985 POSTER DISCUSSION 2*

Phase II trial of mta (LY231514) in patients (PTS) with non-small cell lung cancer (NSCLC) who relapsed after previous platinum or non-platinum chemotherapy

P. Postmus[1], K. Mattson[2], von Pawel[3], C. Manegold[4], E. Smit[1], M. Millward[5], S. Clarke[5], A. Saarinen[1]. *[1]Vrije Universiteit Academic Hospital, Pulmonary Medicine, Amsterdam, Netherlands; [2]Helsinki University Central Hospital, Division of Pulmonary Medicine, Helsinki, Finland; [3]Askelpios Fachklinik Munchen-Gauting, Gauting; [4]Thorax Hospital, Heidelberg, Germany; [5]Sydney Cancer Center, Sydney, Australia*

Purpose: While new chemotherapeutic agents for NSCLC have emerged in the recent past, there remains a critical need for agents which are also active in the second-line setting. This study was designed to evaluate the activity of MTA (multitargeted antifolate), in the treatment of NSCLC pts who relapsed following front-line therapy. MTA inhibits multilple folate-dependent enzymes and has shown promising activity in a wide range of tumor types.

Methods: Pts with Stage IIIb or IV NSCLC who had relapsed during or within 3 months of prior therapy were entered into two cohorts, depending on whether their prior therapy did (PT) or did not contain platinum (NP) (i.e. mitomycin, docetaxel, paclitaxel, vinorelbine, and/or gemcitabine). All pts received MTA 500 mg/m^2 every 21 days with prophylactic dexamethasone.

Results: 67 pts have been enrolled, with 43 evaluable for response. Pts received a median of 2 cycles of therapy (range 1–7), with 6% and 3% of cycles delayed or reduced, respectively. In the PT arm, there have been 3 partial responses (PRs) in 23 evaluable pts, for an overall response rate (RR) of 13%. The NP arm has included 1 complete and 5 PRs in 20 evaluable pts, for a RR of 30%. Grade 3/4 toxicity (as % of cycles) includes Hgb: 6/1, WBC: 19/3, ANC: 14/9, platelets: 3/4, bilirubin: 2/0, elevated transaminases: 3/0, and infection: 1/2, respectively. One pt discontinued due to drug-related pneumonia. Four on-study deaths are thought not to be drug-related.

Conclusion: MTA has activity in the second-line treatment of NSCLC, and appears to be non-cross resistant with a variety of front-line agents

986 POSTER DISCUSSION 2*

Docetaxel plus cisplatin versus docetaxel plus gemcitabine chemotherapy in advanced non-small cell lung cancer: A preliminary analysis of a multicenter randomized phase II trial

V. Georgoulias, E. Papadakis, A. Alexopoulos, E. Stavrinidis, E. Bania, A. Rapti, Th. Grigoratou, Ch. Kouroussis, S. Kakolyris, G. Samonis. *The Greek Cooperative Group for Lung Cancer, Greece*

Background: Docetaxel/CDDP (D/C) and docetaxel/gemcitabine (D/G) are active and well tolerated chemotherapy regimens for the treatment of patients with advanced non-small-cell lung cancer (NSCLC). A phase II randomized trial was conducted in order to compare the efficacy and toxicity of these regimens.

Patients: 315 chemotherapy-naive patients with stage IIIB and IV NSCLC were enrolled onto the study. Patients were treated with either Arm A: docetaxel (100 mg/m^2; day 1) and CDDP (80 mg/m^2; day 2) or with Arm B: gemcitabine (1100 mg/m^2; days 1 and 8) and docetaxel (100 mg/m^2; day 8); rhG-CSF (150 mcg/m^2 s.c.) was given in arm A (day 3–9) and in arm B (day 9–15). Both regimens were repeated every 3 weeks.

Results: Arm A (D/C): [No of pts treated/evaluated: 152/132, CR (%) + PR (%): 3 (2.3% + 39 (30%), overall response rate (95%CI): 32% (24–40), SD (%)/PD (%): 42 (32%)/48 (36%), duration of response (months): 5, time to progression (months) 8, median survival (months): 10, 1-year survival (%): 42%]. Arm B (D/G): [No of pts treated/evaluated: 144/114, CR (%) + PR (%): 1 (0.9%) + 38 (33%), overall response rate (95% CI): 34% (25–43), SD (%)/PD (%): 37 (32%)/38 (33%), duration to response (months): 4, time to progression (months): 8, median survival (months): 9, 1-year survival (%): 38%]. The probability of response to the docetaxel/CDDP was significantly higher (p = 0.03) in patients with a non-adenocarcinoma whilst the opposite was observed in patients with an adenocarcinoma (p = 0.002). A total of 1161 cycles were administered (Arm A = 595; Arm B = 566) with a median of 3 and 4 cycles/patient, respectively. Toxicity by WHO criteria (Arm A/Arm B) was: grade 3/4 anemia 9 pts (6%)/6 pts (4%); grade 3/4 neutropenia 50 pts (33%)/31 pts (22%); grade 3/4 thrombocytopenia 4 pts (3%)/7 pts (5%); febrile neutropenia 24 pts (16%)/20 pts (14%); grade 3/4 diarrhea 18 pts/4 pts (p = 0.00296); grade 3/4 fatigue 45 pts (30%)/49 pts (33%); grade 2/4 neurotoxicity 10 pts (7%)/6 pts (4%).

