6503 ORAL

Efficacy and safety results from BO17704, a randomised, placebo-controlled phase III study of bevacizumab in combination with cisplatin and gemcitabine in patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC)

C. Manegold[1], J. von Pawel[2], P. Zatloukal[3], R. Ramlau[4], V. Gorbounova[5], V. Hirsh[6], N. Leighl[7], J. Mezger[8], N. Moore[9], M. Reck[10]. [1]*Klinikum Mannheim gGmbH Universitatsklinikum, Chirurgische Klinik, Mannheim, Germany;* [2]*Asklepios Klinikum, Onkologie, Muenchen-Gauting, Germany;* [3]*Faculty Hospital Bulovka, Department of Pneumology, Prague, Czech Republic;* [4]*Wielkopolskie Centrum Chorob Pluc i Gruzlicy, Oddzial Onkologii, Poznan, Poland;* [5]*Cancer Research Center, Department of Chemotherapy, Moscow, Russian Federation;* [6]*MUHC – Royal Victoria Hospital, Department of Oncology, Montreal, Canada;* [7]*Princess Margaret Hospital, Department of Medical Oncology, Toronto, Canada;* [8]*St-Vincentius-Kliniken, Medizinische Klinik 2 Hämatologie-Onkologie, Karlsruhe, Germany;* [9]*F. Hoffmann-La Roche, Biostatistics, Basel, Switzerland;* [10]*Krankenhaus Grosshansdorf, Onkologischer Schwerpunkt, Grosshansdorf, Germany*

Background: Bevacizumab (B) combined with carboplatin/paclitaxel improved overall survival (OS) and progression-free survival (PFS) in patients with advanced non-squamous NSCLC in the phase III E4599 trial [Sandler et al. NEJM 2006]. The BO17704 study was initiated to determine the clinical benefits of B combined with cisplatin/gemcitabine (CG), which is commonly used in Europe.
Methods: This phase III, randomised, placebo (Pb)-controlled, multicentre study compared CG with two doses of B versus CG with Pb. The primary endpoint was PFS. Secondary endpoints included OS, response rate (RR) and safety. A prespecified exploratory PFS analysis was performed that censored patients who received anti-neoplastic therapy (NPT) prior to progression (as per the E4599 trial). Eligibility criteria: previously untreated histologically or cytologically documented locally advanced, metastatic or recurrent non-squamous NSCLC, ECOG PS 0–1, adequate renal, liver and haematological function, no brain metastases, no history of grade (Gr) $\geqslant$2 haemoptysis. Patients were randomised to C (80 mg/m^2) on day 1 and G (1250 mg/m^2) on days 1 and 8 every 3 weeks for up to 6 cycles plus B (7.5 mg/kg or 15 mg/kg) or Pb every 3 weeks continued to progression.

Endpoint	Intent to treat (n = 1043)		
	CG/Pb n = 347	CG/B 7.5 mg/kg n = 345	CG/B 15 mg/kg n = 351
PFS – Primary Analysis HR (95% CI)		0.75 (0.62, 0.91) p = 0.0026	0.82 (0.68, 0.98) p = 0.0301
Median PFS (mo)	6.1	6.7	6.5
PFS by NPT HR (95% CI)		0.68 (0.56, 0.83) p = 0.0001	0.74 (0.60, 0.90) p = 0.0021
RR (%)	20.1	34.1	30.4
Adverse events	n = 327	n = 330	n = 329
$\geqslant$Grade 3 AEs (%)	75	76	81
Proteinuria			
all Grades (%)	<1	3	3
$\geqslant$Grade 3 (%)	–	<1	1
Hypertension			
all Grades (%)	10	23	31
$\geqslant$Grade 3 (%)	2	6	9
Bleeding			
all Grades (%)	20	35	38
$\geqslant$ Grade 3 (%)	2	4	4
Haemoptysis			
all Grades (%)	5	7	9
$\geqslant$Grade 3 (%)	<1	1.5	<1
AEs leading to death (%)	4	4	5

Results: Between 02/05 and 08/06, 1043 patients were enrolled. Both B doses significantly improved PFS in the primary analysis (no censoring for NPT prior to progression) and in the NPT analysis. Rate and duration of response increased with B compared with Pb. OS data are immature due to the short duration of follow-up. The frequency of serious adverse events (AEs) was comparable between arms (35%, 35%, 44% for CG/Pb, CG/B 7.5 mg/kg, CG/B 15 mg/kg, respectively), as was withdrawal due to an AE (23%, 26%, 30%). No unexpected safety signals were noted.
Conclusions: The addition of B (7.5 or 15 mg/kg) to CG significantly improved PFS and RR in patients with advanced NSCLC, consistent with the results of the E4599 phase III study (HR 0.69 [0.60, 0.79]).

