low expression of gaplen-3. Five-year DFS and OS of all patients were 37% and 46%, respectively. High expressions of p53 and gaplen-3 were not associated with poor DFS or OS, and no significant correlation existed between low expression of Bax and outcome of patients either. However, in patients with nonsquamous histology (108 patients), low expression of Bax was a significant independent predictor of poor DFS (p=0.017) and overall survival (p=0.037). In addition, in patients with stage II or III, low expression of Bax significantly correlated with poor DFS (p=0.004). It was also the most significant independent poor prognostic factor second only to a large primary tumor size in stage II or III patients with nonsquamous histology.

**Conclusions**: Low expression of Bax was significantly associated with poor prognosis in resected NSCLC patients with nonsquamous histology.

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**ELEVATED PRE-TREATMENT SERUM CONCENTRATION OF YKL-40 - AN INDEPENDENT PROGNOSTIC BIOMARKER FOR POOR SURVIVAL IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER**

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**Background**: YKL-40 is produced by cancer cells and tumor-associated macrophages and may play a role in cancer cell proliferation, differentiation, survival, invasiveness, metastasis and angiogenesis. A high serum YKL-40 level has been associated with poor prognosis in patients (pts) with several cancer types, but has not been studied in pts with non-small cell lung cancer (NSCLC). The purpose of this study was to evaluate YKL-40 in pre-treatment serum samples from patients with metastatic NSCLC.

**Methods**: Pre-treatment serum levels (sl) of YKL-40, VEGF, and MMP-9 were analyzed with ELISA in 189 pts. 23 pts (12%) had stage IIIB disease with malignant pleural effusion and 166 pts (88%) had stage IV disease. 143 pts were male, 46 female. The median age was 62 years, median Karnofsky performance status (KPS) 90%. 98 pts received gemcitabine and vinorelbine, and 91 pts received gemcitabine, vinorelbine and cisplatin as first line chemotherapy.

**Results**: Pts with metastatic NSCLC had significantly higher YKL-40 sl (median sl 209 pg/l, range 19-2155 pg/l) than healthy controls (n=245, median sl 43 pg/l, range 20-184 pg/l) (p<0.001). The median overall survival (OS) of all 189 pts was 36.9 weeks. No significant difference in OS was observed between the two chemotherapy regimens, tumor stage, sex, histological types, and between high and low MMP-9 sl. Whereas pts with a pre-treatment YKL-40 sl above the median sl of 209 pg/l had a significantly shorter OS than pts with lower serum YKL-40 (median survival 31.6 vs. 41.4 weeks; p=0.017). Pts with higher VEGF sl than the median serum level of 1099.5 pg/ml also had a shorter OS compared to pts with lower serum VEGF (34.4 vs. 38.0 weeks; p=0.04). In univariate Cox regression analysis the pre-treatment YKL-40 and VEGF sl, the KPS, and the presence of bone metastases had prognostic significance. In
multivariate analysis only the pre-treatment YKL-40 sl and the presence of bone
metastases were identified as independent prognostic factors.

Conclusion: The pre-treatment YKL-40 sl was identified as an independent prognostic
biomarker in metastatic NSCLC and may help to determine the individual prognosis of
these patients.

## [314P] HIGH EXPRESSION OF EXCISION REPAIR CROSS-
COMPLEMENTATION GROUP 1 PROTEIN PREDICTS POOR
OUTCOME IN PATIENTS WITH ADVANCED NON-SMALL
CELL LUNG CANCER TREATED WITH PLATINUM-BASED
THIRD-GENERATION CHEMOTHERAPY DOUBLETS.

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Purpose: Apoptosis and DNA damage repair related proteins are associated with
resistance to chemotherapy, which is the most important cause of treatment failure in
non small cell lung cancer (NSCLC).

Patients and methods: Pretreatment tumor biopsy specimens from 50 patients with
NSCLC stage IIIb with malignant pleural effusion or stage IV were analyzed for Bax
and ERCC1 expression by immunohistochemistry. All patients were treated with
platinum-based third-generation chemotherapy doublets.

Results: High expression of Bax and ERCC1 was observed in 32 (63%), 28 (55%)
patients, respectively. In univariate analysis, high expression of ERCC1 demonstrated
association with poor overall survival (OS) (9 months vs. 13 months; P = 0.008). High expression of Bax was not correlated with patient outcome. In
multivariate analysis, high expression of ERCC1 (p = 0.005), poor performance
status (p = 0.031), absence of disease control (p = 0.002) were independent prognostic
factors for poor OS.

Conclusions: High expression of ERCC1 may be a useful predictor of poor outcome in
advanced NSCLC patients treated with third-generation platinum doublets chemotherapy.

## [315P] -592 IL10 POLYMORPHISM AS A PROGNOSTIC FACTOR IN
LUNG CANCER PATIENTS

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Background: Lung cancer remains a major worldwide health problem, representing 17.8% of the total number of deaths caused by cancer. Chronic inflammation and
related pathways have an important role in lung cancer pathogenesis, especially in the
respiratory epithelium of smokers. IL-10 is a multifunctional cytokine with both
immunosuppressive and antiangiogenic functions and may have both tumour
promoting and tumour inhibiting properties. Polymorphisms in IL-10 gene promoter
are involved in predisposing to Non-Small Cell Lung Cancer (NSCLC). The aim of this
study was to evaluate the genetic influence of one of such polymorphisms, namely, -
592IL-10 polymorphism, (consisting of a C to A substitution), as a prognostic factor in lung cancer patients.

Patients and methods: DNA samples extracted from peripheral blood cells of 261 patients with
NSCLC. The -592IL-10 polymorphism was analyzed through PCR-RFLP. Survival data were analyzed according to -592IL-10 genotypes.

Results: The median survival rates NSCLC were statistically different according to the patients' genotype (18 months for AA and 35 months for C carrier genotypes; p = 0.015).

Conclusions: Convincing evidence demonstrates that -592IL-10 polymorphism is associated with differential expression of IL-10 in vitro and in vivo, with genotypes carrying the C allele expressing higher levels of IL-10. Our results suggest that -592IL-
10 C, carrier genotypes are correlated with a longer overall survival and -592IL-10 polymorphism may be a useful prognostic marker in lung cancer patients. According to these results, IL-10 gene can constitute an attractive target to immunotherapeutical strategies in lung cancer treatment.

## [316P] IMPACT OF CLINICAL PARAMETERS ON OUTCOME OF
PATIENTS TREATED WITH GAMMA KNIFE STEREOTACTIC
RADIOSURGERY FOR BRAIN METASTASES FROM NON-
SMALL CELL LUNG CANCER

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A retrospective study was conducted analyzing the clinical outcome and
prognostic factors in patients treated with gamma knife stereotactic radiosurgery
(GK-SRS) for brain metastasis from non-small cell lung carcinoma (NSCLC).

