556 ORAL

Cisplatin and etoposide (EP-regimen) is superior to cyclophosphamide, epirubicin, and vincristin (CEV-regimen) in small cell lung cancer: results from a randomized phase III trial with 5 years follow-up

S. Sundstrøm[1], R.M. Bremnes[2], S. Kaasa[1], S. Aamdal[3]. [1] *University Hospital of Trondheim, Dept Oncology, Trondheim, Norway;* [2] *University Hospital of Tromsø, Dept Oncology, Tromsø, Norway;* [3] *The Norwegian Radium Hospital, Dept Oncology, Oslo, Norway*

Purpose: To investigate whether chemotherapy with etoposide and cisplatin (EP) is superior to cyclophosphamide, epirubicin, vincristine (CEV) in the treatment of patients with small cell lung cancer (SCLC).

Methods: 436 eligible patient were randomized to chemotherapy with EP (N=218) or CEV (N=218). The patients were stratified according to extent of disease [218 limited disease (LD); 214 extensive disease (ED)]. The EP group received 5 courses of etoposide 100 mg/m2 IV and cisplatin 75 mg/m2 IV on day one, followed by oral etoposide 200 mg/m2 daily on day 2-4. The CEV group received 5 courses of epirubicin 50 mg/m2, cyclophosphamide 1000 mg/m2, and vincristine 2 mg, all IV on day one. In addition, LD patients received thoracic radiotherapy concurrent with chemotherapy cycle 3, and those achieving complete remission during the treatment period received prophylactic cranial irradiation.

Results: The treatment groups were well balanced with regard to age, gender, and prognostic factors such as weight loss, performance status, and biochemical markers. For all patients, the 2- and 5-year survival in the EP arm (14% and 5%, P=0.0004) were significantly higher as compared to the CEV arm (6% and 2%). Among LD patients, the median survival time was 14.5 months versus 9.7 months in the EP and CEV arm, respectively (P=0.001). The 2- and 5-year survival of 25% and 10% in the EP arm compared to 8% and 3% in the CEV arm (P=0.0001). For ED patients there was no significant survival difference between the treatment arms. The quality of life (QoL) assessments revealed no major differences between the randomized groups.

Conclusion: The EP-regimen is superior to the CEV-regimen in LD-SCLC patients. In ED-SCLC patients, the benefits of EP and CEV chemotherapy appear equivalent with similar survival time and QoL.

557 ORAL

First - line chemotherapy in SCLC: a phase III study of taxol, etoposide phosphate and carboplatin (TEC) versus carboplatin, etoposide phosphate and vincristin (CEV)

M. Reck[1], J. Von Pawel[2], H. Macha[3], E. Kaukel[4], K. Deppermann[5], B. Bonnet[6], S. Hessler[7], U. Gatzemeier[1]. [1] *Krankenhaus Grosshansdorf, Oncology, Grosshansdorf, Germany;* [2] *Asklepios Kliniken, Oncology, Gauting, Germany;* [3] *Lungenklinik Hemer, Oncology, Hemer, Germany;* [4] *Ak Harburg, Oncology, Hamburg, Germany;* [5] *Bristol-Myers Squibb, Munchen, Germany*

Introduction: Paclitaxel, Carboplatin and Etoposide has shown great activity combined with a very moderate toxicity profile in first-line treatment of SCLC. We now established a Phase III trial to compare efficiacy and toxicity of TEC with the standard regimen Carboplatin, Etoposide and Vincristin (CEV).

Methods: From 2/1998 to 11/1999 we enrolled 615 chemonaive patients with SCLC. 306 patients (group A) were randomized to receive Paclitaxel 175 mg/m2 IV (3h) day 4, Etoposide Phosphate 125 mg/m2 IV day 1-3 and Carboplatin AUC 5 IV day 4. 309 patients (group B) were randomized to receive Carboplatin AUC 5 IV day 1, Etoposide phosphate 159 mg/m2 IV day 1-3 and Vincristin 2 mg IV day 1 and 8. Patients with Stage IV disease received a lower dose of Etoposide Phosphate because of safety reasons (group A: 102,2 mg/m2, group B: 125 mg/m2). Treatment courses were repeated every 21 days up to 6 cycles. Eligibility criteria included chemonaive SCLC (stage I-IV), an adequate renal, hepatic and hematologic function and a performance status according to ECOG 0-2.