6504 ORAL

Evaluation of the use of prophylactic cranial irradiation in small cell lung cancer

S. Patel[1], K. Macdonald[2], M. Suntha[3]. [1]*University of Washington, Radiation Oncology, Seattle WA, USA;* [2]*University of Utah, Radiation Oncology, Salt Lake City UT, USA;* [3]*University of Maryland, Radiation Oncology, Baltimore MD, USA*

Background: Prophylactic cranial irradiation is used in patients with Small Cell Lung Cancer to reduce the incidence of brain metastasis following primary therapy. Our purpose was to evaluate the effects of prophylactic cranial irradiation (PCI) on overall survival and cause specific survival.
Methods: 7995 patients with limited stage small cell lung cancer diagnosed between 1988 and 1997 were retrospectively identified from centers participating in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. 670 were identified as having received PCI as a component of their first course of therapy. Overall survival and cause specific survival were estimated by the Kaplan Meier method, comparing patients treated with or without prophylactic whole brain radiation therapy. Cox proportional hazards model was used in the multivariate analysis to evaluate potential prognostic factors.
Results: The median follow-up time was 13 months (range, 1–180 months). Overall survival at 2, 5, and 10-years was 23%, 11%, and 6% in patients who did not receive PCI. In patients who received PCI, 2, 5, and 10-year overall survival was 42%, 19%, and 9% respectively ($p \leqslant 0.001$). Cause specific survival at 2, 5, and 10 years was 28%, 15%, 11% in patients who did not receive PCI and 45%, 24%, 17% in patients who did receive PCI ($p \leqslant 0.001$). On multivariate analysis of cause specific and overall survival, age at diagnosis, gender, grade, extent of primary disease, size of disease, extent of nodal involvement, and PCI were significant ($p \leqslant 0.001$). The hazard ratios for disease-specific and all cause mortality were 1.13 and 1.11 for those not receiving PCI, respectively.
Conclusions: Significantly improved overall and cause specific survival were observed in patients treated with prophylactic cranial irradiation on unadjusted and adjusted analyses. This study concurs with the European experience which has been published. Prophylactic cranial irradiation should be considered standard of care in small cell lung cancer.

6505 ORAL

Survival of non-small cell lung cancer patients treated with (chemo)radiotherapy can be predicted by a combination of total tumor volume, number of positive lymph node stations on PET, performance status, gender and radiation dose

C. Dehing[1], D. De Ruysscher[1], H. van der Weide[1], H. Steck[2], P. Lambin[1]. [1]*MAASTRO Clinic, Radiation Oncology, Maastricht, The Netherlands;* [2]*Siemens Medical Solutions, Computer aided diagnosis and therapy, Malvern, USA*

Background: Accurately predicting survival of NSCLC patients is important for treatment decision making. However, it is widely recognized that the TNM staging system has its shortcomings when used for the risk stratification of inoperable NSCLC patients treated with (chemo)radiotherapy. Factors that are lacking and may be important for the outcome include size of the tumor, gender, performance status and radiation dose. In addition, the number of positive lymph nodes is of prognostic value for surgical patients. As it is possible to assess the mediastinal lymph nodes with FDG-PET scans, we hypothesized that also for non-surgical patients, this would affect survival.
We decided to investigate the prognostic value of tumor volume (assessed by CT), the number of positive lymph node stations (PLNS) (assessed by PET), gender, performance status and equivalent radiation dose corrected for time ($EQD_{2,T}$) for overall survival, and compare this with TNM stage in patients with inoperable NSCLC treated with (chemo)radiotherapy.
Methods: Clinical data from 270 inoperable NSCLC patients, stage I-IIIB, treated at MAASTRO clinic with (chemo)radiotherapy, was collected retrospectively. Diagnostic imaging was performed either with an integrated PET-CT or with CT-scan and PET-scan separately. A logarithmic transformation was applied to obtain more symmetrically distributed data for the tumor volume. The Kaplan-Meier method as well as Cox regression were used to analyze the data. In addition, Akaike's information criterion (AIC) was calculated to compare the performance of the models. The AIC takes into account how well the model fits the data as well as the complexity of a model, e.g. the number of estimated parameters, thereby reducing the risk of overfitting. The preferred model is the one with the lowest AIC value. To assess the relative merits of a model, the difference is interpreted as follows: a decrease by 4−7 indicates weak support, $\geqslant$10 indicates strong support for a model.
Results: The Kaplan Meier curves showed that PLNS, N-stage as well as T-stage were associated with survival; the logrank test resulted in a p-value