From November 2000 to May 2007 116 were treated. All patients received GK-SRS
to a median peripheral and maximal dose of 25 and 46 Gy, respectively. Median
age was 63 years, 26 were females, 90 males; 56 patients had solitary brain
metastasis, the average number of lesions per patient treated was 1.9; 27.5% of pts
showed Karnofsky performance status (KPS) 100, 18.1% 90, 38.8% 80, 13% 70,
2.6% 60; about RPA score (RPA I: age <65, KPS>70, controlled primary tumor, no
extracranial metastasis; RPA II: KPS <70 20.7% were classified RPA I, 75.5%
RPA II and only 3.8% RPA III. The median follow-up was 9.1 months for the
entire population and 31.4 months for those who were alive at the last follow up
(4 pts were lost at follow up). Univariate and multivariate analyses were used to
test the impact on survival of various clinical parameters such as age, gender, KPS,
RPA score, brain metastasis presentation (synchronous vs metachronous),
presence of extracranial metastasis, number of brain lesions (solitary vs. multiple)
and brain lesion site (sorventralntal vs subventral). The overall median and
3-year survival for the entire cohort were 8.7 months and 9%, (95% CI 4.5-17.4), respectively. Younger patients, particularly those younger than 50 years
(p = 0.02) with good KPS score, particularly KPS 100 (P=0.005) scoring RPA I/I
(P=0.001) achieved longer survival. At the multivariate analysis poor KPS
(P<0.001), age >55 years (P=0.02), low RPA score (P=0.03), subентoral lesions
with synchronous presentation (P<0.01) and synchronous brain lesions associated
with extracranial metastasis (P=0.04) seem to be detrimental to survival. In
conclusion, clinical parameters seem to be the strongest and the most useful
drivers to be considered for selection of NSCLC pts who really benefit from
Gamma Knife stereotactic radiosurgery.
During a recent National Institute of Health and Clinical Excellence (NICE) review, the efficacy of erlotinib was compared to that of docetaxel for the second-line treatment of stage III/IV NSCLC. As there were no trials including both treatments, an indirect comparison was performed based on trials including the common comparator placebo. We demonstrate that widening the scope of an indirect comparison to incorporate trials including comparators other than those of immediate interest, can improve precision and alter the final results; in this case swapping the ranking of the estimated mean treatment effects for docetaxel and erlotinib. A systematic review was conducted to identify randomised controlled trials of the following licensed second-line treatments for stage III/IV NSCLC: erlotinib, docetaxel, gefitinib or pemetrexed.

A network meta-analysis was then performed assuming that the estimated log-hazard ratios (LHRs) comparing treatments are exchangeable between trials and that we can add and subtract estimates of the LHR to obtain indirect estimates of treatment effects (ie. LHR<sub>AB</sub> = LHR<sub>AC</sub> - LHR<sub>BC</sub>). The analysis of the limited network only included the two trials that compared erlotinib (n=731) and docetaxel (n=155) to the common comparator placebo (HR for docetaxel (0.91, 95% CI 0.74-1.11) lower than that of erlotinib (0.70, 0.58-0.85), suggesting that docetaxel may be associated with better outcomes. Analysis of the extended network including all six trials of licensed treatments and using the same methodology produced an estimated HR for docetaxel of 0.85 (95% CI: 0.72-1.00). This is now higher than that of erlotinib (0.70; 0.58-0.85) (unchanged in this analysis), suggesting erlotinib may be associated with better outcomes. Results for the second period will be presented. Network meta-analysis provides a useful synthesis of trial data for decision-makers, particularly when more complex networks of evidence exist. Extending the network of trial evidence to include further indirect data may alter the conclusion of an analysis; care should therefore be taken to consider all relevant information when comparing treatments.
AMRUBICIN (AMR) vs TOPOTECAN AS SECOND-LINE TREATMENT OF EXTENSIVE-DISEASE SMALL CELL LUNG CANCER (SCLC) SENSITIVE TO PLATINUM-BASED FIRST-LINE CHEMOTHERAPY: A RANDOMIZED PHASE 2 TRIAL

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Background: SCLC accounts for about 15% of lung cancers and presents as extensive disease (ED-SCLC) in 68-70% of patients (pts). Pts sensitive to 1st line therapy have an expected response rate to 2nd line therapy of 25%. This study assesses whether single-agent AMR, a synthetic anthracycline analog and potent DNA topoisomerase II inhibitor previously shown to be active, improves response rates in SCLC pts compared to standard therapy.

Methods: This Phase 2 open-label, multicenter trial compares 2nd line therapy with AMR vs topotecan in ED-SCLC pts (pt 18 years, ECOG performance status 0-3) sensitive to 1st line platinum-based therapy (recurrence or progression ≥90 days after 1st line therapy). Pts were to be randomized 2:1 to AMR 40 mg/m2 by IV infusion on Days 1-3 or topotecan 1.5 mg/m2 by IV infusion on Days 1-5 of a 21-day cycle. Therapy was continued until disease progression, unacceptable toxicity, or withdrawal. The primary endpoint was response (RECIST). Progression-free survival (PFS) and overall survival (OS) were also measured. 75 evaluable pts were randomized to 47 AMR and 28 topotecan pts with at least 1 cycle of drug. Mean number of cycles administered was 4.8 for AMR (range 1-14) and 3.3 for topotecan (range 1-12). To date, there are 18 (38%) confirmed responses to AMR: 14 partial (PR) (30%) and 4 complete (CR) (8%). 3 additional PRs (6%) are pending follow-up scans. There is 1 confirmed PR to topotecan (6%) and 2 additional PRs (12%) pending follow-up scans. Degrees of myelosuppression were well balanced in the 2 arms.

Conclusions: AMR provides promising response rates and acceptable safety vs topotecan as 2nd line therapy in sensitive ED-SCLC pts.
were 51.4% and 55.2% respectively. Duration of response was similar in both regimens, 4.3 months for the sequential arm and 5.2 for the alternate arm. Patients experienced similar lethargy, diarrhea, neurotoxicity and stomatitis, but more infections on the B arm. Grade 3 and 4 neutropenia were observed in 53.8% patients on the A arm vs. 54.7 % on the B arm. Thrombocytopenia was 19.7% vs. 23.2% and anaemia 13.1% vs. 11.6%.

Conclusions: Sequential versus the alternate administration of cisplatin-etoposide and topotecan regimens as first line treatment in extensive stage SCLC patients is associated with acceptable and comparable toxicity for both arms, with no significant difference in terms of response rate, duration of response and overall survival.