Results: Both groups were well balanced with 50% stage I-IIIb patients and 50% stage IV patients in each group. In group A we observed a response rate of 81.8% (CR 19.3%) and in group B a response rate of 76.3% (CR 16.6%). There was no statistical significant difference between the groups. Up to now survival data are not available but they will be presented at the meeting. Hematologic toxities (CTC-grade 3 + 4, % of courses) were as follows: TEC: Neutropenia 45.8%, febrile Neutropenia 2.9%, Anemia 1.8%; CEV: Neutropenia 47.9%, febrile Neutropenia 4.0%, Anemia 5.8%. Following non-hematologic toxicities (CTC-grade 3 + 4, % of courses occurred: TEC: PNP 0.7%, pain 0.7%, nausea 0.9%; CEV: PNP2.2%, pain 1.4%, Nausea 0.7%.

Conclusion: Both regimens showed high activity in treatment of SCLC with a comparable low toxicity profile. Further efficacy data will be presented at the meeting.

558 ORAL

Cancer-associated molecular alterations in bronchial epithelium of former Chernobyl cleanup workers in comparison with smokers and nonsmokers without ionizing radiation exposure

V. Chizhikov[1], S. Chikina[2], A. Gasparian[1], A. Chuchalin[2], I. Zborovskaya[1], A. Tatosyan[1]. [1] *Institute of Carcinogenesis, Cancer Research Center RAMS, Moscow, Russia;* [2] *Institute of Pulmonology, Moscow, Russia*

Purpose: Earlier it has been shown a considerable link between chronic respiratory problems in former Chernobyl cleanup workers (FChCW) and persistence of the inhaled radioactive particles in their lungs (Chuchalin et al, 1997). Since ionizing radiation is suspected to be a potent lung carcinogen, we questioned whether cancer-related molecular abnormalities could be detected in their bronchial epithelium.

Methods: k-ras mutations, p16INK4a promoter hypermethylation, and LOH and MI involving 14 microsatellite markers were investigated in multiple successive biopsies obtained from 43 FChCW (36 smokers and 7 nonsmokers) with evidence of inhaled radioactive dust in their lungs. Control group included 21 smokers and 23 nonsmokers who have never had radiation exposure.

Results: 1) LOH and MA at any chromosomal locus, p16INK4a promoter hypermethylation, and k-ras mutations were detected in 60.9%, 23.4%, 15.6%, and 7.8% of the subjects with a history of any carcinogen exposure, respectively. No molecular alterations were detected in nonsmokers who have never had radiation exposure. 2) FChCW exhibited more frequent allelic loss than the control group of smokers in five out of 7 loci investigated and the difference between these two groups was significant for LOH at 3p14.2 (FHIT), ($p<0.05$). 3) Frequency of molecular alterations corresponded to the severity of histopathologic changes with significant rise occurred at dysplasia stage. In all groups of subjects LOH at 3p12, 3p21, 3p22-24 (hMLH1), 9p21 (p16INK4a) and MI at any locus were early events frequently detected in histologically normal or mildly abnormal (hyperlasia or metaplasia) epithelium. Allelic loss at 3p14.2 (FHIT), 3p25 and 17p13 (TP53), p16INK4a promoter hypermethylation, and k-ras mutations that were strongly associated with dysplasia lesions. 4) Frequency of molecular abnormalities was significantly higher in normal or mildly abnormal epithelial foci that would subsequently progressed to dysplasia than in those without evidence of such progression. 5) Comparative RT-PCR showed significant concordance between decreased mRNA expression and molecular alterations for FHIT, hMLH1 and p16INK4a genes. 6) Occurrence of MI at any locus correlated with both hMHL1 reduced expression and 3p22-24 allelic loss (both $p<0.05$).

Conclusion: FChCW have distinct spectrum of molecular alterations in their bronchial epithelium. Similar to smokers they are at high risk of lung cancer.

559 ORAL

Single-agent versus combination chemotherapy in advanced non-small cell lung cancer (NSCLC): A CALGB randomized trial of efficacy, quality of life, and cost-effectiveness

R. Lilenbaum, J. Herndon, M. List, C. Desch, D. Watson, J. Holland, J. Weeks, M. Green. *Cancer and Leukemia Group B, Chicago, IL, USA*