Conclusions: These preliminary results seem to indicate that the docetaxel/CDDP and the docetaxel/gemcitabine regimens have a comparable activity and toxicity profile in patients with advanced NSCLC.

*Poster Discussion 2 will be held on Thursday 16 September 1999

987 POSTER DISCUSSION 2*

Gemcitabine + vinorelbine (GV) vs vinorelbine (V) alone in elderly or frail non-small cell lung cancer (NSCLC) patients. Interim analysis of a SICOG phase III trial

G. Frasci, V. Lorusso, N. Panza, G. DeCataldis, F. Del Gaizo, G.P. Nicolella, V. Mascia, B. Massidda, G. Comella, M. De Lena. *Southern Italy Cooperative Oncology Group (SICOG), c/o National Tumor Institute of Naples, Italy*

Purpose: To compare the impact on survival and QoL of the GV regimen with that of V alone.

Patients and Methods: NSCLC pts with locally advanced or metastatic disease aged between 71 and 80 years with ECOG PS ≤ 2 or younger with PS = 2, were randomized to receive GV (G 1,200 mg/m^2 + V 30 mg/m^2 d 1 & 8 q 3 wk) or V (30 mg/m^2 d 1 & 8 q3wk) alone. A final sample size of 120 pts for each arm had been chosen. An interim analysis had been planned after that 60 pts per arm had been enrolled.

Results: The survival data of 138 randomized pts (GV = 70 and V = 68) were analysed. 103 pts were elderly (>70) and 35 were younger with poor PS. At a 13 (range; 1–19)-month median potential follow-up, the observed MSTs were: GV = 25 wks and V = 23 wks. If only the 103 elderly pts are taken into account, the MSTs were slightly shorter (GV = 23 wks and V = 18 wks). At the present analysis the observed difference in the risk of death between the two arms was not statistically significant.

Conclusions: These data suggest that either GV or V alone do not represent an effective treatment for both elderly and frail NSCLC pts, since the MSTs in both arms were not substantially longer than that recently reported with the best supportive care alone (21 weeks) in elderly pts. A further analysis will be performed after 120 elderly pts have been enrolled.

Other Participant Investigators: Comella P, Di Rienzo G, Cioffi R, Natale M, Bilancia D, Micillo E, Pusceddu G, Contu A, Filippelli G.

988 POSTER DISCUSSION 2*

Chemotherapy (CT) and twice daily radio-chemotherapy (HA RT/CT) *versus* chemotherapy (CT) alone before surgery in stage III non small cell lung cancer (NSCLC): Analysis of toxicity of a randomized trial

Ch. Rübe[1], M. Thomas[2], M. Semik[3], D. Riesenbeck[1]. *[1]For the MS-Lung Cancer Study Group, Depts. for Radiotherapy; [2]Medical Oncol.; [3]Thoracic Surgery, University of Münster, Germany*

In 10/95 a multicenter randomized phase III study was started to evaluate the contribution of preoperative radiochemotherapy on tumor downstaging and survival in locally advanced NSCLC. After mediastinoscopy and stratification according to stage and institution pts. were randomized to *(Arm A)* 3 cycles PE (cisplatin 55 mg/m^2 (d1 + 4)/etoposide 100 mg/m^2 (d1 – 4)), followed by hyperfractionated accelerated RT (HA RT, 45 Gy; 2 × 1.5 Gy/d) with concurrent CT (carboplatin 100 mg/m^2, vindesin 3 mg, d 1, 8, 15) and surgery (if no or R1/2 – resection additional HA RT 24 Gy) *versus (Arm B)* 3 cycles PE followed by surgery and postop. RT (54 Gy or (if no or R1/2 resection) 68.4 Gy, 1 × 1.8 Gy/d). Study endpoints are survival, resectability and toxicity. Of 234 pts. entered up to 10/98 (IIIA/IIIB 69/132), 186 are evaluable for toxicity. Toxicity (WHO 3, 4) to PE was 19%, 9%, 9% leukocytopenia, 2%, 3%, 2% thrombocytopenia without treatment related deaths (TRD). Esophagitis and pneumonitis rates were 31% and 3% after HA RT/CT and 6% and 9% after RT. TRD (pneumonitis) occurred in 3 cases (Ann B). Overall response rate to induction was 55%. 104/162 pts were considered for surgery. So fare, R0-resection rate is 79% (IIIA:87%, IIIB:73%), TRD occurred in 7 pts. As toxicities are acceptable and response- and resection rates are good, the trial will be continued to 350 randomized pts. (Supported by "Deutsche Krebshilfe")