GENDER IN SMALL-CELL LUNG CANCER (SCLC); AN ANALYSIS OF CHEMOTHERAPY TRIALS FROM THE MANCHESTER LUNG CANCER GROUP (MLCG) AND THE UK MEDICAL RESEARCH COUNCIL CLINICAL TRIALS UNIT (MRC CTU)

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The proportion of SCLC patients who are women has increased over recent decades. A Canadian analysis of 1006 patients in chemotherapy trials demonstrated improved survival for women, but with greater toxicity. To independently validate these findings we analysed recent UK SCLC studies. Six phase III chemotherapy regimens, performed by the MLCG and MRC CTU between 1993 and 2005, were pooled for analysis. Two trials investigated a dose-dense approach and 4 trials compared chemotherapy regimens. Endpoints included overall survival (OS), response rate (RR), haematological and non-haematological toxicity. Of 1707 patients treated, 749 (44%) were women. An overall study entry women had poorer performance status (PS) (57% v. 67% ECOG PS 0-1 or Karnofsky 80-100; p=0.0004) and were more likely to be of normal or underweight (57% v. 48%; p=0.003), but less likely to be anaemic (25% v. 62%; p=0.0001) or have elevated creatinine (3% v. 14%; p=0.0001). There were no differences in age, stage or type of chemotherapy received. Unlike the Canadian series, overall RR between women and men were similar (77% v. 75%, p=0.64). In univariate analysis, female sex, good PS, limited stage, dose-dense therapy, platinum-based therapy and normal baseline haemoglobin and leucocytes predicted for better survival. In multivariate analyses, after adjusting for these factors, female sex was still associated with significantly longer OS (adjusted hazard ratio 0.85, 95% confidence interval 0.76–0.96; p=0.0086; 42% v. 36% 1-year survival, 10.2 v. 9.6 months median survival), as seen in previous analyses. Women experienced marginally more leucopenia of any grade (75% v. 71%, p=0.05) but there was no difference in grade 3 or 4 haematological toxicities. Women experienced more severe nausea or vomiting (18% v. 9%, p=0.0001) and mucositis (13% v. 8%, p=0.005). There was no difference in infection rates, blood or platelet transfusions or treatment related deaths. In conclusion, women treated with chemotherapy for SCLC survived modestly longer than men, but experienced greater grade 3 and 4 non-haematological toxicity. These results validate findings of previous studies.

PHASE II STUDY OF IRINOTECAN PLUS CISPLATIN FOLLOWED BY AMRUBICIN IN PATIENTS WITH EXTENSIVE-STAGE SMALL-CELL LUNG CANCER (WJTOG 0301)

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Background: The combination chemotherapy of irinotecan (CPT-11), that is a topoisomerase (topo) I inhibitor, and cisplatin (CDDP) is one of the standard treatments in patients with extensive-stage small-cell lung cancer (SCLC). Amrubicin (AMR), that is a novel 9-aminooanthracine, inhibits topo II. Some preclinical studies reported that a combination of topo I and II inhibitors shows a synergistic cytotoxicity. We investigated the sequential chemotherapy that consisted of CPT-11 plus CDDP followed by AMR in patients with extensive-stage SCLC.

Methods: Eligible patients had an ECOG performance status of 0 or 1, an age of ≤ 70 years, measurable lesions, and adequate organ functions. Treatment consisted of CPT-11 60 mg/m² on days 1 and 8 plus CDDP 60 mg/m² on day 1 every three weeks for three cycles, and then AMR 40 mg/m² on days 1 to 3 every three weeks for three cycles. We evaluated the efficacy and toxicity of this treatment.

Results: From Sep. 2004 to Sep. 2006, 45 patients were enrolled, of whom, 43 patients were assessable for response and survival, and 44 patients were assessable for toxicity. Twenty-eight (64%) patients received full planned chemotherapy. One patient achieved a CR and 2 patients had a PR, with a response rate of 79% (95% CL 64% to 92%). The median overall survival time was 15.4 months and the median progression-free survival was 6.5 months. The major toxicity was myelosuppression. Grade 3 or 4 neutropenia, neutropenic fever, and anemia occurred in 27%, 7%, and 7% of patients during the CPT-11 plus CDDP phase, and 91%, 15%, and 27% of patients during the AMR phase, respectively. No treatment-related death was observed.

Conclusions: CPT-11 plus CDDP followed by AMR is an effective and well-tolerated treatment in patients with extensive-stage SCLC. It is likely that the sequential AMR prolongs the survival.

PHASE II STUDY OF AMRUBICIN (AMR) COMBINED WITH CARBOPLATIN (CBDCA) FOR ELDERLY PATIENTS WITH SMALL CELL LUNG CANCER (SCLC). (NORTH JAPAN LUNG CANCER GROUP 0405)

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Background: AMR, a new anthracine-like agent, is active for SCLC. We had previously reported a phase I study of AMR combined with CBDCA for elderly patients with SCLC. It (Thora Oncol 1:555.2006). The objective of this study is to evaluate the efficacy and the safety of this combination for elderly patients with SCLC.

Methods: Elderly patients (70 years or older) with SCLC received AMR (35 mg/m², day 1) and CBDCA (AUC 4, 0.5) every 3 days. The primary endpoint was overall response rate (ORR), and secondary endpoints were progression-free survival (PFS), overall survival and toxicity profile. Assuming that ORR of 60% in eligible pts would indicate potential usefulness while ORR of 40% would be the lower limit of interest, with α = 0.10 and beta = 0.20, the estimated accrual was 30 patients.
**Background:** Limited stage SCLC is treated with curative intent using an aggressive combined modality approach which includes chemotherapy and radiotherapy. We analyzed our data of patients with limited stage SCLC treated with induction chemotherapy followed by sequential radiotherapy or chemoradiotherapy.

**Methods:** Records of patients treated during 2003-2006 were analyzed. The response to treatment and outcome was studied.

**Results:** Records of a total of 23 patients were available for analysis. The group consisted of 21 males and 2 females between 32 and 69 years of age (Median age - 51 years). Twenty two of 23 patients were smokers. Four patients presented with superior vena-caval obstruction. All patients received initial combination chemotherapy with either Cisplatin-Irinotecan (n=17) or cisplatin-etoposide (n=6). Therefore, 12 out of 23 patients (52.2%) received sequential chest irradiation (50Gy in 25 fractions) while 6 out of 23 (26.1%) received concurrent chemoradiation with weekly cisplatin (same radiotherapy doses). Only 9 patients had adequate performance status to receive prophylactic cranial irradiation (PCI) as part of planned treatment. Complete response (CR) was seen in 3 out of 23 patients while partial response (PR) was seen in 11 patients yielding an overall response rate of 60.8%. Stable disease was noted in 2 patients while progressive disease was encountered in 5 patients. Two patients were lost to follow up. Among the responders a median follow up of 9 months (11-44 months), 6 patients are disease free while 10 experienced disease progression. The median relapse-free survival for the group was 9 months (CI - 8 to 10.5 months). All six patients who remain disease free are those who received PCI.

**Conclusions:** Combined modality approach is integral to the treatment of limited stage SCLC yielding high response rates. We used induction chemotherapy followed by radiotherapy since our patients presented with large volume limited stage disease. PCI should be exercised in all patients with limited stage SCLC in order to improve long term outcomes.

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**Background:** Although improvements have been made in the treatment of ED-SCLC, overall results remain disappointing, and there is a clear need to evaluate innovative and less toxic chemotherapeutic agents in this tumor type. Sagopilone, a novel chemotherapy-naive ED-SCLC were to receive a 3-h infusion of sagopilone followed by a fixed dose of P (75 mg/m2 1-h infusion) d1 q3w.

**Methods:** A combination of 75 mg/m2 P and sagopilone up to a dose of 22 mg/m2 was safely administered to pts with ED-SCLC, and showed promising clinical activity. Further results of the 22 mg/m2 cohort will be available at the meeting, but Phase II evaluation of this combination in ED-SCLC appears to be warranted.

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**Background:** Several studies have shown lack of survival benefit in patients (pts) with SCLC receiving chemotherapy treated with erythropoiesis-stimulating agents but have shown significant reduction in the incidence of blood transfusions and improvement in quality of life.