Combination chemotherapy is considered the standard of care for patients with advanced NSCLC and good performance status. However, data from selected randomized trials and meta-analyses do not conclusively demonstrate that, despite higher response rates, combination regimens produce superior survival compared to optimal single-agent therapy. For example, phase II studies of paclitaxel (P) in advanced NSCLC showed 1-year survival rates of approximately 40%, clearly comparable to the newer platinum-based combination regimens. Furthermore, data on the impact of combination versus single-agent therapy on quality of life (QoL) and economic resources are conspicuously lacking. Therefore, CALGB performed a phase III randomized trial of carboplatin (C) and P (CP) vs. P alone in patients (pts) with stage IIIB (malignant pleural effusion) and IV NSCLC to compare survival, QoL, and cost-effectiveness. Eligible pts were required to have measurable of evaluable disease, PS 0–2, no brain metastases, and adequate organ function. Pts were stratified by stage (IIIB vs. IV vs. recurrent), PS (0–1 vs. 2), and age (<70 vs. ≥70). Treatment arms consisted of P

at a dose of 225 mg/m2 administered over 3 hours, of the same P combined with C at an AUC of 6, both administered on day 1 and repeated every 3 weeks to a maximum of 6 cycles. QoL was assessed by the EORTC C-30 and EORTC Lung Module questionnaires, in addition to utility assessment forms. A total of 584 pts were accrued from 10/97 to 12/00. Median age 64, M/F: 399/185, PS 0–1/2: 485/99. Toxicities (Gr 3/4) included:

	P [N = 267] (%)	CP [N = 268] (%)
ANC	32	62
PLT	1	11
HGB	3	13
Febrile neutropenia	5	8
N/V	3	8
Dyspnea	7	6
Peripheral neuropathy	12	13
At least one grade 3/4 toxicity	70	90
Toxic death	<1	<1

Response and survival data will be mature as of September 2001 and will be available for an original presentation at the time of the meeting. Preliminary QoL data will also be presented.

560 ORAL

Cisplatin and gemcitabine combined with herceptin in patients (pt) with her2 overexpressing, untreated, advanced, non-small-cell lung cancer (NSCLC): a phase II trial

R. Zinner, B. Glisson, K. Pisters, F. Khuri, Y. Oh, J. Ro, N. Ordonez, A. El-Naggar, H. Tran, R. Herbst. *University of Texas, M.D. Anderson Cancer Center, Houston, TX, USA*

Herceptin has been shown to be synergistic with cisplatin and gemcitabine in NSCLC with HER2 overexpressing. We studied Herceptin plus gemcitabine/cisplatin in HER2 overexpressing advanced NSCLC pts. Eligibility was, zubrod <2, chemonaive stage IIIB/IV, ejection fraction (EF) >40%, >1+HER2 by immunohistochemistry (IHC) (DAKO, HercepTest®) or >15ng/ml serum HER2 shed antigen by (ELISA) (Oncogene Science®). Treatment was Herceptin 2mg/kg/wk IV, gemcitabine 1250mg/m2 IV d1/d8, cisplatin 75mg/m2 IV d1 every 3weeks x 6 followed by maintenance Herceptin 2m/kg/wk IV until progression. 76 pts had both IHC and ELISA. By ELISA, 13/76(17%) pts >15ng/ml of whom 6/13(46%) had IHC >1+. By IHC, 18/76(24%) pts >1+ of whom 6/18(33%) had ELISA >15ng/ml. Pharmacokinetics on 7 pts showed no differences in clearance (paired t-test) of gemcitabine when given with cisplatin versus this study's internal control; cisplatin/Herceptin. At present, 12/14(86%) pts are evaluable for response. Median age 60 (range 46-69), gender, 8 females/4 males. No pts had EF decrease by >10% or below <40%. Grade 3 toxicities: neutropenia 6/12(50%), thrombocytopenia 5/12(42%), anemia 2/12(17%), fatigue 2/12(17%), nausea 1/12(8%). Grade 4: neutropenia 4/12(33%). During maintenance, there was no toxicity >grade 1. Responses are as follows: partial response 6/12(50%), stable disease 5/12(42%), progression 1/12(8%). There are 4/12(33%) pts still receiving chemotherapy/Herceptin. Maintenance was begun on 7/12(58%) and durations were 8-50+ weeks. We conclude that this regimen is well tolerated and response rates are encouraging. Herceptin does not alter gemcitabine clearance. Elevated expression by HER2 IHC is associated with increased serum antigen titers. Since maintenance Herceptin causes minimal toxicity with prolonged treatment, time to progression and survival will be critical endpoints.

