6519 ORAL

Favorable benefit to risk profile for pemetrexed plus cisplatin versus gemcitabine plus cisplatin in a large phase III study of first-line therapy in advanced non-small cell lung cancer

G. Scagliotti[1], K. Park[2], S. Patil[3], J. Rolski[4], T. Gorksel[5], S.J.M. Gans[6], R. Martins[7], C. Visseren-Grul[8], P. Peterson[9]. *[1]University of Torino, Department of Clinical & Biological Sciences Thoracic Oncology Unit, Orbassano, Italy; [2]Samsung Medical Center, Division of Hematology/Oncology Deparment of Medicine, Seoul, Korea; [3]Bangalore Institute of Oncology, Medical Oncology, Bangalore, India; [4]Oncological Institute, Medical Oncology, Krakow, Poland; [5]Ege University Medical School, Pulmonary Medicine, Izmir, Turkey; [6]St. Jansdal Hospital, Pulmonary Diseases, Harderwijk, The Netherlands; [7]University of Washington, Medical Oncology, Seattle, USA; [8]Eli Lilly and Company, Lilly Medical, Houten, The Netherlands; [9]Eli Lilly and Company, Lilly Medical, Indianapolis, USA*

Background: In a recently concluded large phase III study, chemonaive patients with stage IIIB/IV non-small cell lung cancer (NSCLC) who were treated with pemetrexed plus cisplatin (PC) had similar efficacy with better tolerability and more convenient administration than patients who received gemcitabine plus cisplatin (GC). Overall survival for patients treated with PC was non-inferior to those on GC (HR 0.94, 95% CI 0.84−1.05) with the entire 95% CI well below the 1.176 non-inferiority margin.
Methods: In the aforementioned study, survival without grade 4 toxicity was defined (for all randomized patients receiving study treatment) as the time to the first occurrence of CTC grade 4 toxicity or death, analyzed using Kaplan-Meier and Cox methods. This prospectively defined analysis is a measure of benefit relative to risk in that overall survival time (ie, clinical benefit) relative to the first occurrence of CTC grade 4 toxicity (ie, clinical risk) was compared between treatments. A similar additional analysis also included grade 3 toxicities. The phase III study randomized 1725 patients to receive PC (P 500 mg/m^2 d1; C 75 mg/m^2 d1) or GC (G 1250 mg/m^2 d1, 8; C 75 mg/m^2 d1) every 3 weeks for up to 6 cycles. Both arms received dexamethasone prophylaxis, folic acid and vitamin B_{12} supplementation. Patients had previously untreated stage IIIB (24%) or IV (76%) NSCLC and an ECOG PS of 0−1 (37%/63%).
Results: 839 pts receiving PC and 830 pts receiving GC were included in these analyses. Baseline characteristics and known prognostic factors were well balanced across treatment arms. PC demonstrated a statistically significantly longer survival without grade 4 toxicity compared with GC (HR = 0.83; 95% CI = 0.74−0.92, p < 0.001); with a median time of 9.0 vs 7.3 mos. PC also demonstrated statistically longer survival without grade 3/4 toxicity compared with GC (HR = 0.82, 95% CI = 0.74−0.91 p < 0.001); with a median time of 1.6 vs 1.1 mos.
Conclusion: This analysis of survival without grade 4 toxicity or without grade 3/4 toxicity shows a statistically significant advantage for PC over GC and suggests a benefit-to-risk profile that favors PC over GC in first-line treatment of patients with NSCLC. This analysis helps to further characterize PC as a favorable treatment option in this setting.