**Objectives:** A Phase II trial of treatment with darbeopetin alfa (DA) was conducted in pts with SCLC receiving high dose chemotherapy with carboplatin / etoposide. Primary objective was progression free survival (PFS), secondary objectives were overall survival (OS), response rate (RR), toxicity, transfusion incidence, course of Hb level over time and quality of life (QoL).

**Patients and methods:** From 2004 to 2007, pts (n=74) with either limited or extensive stage of SCLC were randomly assigned (1:1) to receive either DA (group A) or not (group B). Up to 6 cycles Chemotherapy were given as carboplatin AUC 5-6 on day 1 and etoposide 100-120 mg/m2 on day 1, 2, 3, then every two weeks. Also GCSF (pegfilgrastim 6mg sc) was administered on day 4. DA (300µg) was administered every 2 weeks when Hb <12 g/dL, but withheld if Hb >14 g/dL and then resumed once Hb <13 g/dL.

**Results:** PFS was 7.0 months in each group; RR was similar in both groups: 72.2% in group A vs 69.4% in group B, but this difference was not significant. Similar incidences of grade 3 and 4 toxicities were observed between groups. Only 30% of pts were evaluable for quality of life (measured by EORTC QLQ-C30 score). There was a slight beneficial trend for pts receiving concomitant DA until first follow up.

**Conclusions:** Similar rates of PFS and OS, as well as similar response rates in both treatment groups were observed. Use of DA did not appear to affect survival adversely and decreased the rate of transfusions.

The study was supported by AMGEN GmbH.
Results: Twenty-four RCTs (5212 patients) were eligible for the present analysis: 4 employing in II-III, 5 antiangiogenic agents, 1 other immunotherapy and 14 chemotherapy. A statistically significant reduction of mortality was detected (HR 0.80 95%CI 0.75-0.85) in the two-year survival in SCCLC. Final results and their comparison, including maintenance or consolidation chemotherapy, will be presented at ESMO 2008.

Conclusions: Maintenance or consolidation approach in interferon improves survival in SCCLC. New RCTs needed to further refine the place of this approach in the management of SCCLC. Final results and their comparison, including maintenance or consolidation chemotherapy, will be presented at ESMO 2008.

Background: NGR-NGTF is a VTA exploiting a tumour-homing peptide (NGR) that selectively binds to aminopeptidase N/CD13 highly expressed on tumour blood vessels. In preclinical models, NGR-NGTF showed antitumour activity both at low and at high doses.

Methods: Patients (pts) with advanced MPM were treated with low-dose NGR-NGTF given at 0.8 mg/m² as 1-hour intravenous infusion every 3 weeks (q3w). This dose was previously selected in phase I trial based on dynamic imaging changes and preliminary clinical activity. The trial had a 2-stage design with 16 and 27 pts to be enrolled. Progression-free survival (PFS) was the primary endpoint with reassessment performed q6w according to MPM-modified RECIST criteria.

Results: From May 2007 to January 2008, forty-three pts with progressive disease after pemetrexed-platinum-based regimens were enrolled. Globally, 41 pts were treated with 142 cycles (median, 2; range, 1-144). 16 pts (39%) and 10 pts (24%) have received 26 and 26 doses, respectively. Pts characteristics were: median age 64 years (range, 34-80); M/F 27/14; histology epithelial/non-epithelial (E/NE) 32/9; PS 0/1/2 24/10/7; EORTC performance status > 90). The following table shows the results of best response (n, %).

<table>
<thead>
<tr>
<th>Chemo-naïve N(%)</th>
<th>Previously treated N(%)</th>
<th>P(C) N(%)</th>
<th>P( ) N(%)</th>
<th>P(C/A) N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR 95%CI</td>
<td>113 (20.9)</td>
<td>34 (10.0)</td>
<td>64 (23.5)</td>
<td>98 (28.7)</td>
</tr>
<tr>
<td>SD 270 (49.0)</td>
<td>157 (46.0)</td>
<td>122 (48.2)</td>
<td>136 (46.6)</td>
<td>172 (49.9)</td>
</tr>
<tr>
<td>PD 140 (25.9)</td>
<td>138 (40.5)</td>
<td>78 (22.9)</td>
<td>124 (42.5)</td>
<td>98 (28.7)</td>
</tr>
</tbody>
</table>

The one-year survival rate was 67.5%(95% CI:1.4-2.8;98.9) with P(C)/75.9%(66.9-83.3)% with P and 73.9%(59.3-88.4)% with P/C/A. The median number of cycles was 4.0 with P and 6.0 with other regimens. The relative dose intensity of P was greater than 96% with all options. Grade 3/4 neutropenia occurred in 20.2% of patients on P/C/A, in 15.4% on P, in 28.6% on P/C/A, and was reported in 24.0% of naive and 18.4% of previously-treated patients. Rates of grade 3/4 anemia were 10.6% with P/C/A, 11.6% with P, and 16.7% with P/C/A. Conclusions: In this non-randomized study, the combination arms had a higher response rate compared to P alone, but no additional one-year survival benefit. Toxicity with P/C/A was worse compared to P/C or P alone.

Background: Doctaxel is an active agent for NSCLC. Combination chemotherapy has been shown to extend survival rate and improve symptoms for patients with advanced stages. We conducted a phase II study to evaluate the efficacy and toxicity of bi-weekly docetaxel and carboplatin for stage III unresectable NSCLC. Primary endpoint was overall response rate. Secondary endpoints were toxicity and time to progression.

Methods: 21 Patients with unresectable pathologically confirmed stage III NSCLC were included in this study. ECOG PS was 0-1 and adequate organ functions were included. Patients received Docetaxel 30mg/m² and Carboplatin AUC=2, intravenously 14 days interval for 6 cycles.

Results: From January 2005 to December 2006, 21 pts were enrolled. Among them 15 (71.42%) were male and 7 (28.58%) were female. Median age was 58 years (range 52-64 years). 9 (42.85%) were adenocarcinoma and 11 (52.38%) squamous cell carcinoma. Among 252 planned chemotherapy, 235 cycles were administered. There were 7 chemotherapy dose reductions (mainly due to neutropenia and renal dysfunction). There were no treatment related deaths. All of the patients were evaluable. We found complete response in 1 (4.76%), partial response in 16 (76.95%), stable disease in 2 (9.52%) and progressive disease in 2 (9.52%). The most common drug related toxicities were neuropathy (28.57%), fatigue (23.80%) and esophagitis (19.04%). No severe febrile neutropenia and no fatal events were observed. Median progression free survival was 15.6 months.

Conclusion: Doctaxel containing regimen showed a very significant role in stage III unresectable NSCLC. The combination of doctaxel and carboplatin regimen is very effective.

Background: Second-line chemotherapy offers advanced non-small cell lung cancer (NSCLC) patients a small but significant survival improvement. To evaluate whether treatment with single-agent docetaxel would result in longer survival in patients with non-small cell lung cancer that had previously been treated with platinum-based chemotherapy. Secondary end points included assessment of response, toxicity and quality of life.