989 POSTER DISCUSSION 2*

Cisplatin (CDDP) and irinotecan (CPT-11) versus CDDP and vindesine (VDS) in advanced (stage IIIB and stage IV) non-small cell lung cancer (NSCLC). A multicenter phase III study

H. Kunitoh, N. Saijo, K. Nagao, Y. Ohashi, H. Niitani. *For The East Japan Lung Cancer CPT-11 Study Group Tokyo, Japan*

CDDP and CPT-11 combination is an active regimen against advanced

NSCLC. We conducted a prospective multicenter randomized phase III study with survival as primary endpoint. From June 1995 to Oct. 1997, a total of 210 patients (pts) were accrued to the trial; 104 were randomized to CC arm; CDDP 80 mg/m^2 on day 1 and CPT-11 60 mg/m^2 on days 1, 8, 15 q 4 weeks 106 to the control CV arm; CDDP 80 mg/m^2 on day 1 and VDS 3 mg/m^2 on days 1, 8, 15 q 4weeks. All pts were previously untreated, ECOG PS 0-2 and stage IV or Stage IIIB, with no symptomatic brain metastases. Both arms were well-matched with regards to sex, age, stage and PS. 199 pts were assessable for the response and toxicity. Stage IIIB: 41%, Stage IV: 59%, PS 0-1: 95%, PS 2: 5%. The objective tumor response was similar in both treatment groups, with 29% partial response (PR) in the CC pts and 22% PR in the CV. The incidence of grade 4 neutropenia was significantly higher in the CV than in the CC (18% vs 50%; P < 0.001). Conversely, the incidence of grade 3 or worse diarrhea was higher in the CC than in the CV (13% vs 1%; P < 0.001). The incidence of other toxicity was similar in the two groups. Median survival time was 45.4 weeks for CC, 49.9 weeks in CV (p = 0.786). The preliminary results suggest that the both groups are active combination in advanced NSCLC with similar response rate and survival.

990 POSTER

Pre-operative serum levels of angiogenic tumour markers in non-small cell lung cancer and its impact on survival

D. Brattström[1], M. Bergqvist[1], P. Hesselius[1], A. Larsson[2], K. Lamberg[3], G. Wagenius[1], O. Brodin[1]. *[1]Inst. of Oncology/Radiology/Clin. Immunology, Dep. of Oncology, Uppsala; [2]Inst. of Medical Sciences, Dep. of Clinical Chemistry, Uppsala; [3]Inst. of Medical Sciences Dep. of Respiratory Medicine and Allergology, Uppsala, Sweden*

Purpose: Angiogenesis is an important step in the progression of tumours. Several angiogenic factors have been discovered so far and two of the most studied are bFGF and VEGF. Indications are that both might have prognostic information concerning metastasis and survival. Yet, earlier studies of these angiogenic factors in sera have not been conclusive concerning prognostic information.

Patients and Methods: Our group have analysed the levels of bFGF and VEGF in preoperatively collected sera from 58 patients with a histo-pathological verified diagnosis of non-small cell lung cancer, limited disease. A semi-quantitative enzyme linked immunosorbent assay were used for detection of bFGF and VEGF. A cut-off level at the 95 percentile of a normal control subject group both for VEGF and bFGF were estimated at 500 pg/ml and 7.25 pg/ml, respectively.

Results: VEGF; Pre-operative levels of VEGF in sera were detected in all patients (median value 304 pg/ml, range 93–1554 pg/ml), 12 patients had elevated levels as defined by the cut-off level. Pre-operative levels of VEGF proved to be significantly correlated to survival, both as a continuos variable and when cut-off level were used (p-value = 0.006). In univariate analysis relapse was significantly correlated to high levels of VEGF (p-values < 0.05). bFGF; Pre-operative levels of bFGF in sera were detected in 56 patients (median value 4.60 pg/ml, range 0–43.02 pg/ml), 18 patients had elevated levels as defined by the cut-off level. When used as a continuos variable a significant correlation (p-value = 0.0028) could be demonstrated regarding survival.