6520 ORAL

Multi-gene prediction of distant relapse-free survival in early NSCLC: microarray expression-profiling study

M. Jarzab[1], E. Jassem[2], A. Szymanowska[2], W. Rzyman[3], M. Oczko-Wojciechowska[4], K. Fujarewicz[5], E. Chmielik[6], W. Niklinska[7], M. Kozlowski[8], J. Jassem[9]. *[1]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Dept. of Clinical Oncology, Gliwice, Poland; [2]Medical Academy Gdansk, Dept. of Allergology and Pneumonology, Gdansk, Poland; [3]Medical Academy Gdansk, Dept. of Thoracic Surgery, Gdansk, Poland; [4]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Dept. of Nuclear Medicine and Endocrine Oncology, Gliwice, Poland; [5]Silesian University of Technology, Dept. of Automatic Control, Gliwice, Poland; [6]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Dept. of Pathology, Gliwice, Poland; [7]Medical University Bialystok, Dept. of Histology and Embryology, Bialystok, Poland; [8]Medical University Bialystok, Dept. of Thoracic Surgery, Bialystok, Poland; [9]Medical University Gdansk, Dept. of Oncology and Radiotherapy, Gdansk, Poland*

Background: The aim of the study was to obtain a prognostic multi-gene classifier for relapse-free survival in stage I-II NSCLC, in the context of lymph node status as an established prognostic factor.
Materials and Methods: Tumor specimens were collected from 70 NSCLC patients (pts) who underwent curative pulmonary resection between 1999 and 2004 in two Polish centers (Gdansk, Bialystok). There were 54 men and 16 women aged 37−77 yrs (median 62.5 yrs), 45 with squamous cell ca, 22 with adenoca and 3 with large cell ca. Eight pts were staged pT1, 59 pT2 and 3 pT3; there were 49 and 21 pN0 and pN1 pts, respectively. 30 pts had a relapse and 32 pts died (median follow-up 36 months). Samples of tumor tissue were collected intraoperatively and snap-frozen, total RNA was isolated by phenol-chlorophorm extraction followed by RNeasy on-column purification. The transcriptome of lung cancer specimens was analyzed by gene expression profiling (Affymetrix HG-U133 2.0 Plus oligonucleotide microarray). Class prediction was carried out by Support Vector Machines and Bayesian Compound Covariate Classifier, using own procedures and BRB-Array software developed by Simon and Peng Lam. Survival time prediction was carried out by method developed by Bair and Tibshirani (PLoS Biology 2004).
Results: The optimal classifier predictive for relapse, obtained by cross-validation of 70-sample dataset, consisted of 170 transcripts selected by univariate p-value 0.001. In this set, the relapse could be predicted with 75.0% specificity and 53.3% sensitivity (positive predictive value [PPV] 61.5%, negative predictive value [NPV] 68.2%) using Bayesian Compound Covariate method. When the cross-validated prediction was carried out within N1 group of patients, we obtained good sensitivity (73.3%), but poor specificity of the method (33.3%, PPV 64.7%, NPV 42.9%). When N1 group was used to test the relapse predictor obtained within N0 patients, 12 of 21 patients (57.1%) were correctly predicted, much worse than 69% accuracy obtained by cross-validation within N0 dataset.
Further gene selection was based on the prediction of the relapse-free survival time: 1919 genes, obtained by fitting Cox proportional hazard model (p < 0.05) and further used to predict survival by 4 principal components, distinguished between pts with high and low risk of relapse (p < 0.05, log-rank test). For final gene selection, nodal status was included within the model.
Conclusions: Prediction of the risk of relapse in stage I-II NSCLC based on the gene expression profile is feasible, with NPV of 68.2%.
Supported by Polish Ministry of Science grant PBZ-KBN-091/P05/2003/21

Poster presentations (Mon, 24 Sep, 09:00−12:00)
Lung cancer

6521 POSTER

Is pemetrexed more effective in patients with non-squamous histology? A retrospective analysis of a phase III trial of pemetrexed vs docetaxel in previously treated patients with advanced non-small cell lung cancer (NSCLC)