Methods: Patients with performance status of 0 to 2 and stage IIIb/IV non-small cell lung cancer with either measurable or evaluable lesions were eligible for entry into the study if they had undergone one or more platinum-based chemotherapy regimens and if they had adequate hematologic and biochemistry parameters. They were excluded if they had symptomatic brain metastases or if they had previously been treated with paclitaxel. Patients were treated with docetaxel 75mg/m² intravenous infusion for 1 hour repeated every 3 weeks until disease progression or intolerant toxicity.

Results: This phase II study was conducted from January 2003 to December 2006 which was an open-label, non-randomized, single-centered and prospective study. This study consisted of 30 patients which included 25 (83.33%) male and 5 (16.67%) females. Median age was 54 years. On the histological varieties: 20 (66.67%) adenocarcinoma, 5 (16.67%) adenosquamous cell carcinoma, 5 (16.67%) large cell carcinoma were included. A total 140 cycles were administered and 2830 patients were evaluated for responses. The overall response was 14 (30%) with 0 complete and 14 partial responses.
PHASE II STUDY OF IRINOTECAN AND OXALPLATIN (IROX) COMBINATION AS A FIRST-LINE TREATMENT FOR ADVANCED NON-SMALL CELL LUNG CANCER

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Background: We conducted a prospective phase II clinical study of IROX in advanced non-small cell lung cancer patients to evaluate the efficacy and toxicities.

Patients and methods: Patients with histologically or cytologically proven NSCLC, age >18 years, performance status 0 – 1, stage III/IV (pleural effusion) or IV or recurrent disease not suitable for primary surgical treatment, no prior chemotherapy or radiotherapy to chest or immunotherapy or biologic therapy, presence of measurable disease by RECIST, and with signed written informed consent were eligible. Treatment consisted of irinotecan 60 mg/m² day 1 and day 8, oxaliplatin 130 mg/m² day 1, which was repeated every 3 weeks.

Results: From September 2006 to March 2007, 18 patients were prospectively enrolled. The median age was 59 years (47 – 75). In total, 71 cycles were administered with a median of 4 cycles per patient (range, 1 – 6 cycles) and 18 patients were evaluable for treatment response. An independent review of tumor responses resulted in ORR of 27.7% (95% CI, 7% to 48.4%) by intent-to-treat analysis with 5 PRs. The median survival of all patients was 7 months and the median time-to-progression was 4 months. Most common grade 3/4 toxicities were diarrhea (7% of all cycles) and neutropenia (5.6% of all cycles). Grade 3 peripheral neuropathy occurred in 1 patient and grade 1/2 diarrhea occurred in 9 (50% of all patients) patients. One (5.5%) patient died due to sepsis.

Conclusions: The response rate of IROX combination chemotherapy in the first stage of Simon’s two stage design did not meet. These results suggest that IROX combination therapy has moderate activity, but with current dosage and schedule, this regimen would not be recommended as first-line treatment for patients with advanced or metastatic non-small cell lung cancer.

PHASE II TRIAL OF FIRST-LINE TREATMENT WITH ALTERNATE SCHEDULE OF CHEMOTHERAPY IN METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC).

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Background: Nowadays NSCLC is the most frequent and lethal malignant neoplasm, with hopeless results in advanced stages. This trial is proposed in order to search for a better and well-tolerated therapy considering tumor heterogeneity by combining the four most active chemotherapeutic agents in NSCLC -Docetaxel, Gemcitabine, Cisplatin and Vinorelbine- in an alternate schedule.

Methods: We enrolled patients (pts) with stage IV or wet IIIB NSCLC. Additional criteria included an ECOG performance status less than 2, less than 2 comorbidities and the presence of at least one measurable lesion. They received an alternate schedule of treatment consisting of [Docetaxel 35 mg/m² + Cisplatin 35 mg/m²] d1 and 8; and [Cisplatin 35 mg/m² + Vinorelbine 25 mg/m²] d21 and 28, every 42 days. 3 complete regimens would be administered. Primary end point was objective response per RECIST criteria. Secondary endpoints included progression-free survival (PFS), overall survival (OS) and safety.

Results: 27 pts were enrolled. 3 of them left the protocol prematurely within the 1st or 2nd infusion because of docetaxel hypersensitivity (1), severe hepatotoxicity (1) or life-threatening event (1). 24 were evaluable for response and 27 for safety. 96.2% of the programmed treatments were administered. Median age was 57.2 years (range 41-75); 83% were male. Adenocarcinoma/squamous cell/undifferentiated non-small cell carcinoma (50.16/73.3). Stage IIIB/IV (8/3.91); ECOG PS 0/1 (37/63). Clinical benefit was 79% (CR 4.2%, PR 54%, SD 20.8% and PD 21%). PFS 8.5 months (3-26); OS 10.3 months (4.5-20). Toxicity: Anemia 74% (III: 7.4%); Neutropenia 26% (III: 11%); Mucositis 11% (III-IV: None); Nefrotoxicity 11% (III-IV: none); elevated AST and hyperbilirubinemia (III: 3.7%).

Conclusions: These results sugest that the alternating combination of Docetaxel/ Cisplatin 8 with Vinorelbine/Cisplatin is a highly-active regimen in advanced NSCLC. Data of PFS and OS are similar to other found in the scientific literature. This, together with its interesting toxicity profile, make it a feasible treatment to be taken into consideration in NSCLC.

PEMETREXED IN PREVIOUSLY TREATED NON-SMALL-CELL LUNG CANCER

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Background: We conducted a phase II trial to investigate the efficacy and toxicity of pemetrexed monotherapy in patients with previously treated non-small-cell lung cancer (NSCLC).

Patients and Methods: Patients with stage IIIB and IV NSCLC with performance status from 0 to 2, were eligible if they had received one or two prior chemotherapy regimens. Patients received pemetrexed 500 mg/m² intravenously day 1 with vitamin B12, folic acid, and dexamethasone every 3 weeks until disease progression or unacceptable toxicity.

Results: Thirty-eight patients were treated with pemetrexed. Thirty-six (95%) patients were previously treated with either cisplatin (55%) or carboplatin (40%) as first-line platinum-based chemotherapy. The predominant history was adenocarcinoma (45%). The patients’ median age was 62 years (range 39-78) and eight patients (21%) had a performance status of 2. The response rate was 13 percent; the median duration of the response was 2.8 months. Median progression-free survival was 9.1 weeks (95% CI, 5.3-13.0) and median overall survival was 6.5 months (95% CI, 3.5-9.3). A total 150 chemotherapy cycles were delivered (median 3). Therapy was well tolerated: grade 3 to 4 neutropenia and thrombocytopenia occurred 3% and 3% of patients, respectively. Nausea and vomiting were present in 28% of patients and peripheral neuropathy was observed in 5% of patients.

Conclusion: Pemetrexed monotherapy is effective and well tolerated in patients with previously treated NSCLC.

GEMCITABINE PLUS CARBOPLATIN VERSUS TAXANS PLUS CARBOBLATIN, IN NON SMALL CELL LUNG CANCER, A RETROSPECTIVE OBSERVATIONAL STUDY

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Background: Lung cancer remains the main causes of cancer death in the world. Chemotherapy remain one of the most used therapy for advanced stages but the selection of cytostatics adjusted for particularities of patients is not yet achieved.