561 ORAL

An EORTC randomized phase III trial of three chemotherapy regimens in advanced non-small cell lung cancer

E.F. Smit[1], J.P. van Meerbeeck[2], P. Lianes[3], F. Schramel[4], G. Lenz[5]. *[1] VUMC, Pulmonary Diseases, Amsterdam, The Netherlands; [2] University of Rotterdam, Pulmonary Diseases, Rotterdam, The Netherlands; [3] University Hospital, Department of Medical Oncology, Madrid, Spain; [4] Antonius Hospital, Department of Pulmonary Diseases, Nieuwegein, The Netherlands; [5] EORTC Data Centre, Brussels, BelgiumEORTC Lung Cancer Group, Brussels, Belgium*

EORTC 08975 was designed to compare the standard arm cisplatin (P)-paclitaxel (T) (T 175 mg/m2/3h dl + P 80 mg/m2 dl) with cisplatin-gemcitabine (G) (G 1250 mg/m2 d 1, 8 + P 80 mg/m2 dl) and the non-cisplatin-based regimen of T 175/mg/m2/3 hrs d1 + G 1250 mg/m2 d1, 8. All 3 schedules were repeated every 21 days. Eligible patients (pts) were required to have measurable disease; PS = 0-2; and Stage IIIB (malignant pleural effusion and/or supraclavicular nodes) or Stage IV. 480 pts were randomized between 8/98 and 7/00 (T+P 159; G+P 160; T+G 161; PS0=27%; PS1=61%; PS2=12%; IIIB=21%, IV=79%; squamous cell=24%, adeno=41%; undiff=31%; other 4%). In general, the 3 regimens were well tolerated. Gr 4 thrombocytopenia was more common with G+P (table).

Worst toxicities (NCIC) (in evaluated pts)	T+P	G+P	T+G
Gr 4 ANC %	8.8	10.6	8.1
Gr 4 thrombocytopenia %	0.6	11.3	1.9
Gr 3 nausea %	6.3	9.4	3.1
Gr 3 vomiting %	5.0	8.1	3.1
Gr 3 sensory neurotoxicity %	2.5	0.6	0.0
Gr 3 febrile neutropenia %	1.9	2.5	1.2
Worst gr 4-5 %	7.5	8.8	8.1
N of toxic deaths	2	0	4

Severe nausea/vomiting were least common in arm T+G and sensory neuropathy in arm T+P. At the time of the 04/00 analysis, 354 of the 369 deaths needed for final analysis have occurred. The response rate & survival results of the individual arms will be available for presentation October 2001.

562 ORAL

Docetaxel + Cisplatin (DC) and Docetaxel + Carboplatin (DCb) vs Vinorelbine + Cisplatin (VC) in chemotherapy-naïve patients with advanced and metastatic non-small cell lung cancer (NSCLC): Results of a multicenter, randomized phase III study

F. Fossella. *University of Pittsburgh, School of Medicine, 7 Main Montefiore University Hospital, Pittsburgh, PA 15213, USA*

Purpose: To compare the safety and efficacy of DC or DCb with the 'reference' regimen VC in chemotherapy-naïve patients with unresectable locally advanced and/or recurrent (Stage IIIB) or metastatic (Stage IV) NSCLC.

Methods: This open-label, parallel-group, randomized study enrolled 1220 patients from 140 sites in 29 countries. Patients received: DC (D 75 mg/m^2 1 h iv followed by C 75 mg/m^2 iv q3wk); DCb (D 75 mg/m^2 1 h iv followed by Cb AUC = 6 q3wk); or VC (V 25 mg/m^2/wk and C 100 mg/m^2 iv q4wk). 67% of the patients were metastatic and 96% had KPS $\geq$ 80.

Results: Overall survival was significantly better with DC vs VC ($p = 0.0469$). Survival rates with DC and VC were 47% and 42% at 1 year, and 21% and 14% ($p = 0.035$) at 2 years. Median survival was 10.9 mouths with DC vs 10 months with VC. Overall survival with DCb was non-inferior to VC (hazard ratio = 1.046; 95% CI, 0.891–1.227). Survival rates with DCb and VC were 38% and 42% at 1 year, and 16% and 14% at 2 years. The median with DCb was 9.1 months vs 10.0 months with VC. More patients in the VC arm experiencered Grade 3/4 anemia (24%) compared with the DC (7%) or DCb (10%) arms ($p < 0.01$). There was no significant difference in the number of patients in any arm who experienced Grade 3/4 neutropenia, thrombocytopenia, infection or febrile neutropenia. Use of prophylactic antibiotics or G-CSF was similar in all arms. More patients in the VC arm experienced Grade 3/4 nausea (16%) and vomiting (16%) compared with the DC (10% and 8%) or DCb (6% and 5%) arms ($p < 0.01$).

Conclusion: This is the first Phase III study showing an overall survival advantage for a docetaxel + cisplatin regimen compared with a standard doublet in the first-line treatment of advanced NSCLC. Docetaxel + platinum regimens were associated with significantly less Grade 3/4 nausea, vomiting and anemia compared with VC. These results indicate that docetaxel + platinum combinations are safe and effective first-line options in NSCLC.