P. Peterson[1], K. Park[2], F. Fossella[3], U. Gatzemeier[4], W. John[1], G. Scagliotti[5]. *[1]Eli Lilly and Company, Oncology, Indianapolis IN, USA; [2]Samsung Medical Center, HematologyOncology, Seoul, Korea; [3]MD Anderson Cancer Center, Thoracic/Head and Neck Medical Oncology, Houston TX, USA; [4]Hospital Grosshansdorf, Thoracic Oncology, Grosshansdorf, Germany; [5]University of Torino, Clinical and Biological Sciences and Thoracic Oncology, Orbassano Torino, Italy*

Background: Pemetrexed (a multitargeted antifolate and potent TS inhibitor) compared favorably (with similar efficacy and lower toxicity) to docetaxel in a large, randomized phase III trial of previously treated patients with NSCLC. Preclinical data indicates that overexpression of TS correlates with reduced sensitivity to pemetrexed in antifolate-resistant cell lines. A recent study on chemonaive NSCLC patients indicated higher TS expression levels found in squamous cell carcinoma. These data suggest the possibility of improved efficacy for pemetrexed among patients with non-squamous histology.
Methods: This is a retrospective analysis of the large phase III study of pemetrexed (500 mg/m^2 IV with vitamin B_{12} injections + oral folic acid), vs docetaxel (75 mg/m^2 IV) Q 21 days. This analysis assesses whether the efficacy of pemetrexed is higher in patients with non-squamous histology. A Cox model of overall survival (OS) was used to test for a significant treatment-by-histology interaction, and subsequent Cox models were used to estimate hazard ratios (HR) for OS and progression-free survival (PFS) in both squamous and non-squamous groups. All models included baseline cofactors for performance status (ECOG PS), time since prior chemotherapy (TSPC), disease stage, and gender. Medians for OS and PFS were derived by the Kaplan-Meier method.
Results: Treatment-by-histology interaction was statistically significant (p = 0.001), indicating that patients with non-squamous histology treated with pemetrexed had higher survival compared to all others on trial. The table summarizes results by group.
Conclusions: The statistically significant treatment-by-histology interaction indicates that patients with non-squamous histology treated with pemetrexed had higher survival compared to all others on trial. Efficacy with docetaxel did not differ greatly between squamous and non-squamous

groups, however pemetrexed appears to be more effective for non-squamous than for squamous histology. A possible explanation for this result is the previously observed overexpression of TS in squamous cell carcinoma.

	Non-squamous group		Squamous group	
	Pemetrexed (n = 205)	Docetaxel (n = 194)	Pemetrexed (n = 78)	Docetaxel (n = 94)
% ECOG PS 2	12.5	10.1	8.3	17.4
% TSPC <3 months	51.0	51.0	48.7	41.9
% Stage IV	81.5	78.9	57.7	66.0
% Male	60.5	69.1	89.7	88.3
Median OS, months	9.3	8.0	6.2	7.4
OS HR (95% CI)	0.778 (0.607, 0.997)		1.563 (1.079, 2.264)	
Median PFS, months	3.1	3.0	2.3	2.7
PFS HR (95% CI)	0.823 (0.664, 1.020)		1.403 (1.006, 1.957)	

6522 POSTER

EGFR mutations and response to TKIs therapy in NSCLC patients pre-treated with chemotherapy

L. Crinò[1], V. Ludovini[1], L. Pistola[1], I. Floriani[2], M. Betti[1], R. Chiari[1], D. Giuffrida[3], C. Scuderi[3], F.R. Tofanetti[1], M. Tonato[1]. [1]*Ospedale Silvestrini, Medical Oncology, Perugia, Italy;* [2]*Istituto Mario Negri, Medical Oncology, Milano, Italy;* [3]*Istituto Oncologico del Mediterraneo, Medical Oncology, Catania, Italy*