Patients and methodology: A lot of 42 patients treated with gemcitabine and carboplatin or taxubin and carboplatin, was selected by chance from the archives of Institute of Oncology Bucharest. Patients were treated by the some doctors. Patients (P) had stage IIIB and IV and were treated in 2005-2006. 18 P (Lot A) received Gemcitabine 1000mg/m² day 1 and 8 (cycle of 21 days) plus carboplatin AUC3 and 24 P (Lot B) received paclitaxel 175mg/m² or docetaxel 75mg/m² plus carboplatin AUC3 (cycles of 21 days). The survival was estimated by time to progression or time since last of evidence, and calculated by Cqlan Mayer curve.

Results: In Lot A were 3 females, in Lot B 5 females. The mean age ion Lot A was 65 years and 54, 3 in Lot R. The median time since progressive disease or loss of evidence was 4, 7 month for Lot A and 6 for Lot B. The median time since progressive disease or loss of evidence for women in Lot A was 4, 3 month and 9 for Lot B.

Conclusion: This study could generate more questions: Combinations of Gemcitabine is more used in advanced age? The combinations of taxans with carboplatin are more efficient to women with non small-cell lung cancer? The difference in survival is influenced however by number of cycles of chemotherapy? To answer definitively for some of these questions is necessary to design a prospective study for each question.
COST-MINIMIZATION ANALYSIS OF ERLOTINIB VERSUS DOCETAXEL OR PEMETREXED AS SECOND-LINE THERAPY FOR NON- Small-CELL LUNG CANCER (NSCLC) FROM THE PERSPECTIVE OF A PRIVATE PAYER IN BRAZIL ACCORDING TO LOCAL HTA GUIDELINES

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Objective: To perform a cost-minimization and budget impact analysis of erlotinib versus docetaxel or pemetrexed for the treatment of patients with advanced NSCLC who have failed previous chemotherapy.

Methods: In the absence of head-to-head clinical trial data for erlotinib versus docetaxel or pemetrexed, equivalent efficacy was assumed for the three interventions; indirect comparisons of phase III trial results suggest that this was a conservative assumption. We developed a cost-minimization and budget impact model for cost comparison of these three treatments based on the results of the BR.21 study of erlotinib, and pivotal trials for docetaxel and pemetrexed, adopting a Brazilian private payer perspective. A 126-day timeframe was used for the comparison, based on the progression-free survival observed in the BR.21 study. A Delphi panel was conducted to identify local practices and associated costs in Brazil. Other costs such as medical payment, pre- and post-medication, and administration were also included. One-way and multi-way sensitivity analyses were performed to assess the robustness of the outcomes. Discounting was not included due to the short-term perspective of the analysis.

Results: Total costs were R$ 27,500 for erlotinib, R$ 43,299 for docetaxel and R$ 81,833 for pemetrexed. The cost-savings observed for erlotinib were due to lower acquisition costs (R$ 27,470 versus R$ 41,230 for docetaxel and R$ 80,900 for pemetrexed) and its more favourable tolerability profile. Sensitivity analyses confirmed the robustness of the results obtained. The budget impact analysis showed savings in the first year after incorporation of erlotinib starting from R$ 2,543,421 in a conservative scenario, and reaching R$ 25,432,217 at the upper limit, considering 25% of pemetrexed utilization.

Conclusions: The findings of this cost-minimization analysis suggest that erlotinib is a cost-saving alternative under the private healthcare system perspective in Brazil.

SYSTEMIC CHEMOTHERAPY AFTER CRANIAL IRRADIATION IN PATIENTS WITH BRAIN METASTASES FROM NON-SMALL-CELL LUNG CANCER: A RETROSPECTIVE MULTI-CENTER STUDY

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Background: Brain metastases (BM) are found in about 10% of patients with newly diagnosed non-small cell lung cancer (NSCLC). This retrospective study was conducted to assess the clinical outcomes and prognostic factors of patients who received chemotherapy after cranial irradiation for NSCLC with synchronous BM.

Materials and Methods: From January 2008 through July 2007, we reviewed the medical records of patients who received systemic chemotherapy following cranial irradiation for BM from newly diagnosed NSCLC.

Results: A total of 40 patients were included in this study. As the first-line chemotherapy taxane-based regimen was administered in 35%, gemcitabine-based in 37.5%, and irinotecan-based in 5%. Sixteen (40%) patients, eleven of whom had ECOG of 2, only received 1 cycle or less of chemotherapy due to early death, rapid progression, clinical impairment, or toxicity. For 28 patients who were evaluable for response, the extracranial overall response rate was 43%. The median overall survival was 7 months (range, 0.9-25.3 months) and an estimated 1-year survival rate was 23%. Multivariate analysis revealed that ECOG status (P = 0.018) and number of BM (P = 0.038) were independent prognostic factors.

Conclusion: Our results suggest that chemotherapy can be used to increase survival of patients treated with cranial irradiation for newly diagnosed NSCLC with synchronous BM. However, systemic chemotherapy should be carefully considered according to the patient’s prognostic condition. Especially, patients with good performance status and limited number of BM may be good candidates for systemic chemotherapy after cranial irradiation.

PHASE II STUDY OF BEVACIZUMAB IN COMBINATION WITH CISPLA TIN AND VINORELBINE AS FIRST LINE TREATMENT OF PATIENTS (PTS) WITH ADVANCED OR METASTATIC, NON-SQUAMOUS, NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: Bevacizumab (B) has shown to improve response rates and survival in pts with advanced non-squamous NSCLC when combined with carboplatin and paclitaxel (FDA-approved indication) or with cisplatin and gemcitabine (EMA-approved). However, there are limited data on the safety and efficacy of B in combination with other widely used chemotherapy doublets for NSCLC. This is a preliminary safety report of a single-arm, open-labelled, phase II trial of B, cisplatin and vinorelbine for pts with NSCLC.

Methods: In this single-stage phase II trial, patients received cisplatin (80 mg/m² iv) and vinorelbine (25 mg/m² iv days 1 and 8) and B (15 mg/kg IV) on day 1 every 3 weeks for up to 6 cycles followed by B 15 mg/kg alone every 3 weeks until progression. Eligibility criteria included chemotherapy-naive stage IIIb or IV incurable NSCLC of non-squamous histology, PS 0-1, no brain metastases, no history of hemoptysis, stable cardiac condition and no full dose anticoagulation. The primary endpoint was progression-free survival, with secondary endpoints of TTP, RR, OS and safety.

Results: 18 pts have been enrolled of a planned sample size of 92. Data from 9 pts has been included in this analysis. Baseline characteristics were: 4 females, median age 57.5 years old (51-70), PS 0 (2 pts) or 1 (7 pts), stage IIIb (4 pt) or IV (5 pts). Median number of cycles was 1 (range 1-2). 7 pts are evaluable for toxicity. Hematological toxicities: 4 pts with grade I/II neutropenia, 2 pt with grade I/II leukopenia, 1 pt with grade I/II anemia. The most common grade I/II non-hematological toxicities included skin rash (N=1), headache (N=1), asthenia (N=2), stomatitis (N=2), constipation (N=1), nausea (N=3), vomiting (N=1), cough (N=1), diarrhea (N=1), asthenia (N=1). 1/9 pts is off treatment (disease progression) and this was the only SAE reported: grade 3 dyspnea.

Conclusions: preliminary analysis shows that the combination of Bevacizumab, vinorelbine and cisplatin is safe and well tolerated. Enrollment continues and updated results will be presented.

ERLOTINIB-ASSOCIATED TRICHOMEGALY (EXCESSIVE EYELASH GROWTH) IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER: A PHENOMENON WITH POTENTIAL PROGNOSTIC IMPLICATIONS

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Background: Development of skin rash within 2-3 weeks of erlotinib therapy is associated with clinical response in patients with advanced non-small cell lung cancer (NSCLC). Thrichomegaly has been reported in this setting, although its clinical significance remains unknown.

Objective: We report 3 patients who developed bilateral trichomegaly while exhibiting a clinical response to erlotinib.

Methods: Case report.

Results: All 3 cases were diagnosed with metastatic lung adenocarcinoma, had a performance status of at least 2 (ECOG), and were oxygen-dependent at the time of erlotinib initiation. All patients had developed skin rash within 3 weeks of erlotinib therapy. Case 1: A 35-year-old male oligo-smoker (less than 10 cigarettes/day) was diagnosed upfront with metastatic bone disease refractory to initial treatment with gemcitabine/carboplatin and to second line docetaxel. Four months into treatment with erlotinib he noted the development of bilateral, coarse eyelashes, but no associated ocular or visual symptoms. During the 12 months of therapy with erlotinib his skin rash was asymptomatic. Subsequently, the bone metastases progressed, and treatment was discontinued. Case 2: A 72-year-old female heavy smoker (about 100 pack/year) was bed-ridden and agreed to be started on oral erlotinib. Three months into treatment she developed bilateral trichomegaly. Twelve months after starting erlotinib, the patient remains asymptomatic. Case 3: A 68-year-old male heavy smoker (about 100 pack/year) was diagnosed with stage 3B adenocarcinoma of the lung and received initial treatment with concurrent paclitaxel/carboplatin and thoracic radiation. Upon
relapse he received perfuximated. Upon his second relapse he was started on erlotinib. Eleven months into erlotinib therapy, he remains clinically asymptomatic.

**Conclusion:** A relative durable clinical response to the erlotinib was documented in 3 NSCLC patients with poor prognosis features. Clinical outcome of NSCLC patients developing erlotinib-associated trichomegaly needs to be prospectively evaluated.

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**SURVIVAL OUTCOME AND PREDICTORS OF GEFITINIB AND ERLOTINIB TUMOR ACTIVITY IN EAST ASIAN PATIENTS WITH ADVANCED OR RECURRENT NON-Small CELL LUNG CANCER WHO RECEIVED ONE PREVIOUS CHEMOTHERAPY**

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**Background:** The treatment response pattern of chemonaive and previously treated patients are different. The survival and predictors of gefitinib-monotherapy in NSCLC patients who received only one chemotherapy need to be identified.

**Methods:** Medical charts of 74 patients with advanced or recurrent NSCLC treated with gefitinib monotherapy between Jun 2002 and Aug 2006 at 4 major medical centers in Taiwan were retrospectively reviewed. Tumor response, survival, clinicopathologic and laboratory data were collected. Multivariate analyses were performed to identify independent predictors for response and survival to gefitinib.

**Results:** At analysis, 63 out of 74 patients (85.1%) had expired, and the median follow-up duration was 12.0 months (range 9.6–14.4). 30 patients were male (40.5%). 51 patients (68.9%) had adenocarcinoma or bronchioloalveolar carcinoma. 48 patients (64.9%) were never smokers. 61 patients (82.4%) had ECOG performance status 0 to 2. Out of 72 patients with known reasons of stopping previous chemotherapy, 23 patients (31.9%) were due to progression during chemotherapy. The rest patients progressed after chemotherapy. Among 66 patients with documented tumor response, 33 patients (50%) were with evaluable as too early or no measurable disease); objective response rate was 19.7% with a complete response in 1.3% of patients, partial response in 18.4%, stable disease in 23.8% and progressive disease in 25.1%. Median PFS reached 3.0 months and median OS 7.0 months. Rash and diarrhoea were the most common toxicities reported in 48.0% and 23.3% of patients, respectively. Rash was the most common reason for treatment interruption (10.3%). Treatment was permanently stopped due to toxicity in 21 (9.3%) patients.

**Conclusion:** The efficacy and toxicity of erlotinib used in everyday clinical practice are similar to those reported in clinical trials confirming that the drug is an effective and well-tolerated option for the treatment of NSCLC.

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**ERLOTINIB IN THE TREATMENT OF NON-SMALL CELL LUNG CARCINOMA (NSCLC) – A CZECH RETROSPECTIVE ANALYSIS**

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**Background:** Erlotinib (Tarceva®) has been shown to be efficacious in the treatment of recurrent/metastatic NSCLC with progression-free survival (PFS) reaching 9 weeks and overall survival (OS) 6.7 months (Shepherd FA, et al. J Clin Oncol 2004;22(14S):T022). This retrospective analysis evaluated the efficacy and tolerability of erlotinib in NSCLC when used in an everyday clinical environment.

**Methods:** Data were collected retrospectively on all patients with NSCLC treated with erlotinib at 9 pulmonology centres in the Czech Republic (where erlotinib is reimbursed) before July 2007.

**Results:** Data from 223 patients were obtained: median age 61 years (range 33–82); 58.3% males; 25.1% smokers; 49.3% ex-smokers and 22.0% non-smokers (3.6% status unknown). The majority of patients had adenocarcinoma without bronchioloalveolar carcinoma (44.8%) or squamous cell carcinoma (38.1%). 16.6% of patients had prior surgery. 31.4% radiotherapy, 12.1% adjuvant chemotherapy and 4.0% neoadjuvant chemotherapy. 71.3% of patients had metastatic disease. Performance status was documented in 114 patients (51.1%) of which 77.0% had PS0, 64.0% PS1, 26.3% PS2 and 2.6% PS3. Erlotinib was used as 2nd-line therapy in 51.1% of patients and as 3rd-line in 48.4% (1 patient had no prior chemotherapy). Median treatment duration was 59.0 days (range 0–483). 68.6% of patients were evaluable for efficacy (31.4% not evaluable as too early or no measurable disease); objective response rate was 19.7% with a complete response in 1.3% of patients. Partial response was in 18.4%, stable disease in 23.8% and progressive disease in 25.1%. Median PFS reached 3.0 months and median OS 7.0 months. Rash and diarrhoea were the most common toxicities reported in 48.0% and 23.3% of patients, respectively. Rash was the most common reason for treatment interruption (10.3%). Treatment was permanently stopped due to toxicity in 21 (9.3%) patients.

**Conclusion:** The efficacy and toxicity of erlotinib used in everyday clinical practice are similar to those reported in clinical trials confirming that the drug is an effective and well-tolerated option for the treatment of NSCLC.
cases with deletion p16 gene copies. These results, well below those expected, have led us to widen the study trying to correlate the incidence of gene expression alterations to the presence or not of metastasis and patient evolution.