Background: The aim of this work was to study the association between EGFR mutations (mut) and response to conventional chemotherapy (CHT) and tyrosine kinase inhibitors (TKIs) in NSCLC pts of Caucasian origin.
Methods: This retrospective analysis was conducted on 103 consecutive stage I to IV NSCLC pts treated with TKIs (gefitinib or erlotinib) from July 2002 to November 2006 after failure of platinum-based CHT. Genomic DNA was isolated from paraffin-embedded tumor specimens, amplified for EGFR (exons 18 to 21) by touchdown hemi-nested PCR and sequenced in both sense and antisense directions. Response to CHT and TKIs was assessed according to RECIST criteria.
Results: Median age was 60 yrs (range 25−81.5); M/F: 59/44, ECOG-PS 0/1/2/3:68/30/4/1; stage: I/II/III/IV 4/5/35/59; adeno/bac/squamous/large-cells/other:66/9/20/3/5; never/former/current smokers: 26/20/36. EGFR mut were detected in 19 pts (18.5%); 13 (13.8%) deletions in exon 19, 3 (2.9%) point mut in exon 20 (one pt had 2 mutations) and 3 (2.9%) missense mut in exon 21. No associations were detected between EGFR mut and adeno/bac histotype ($p = 0.51$), smoke ($p = 0.23$) and gender ($p = 0.14$). Disease control rate to TKIs therapy was 54.4%, including 1 CR (pt. with EGFR mutation), 21 PR and 34 SD and objective response rate (RR) was 42%. Median time to progression was 4.4 and median survival 23.7 months. EGFR mut had a significant impact on response (PR/CR, 42% $p = 0.015$) to TKIs while they did not influence response to CHT. Cox's multivariate analysis including gender, smoke, stage and histotype showed that EGFR mut did not reach statistical significance for progression free survival (PFS) ($p = 0.52$) and overall survival (OS) ($p = 0.50$); only adeno/bac histotype was a prognostic factor for longer PFS ($p = 0.01$) and OS ($p = 0.04$).
Conclusions: In our experience EGFR mut seem to influence RR in pts treated with TKIs after platinum-based CHT. These data will be refined by FISH analysis of EGFR gene copy number, immunohistochemistry for EGFR and phosphorylated Akt (p-Akt) protein and KRAS mutations.

6523 POSTER

Clinical and potential prognostic significance of serum mesothelin and osteopontin in chemotherapy treated patients affected by malignant pleural mesothelioma

M. Mencoboni[1], M. Serra[2], G. Tunesi[3], M. Gianola[4], L. Rebella[5], V. Galbusera[5], R. Filiberti[6], R. Puntoni[6], M. Paganuzzi[7], M. Bergaglio[8]. [1]*Scassi Hospital, Internal Medicine, Genoa, Italy;* [2]*Scassi Hospital, Pneumology, Genoa, Italy;* [3]*Scassi Hospital, Pathology, Genoa, Italy;* [4]*Scassi Hospital, Thoracic Surgery, Genoa, Italy;* [5]*Scassi Hospital, Oncology, Genoa, Italy;* [6]*National Cancer Institute, Epidemiology, Genoa, Italy;* [7]*National Cancer Institute, Laboratory, Genoa, Italy;* [8]*Scassi Hospital, Oncology, Genoa, Italy*

Background: Malignant pleural mesothelioma (MPM) is a highly aggressive tumour for which no fully reliable serum tumour markers are available for diagnosis and monitoring treatment response. Candidate biomarkers for MPM diagnosis include soluble serum mesothelin-related peptides and osteopontin, and novel ELISA systems have recently been developed for their detection in the sera of MPM patients. The aim of this work was to determine whether a correlation exists between these serum markers and clinical response.
Patients and Methods: serum of 15 patients (11 males, 4 female; median age 61 years) with histologically proven, inoperable MPM were tested; samples were collected before and after at least 2 cycles of chemotherapy. Chemotherapy was always pemetrexed and a platinum compound; only one patient received second line chemotherapy with gemcitabine and vinorelbine. Responses after chemotherapy were recorded according to RECIST criteria. Evaluations were always made by two independent physicians on spiral CT scans.
Results: 8 stable diseases, 2 partial response 1 complete response and 4 progressive diseases have been observed. A strong correlation was observed among Osteopontine and Mesothelin serum levels (R sq linear 0.83 $p < 0.001$). No clear relationship resulted between clinical responses and the levels of the two markers. The patient with a partial response showed the lowest level of mesothelin before treatment, value that declined toward zero after chemotherapy, and a very low level of Osteopontine, which became again the lowest after chemotherapy. Mean level of mesothelin before treatment in responders was considerably lower than in non responders or in stable disease (1.46 vs 5.55).
Conclusions: Osteopontine and Mesothelin levels in serum of MPM are strongly correlated. Clinical response (progression and stable diseases) does not appear to be related to markers levels even if the only patient with partial response showed the lowest levels of the two markers. Other patients will be added to the study and the follow-up will prosecute to evaluate the predictive significance of these two markers and their relationship with patients' survival.

6524 POSTER

Primary tumour standardized uptake value (SUV max) measured on fluorodeoxyglucose positron emission tomography (FDG-PET) is of prognostic value for survival in non-small cell lung cancer (NSCLC): a systematic review and meta-analysis (MA) by the European Lung Cancer Working Party for the IASLC Staging Project

T. Berghmans[1], M. Paesmans[2], M. Dusart[3], C. Hossein-Foucher[4], C. Castaigne[5], C. Mascaux[1], M. Roelandts[6], J.J. Lafitte[7], E.F. Patz[8], J.P. Sculier[1]. [1]*Institut J. Bordet, Intensive Care Unit and Thoracic Oncology, Brussels, Belgium;* [2]*Institut J. Bordet, Data Centre, Brussels, Belgium;* [3]*Institut J. Bordet, Radionuclide Imaging, Brussels, Belgium;* [4]*CHU Calmette, Radionuclide Imaging, Lille, France;* [5]*Hôpital Saint-Pierre, Radionuclide Imaging, Brussels, Belgium;* [6]*Institut J. Bordet, Radiotherapy, Brussels, Belgium;* [7]*CHU Calmette, Pneumology, Lille, France;* [8]*Duke University Medical Center, Radiology and Pharmacology and Cancer Biology, Durham, USA*

Background: FDG-PET is an effective imaging technique for assessing cTNM in NSCLC. The prognostic role of SUV max, measured on the primary tumour, has been suggested in several studies of limited sample sizes. We aimed to assess more precisely its effect on survival by aggregating results of individual studies in a meta-analysis of the literature.
Methods: We searched for all studies assessing the prognostic role of SUV max on survival in NSCLC. We evaluated the methodology of each eligible study (using a non validated quantitative scale with 44 points for the clinical data and 40 points for the FDG-PET data, designed for the purpose of the review). For each publication, we extracted an estimate of the hazard ratio (HR) for comparing patients with a low or high SUV and aggregated the individual HRs into a combined HR, using a random-effects model.
Results: Eleven studies including NSCLC only, published between 1998 and 2006, were eligible. Most of them included patients with stages I to III/IV and used a SUV assessment corrected for weight. Numbers of patients ranged from 38 to 162 (total: 1108); 9 studies identified a high SUV as a poor prognostic factor for survival and 2 concluded to a non significant effect. The qualitative evaluation provided a median of 61% for the clinical data and of 50% for the FDG-PET data. SUV measurement and threshold for defining high SUV were study dependent, 7 studies looked for a "best" cut-off (maximizing the logrank test statistic) however without adjusting the p value for multiplicity.

	Number of patients	HR	95% CI
All studies (n = 11)	1108	2.13	1.54−2.95
"Best cut-off" excluded (n = 6)*	456	1.77	1.01−3.12
Stage IV excluded (n = 5)	558	2.22	1.38−3.58

*for two studies, it was possible to use median value of SUV max instead of the author's best cut-off