**WEAKLY DOCETAXEL AND CARBOPLATIN WITH CONCURRENT RADIATION THERAPY FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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**Purpose:** The aim of this study was to evaluate the efficacy and toxicity of weekly docetaxel and carboplatin with concurrent radiation therapy for locally advanced non-small cell lung cancer (NSCLC).

**Methods:** Between April 2000 and March 2007, 32 patients with locally advanced incurable stage III NSCLC were treated concurrent chemoradiotherapy with carboplatin with area under the concentration-time curve (AUC) of 5.0 given on days 1, 22 and docetaxel 15mg/m2 given on days 1, 8, 15, 22, 29, 36 during 66 Gy of thoracic radiotherapy.

**Result:** Enrolled patients were 29 men and 3 women, with the median age of 70 years. Twenty-nine patients received the scheduled radiotherapy. The cycles of chemotherapy administered ranged from 2 to 6, with a median of 3. Overall toxicities were mild. Grade 3 thrombocytopenia was noted in 1 patient and grade 3 esophagitis in 2 patients, but there were no cases of grade 3 pneumonitis. The overall response rate was 81.3%. The median survival time was 27 months.

**Conclusion:** Weekly docetaxel and carboplatin with concurrent radiation therapy is feasible and promising for locally advanced NSCLC.

**CYTOGENETIC LYMPHOCYTE ANALYSIS IN LUNG CANCER PATIENTS WITH DIFFERENT STAGES OF TUMOUR PROGRESSION

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One of the most aggressive and frequently occurring cancer forms in men is non-small cell lung cancer (NSCLC). In overwhelming majority of patients, the disease is diagnosed at late stages. But the efficiency of advanced therapy of this cancer form depends directly on the disease stage. In view of this, the aim of the given work was to study cytogenetic features of this disease at different stages of tumour progression. The method of interphase cell analysis without cultivation (in vivo) was used for cytogenetic investigations. The frequency of cells with micronuclei and of binuclear lymphocytes was determined in peripheral blood lymphocytes (PBL) of lung cancer patients. Some investigation have shown that there is the possibility to detect a tumoral process in organism by the whole complex of specific and non-specific chromosome and genome damages in somatic cells including PBL. The cytogenetic analysis has shown that the frequency of cells with micronuclei was lower in PBL of the patients with the 1st stage of the disease (0.29±0.07%) as against with the 1st stage of the disease (0.53±0.07%). Thus, the revealed significant differences in the presence of the cells with cytogenetic damages in lung cancer patients with various stages of the disease can be used in cytologic diagnostics. An increase in the quantity of binuclear lymphocytes in blood of oncologic patients seems to point to stimulation of proliferative processes in tissues of these individuals. In this connection, at present the gene polymorphism of epidermal growth factor (EGF) in +66 position (G→A) is carried out simultaneously. The results obtained indicate an increased level of binuclear lymphocytes in patients with adile A.

**EFFICACY AND SAFETY OF PEMETREXED IN ASIAN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) AND MESOTHELIOMA: A RETROSPECTIVE REVIEW FROM THE JOHNS HOPKINS SINGAPORE INTERNATIONAL MEDICAL CENTRE

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**Background:** The efficacy and toxicity of Pemetrexed in Asian patients is unknown. Methods: Retrospective review of patients treated with Pemetrexed. REGIST were used to assess efficacy independently of the treating physician’s assessment. GCITCAE version 3.0 were used for the description of adverse events.

**Results:** Forty-three patients received Pemetrexed: 37 had NSCLC and 6 had mesothelioma. Patients with NSCLC had a median age of 60 years, and were predominantly male (29 men and 8 women), ethnic Chinese (32 patients) and smokers (22 patients). Histology was as follows: NSCLC not otherwise specified, 19; adenocarcinoma, 12; squamous cell carcinoma, 4; bronchoalveolar and large cell, 1 each. Twenty-four patients had stage IV at diagnosis, 12 had stage III and 11 had stage II. All had received at least one prior regimen (median 1, range 1 to 4): Carboflan, 21 patients; Carboplatin, gemcitabine, 21 patients; Carboplatin, irinotecan and paclitaxel, 9; Gefitinib, 9; Carboplatin and Paclitaxel, 6; Erlotinib, 2; gemcitabine and Cisplatin, Single agent paclitaxel, Carboplatin and Docetaxel, Cisplatin and Etoposide, 1 patient each. Twenty-nine individuals had an ECOG PS of 0 or 1. Patients received a median of 2 cycles of treatment (total, 9% range 1 to 12). Grade 3 and 4 adverse events were as follows: anemia, 3 patients; pneumonia, 2 patients; neutropenic fever, 1 patient; thrombocytopenia, 1 patient. Five (14%) patients had an objective response (1 CR, 4 PR) and (15%) had stable disease. Median Time to Treatment Failure was 8 weeks (95% CI, 0 to 27.7). Median Overall Survival was 80 weeks (95% CI, 53.7 to 118.9) The median age for patients with mesothelioma was 65 years. Five men and one woman (4 ethnic Chinese, 1 Indian and 1 Arab) received a median of 4 cycles (total, 30, range 1 to 15) of Pemetrexed in combination with cisplatin. Three patients had a PR, 2 had stable disease and one had progressed at the time of first evaluation. Grade 3 and 4 toxicity was as follows: leukocytopenia, neutropenia, and thrombocytopenia, 1 patient.

**Conclusion:** Pemetrexed seems to be safe and efficacious in the treatment of Asian patients with NSCLC and mesothelioma.
MEDICAL THORACOSCOPY: DIAGNOSIS AND MANAGEMENT OF MALIGNANT PLEURAL EFFUSIONS

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Objective: To evaluate the efficacy and safety of medical thoracoscopy under local anesthesia in patients with pleural effusions retrospectively.

Methods: We reviewed patients with pleural effusion who underwent medical thoracoscopy to make a definite diagnosis or pleurodesis under local anesthesia in the Nagoya Medical Center from June 2001 to April 2007. We assessed the diagnosis rate and safety of medical thoracoscopy to make a diagnosis or pleurodesis under local anesthesia for these patients. We also evaluated the success rate of the pleurodesis.

Results: Twenty-six patients were recruited (15 male and 11 female). Median age was 66.5 years (range 45-84). The medical thoracoscopy were performed to make a definite diagnosis and pleurodesis for 9 patients and to pleurodesis for 17 patients. Median examination time was 52.5 minutes (range 28-170). Grade 1 fever was occurred in 3 patients (12%) and Grade 1 pain was occurred in all patients (100%). Grade 5 acute respiratory distress syndrome (ARDS) in a patient (4%) was observed. Of the 9 patients, 8 patients got diagnoses (4 carcinoma, invasive thymoma, malignant mesotheloma, dermatofibrosarcoma and tuberculous pleuritis). The diagnosis rate was 88.9%. Although the residual patient had malignant pleural effusion, the primary lesion was unknown. Pleurodesis was carried out with dry sterile talc poudrage in all patients. We succeeded the pleurodesis in 22 patients and success rate was 87.5%. 3 patients were needed additional pleurodesis with OK-432.

Conclusions: We considered medical thoracoscopy under local anesthesia had high diagnostic rate and useful examination because of ability to performing pleurodesis. Complications with medical thoracoscopy were Grade 1 fever and pain, Grade 5 ARDS.