Conclusion: Both bFGF and VEGF proved to have statistical significant association to survival in patients with non-small cell lung cancer.

991 POSTER

Genetic polymorphisms of cytochrome P4501A1 and glutathione S-transferase M1: A lung cancer case control study

A. Gsur[1], G. Haidinger[2], K. Hohenstein[1], N. Vetter[3], N. Pridun[3], P. Hollaus[3], S. Madersbacher[4], K. Trieb[5], C. Vutuc[2], M. Micksche[1]. *[1]Tumorbiology, Appl. and Exp. Oncology, Vienna; [2]Tumorbiology, Epidemiology, Vienna; [3]Pulmological Center, Vienna; [4]AKH, Urology, Vienna; [5]AKH, Orthopedics, Vienna, Austria*

150 lung cancer patients and 300 age and sex matched control subjects have been examined for the association between polymorphisms of the CYP1A1 gene and homozygous deletion of the GSTM1 gene and lung cancer risk among Caucasians.

Methods: The CYP1A1 polymorphisms were detected by PCR/RFLP using DNA from peripheral white blood cells: the mutation m1 (MspI polymorphism in the 3'flanking region), m2 (BsrDI polymorphism in exon 7) and m4 (BsaI polymorphism is located two bp upstream from m2). GSTM1 genotype has been analyzed by PCR. Differences between groups were calculated by using Pearsons chi-square test.

Results and Conclusion: We could not find any significant difference between patients and controls for the homozygous and heterozygous MspI polymorphism. In contrast cases with heterozygous BsrDI polymorphism were at greater risk for adenocarcinoma (OR: 2.50; CL: 1.19–5.24; P < 0.01). The BsaI polymorphism was higher in control subjects than in patients and may therefore not represent a susceptibility factor for lung cancer. Our results show no influence of GSTM1 null genotype for lung cancer risk (OR: 1.04; CL: 0.69–1.57). Recruitment for this study is ongoing in order to further verify the obtained data.

(Supported by the "Medizinisch wissenschaftlicher Fond des Bürgermeisters der Stadt Wien" '522)

992 POSTER

Æ-941, an inhibitor of angiogenesis: Rationale for development in combination with induction chemotherapy/radiotherapy in patients with non-small-cell lung cancer (nsclc)

W.K. Evans[1], J. Latreille[2], G. Batist[3], P. Falardeau[4], P. Champagne[4], M. Rivière[4], E. Dupont[4]. *[1]Ottawa Regional Cancer Centre, General Division, Ottawa; [2]CHUM, Campus Hotel-Dieu, Montréal; [3]Jewish General Hospital, Clinical Research Unit, Montréal; [4]Aeterna Laboratories, Québec, Canada*

Æ-941, a standardized shark cartilage extract, shows antiangiogenic and antimetalloprotease activities in vitro and ex ovo. It was selected by the US National Cancer Institute for phase III clinical evaluation of its efficacy and safety in advanced NSCLC patients. This double-blind placebo-controlled study will evaluate the effect on survival of treatment in inoperable stage III patients. The preclinical rationale for this study is based on the antimetastatic activity of Æ-941 in the Lewis Lung Carcinoma mouse model where a 70% reduction in pulmonary metastases was observed. Æ-941 was additive to cisplatin in reducing the number of lung metastases (83% reduction in combination compared to 54% with cisplatin alone). No mortality and no loss of body weight were observed at 500 mg/kg, the highest dose administered. Toxicology studies demonstrated no dose-limiting toxicity or target organ. The clinical rationale to support this phase III trial is based on the safety profile and clinical benefit obtained in the following studies. During a phase I/II study, 80 refractory lung cancer patients (64% with distant metastases) received Æ-941 in monotherapy (5 to 95 mg/kg/day orally). Patients receiving Æ-941 at 240 ml/day showed greater clinical stability in analgesics consumption and weight loss compared to patients during the first 12 weeks. Additionally, 72 refractory prostate cancer patients received Æ-941 in monotherapy in this study. No serious adverse events were observed in these two cohorts; seven percent of non-serious adverse events were related to Æ-941, most commonly nausea, vomiting. In another study, 61 patients received Æ-941 in combination with chemotherapy and/or radiotherapy. No serious adverse events occurred with Æ-941 in this cohort. In all clinical studies involving 375 patients (194 treated >3 months), only one drug-related serious adverse event was reported (hypoglycemic episode in a type II diabetic patient with renal cell carcinoma). Based on the potential antimetastatic activity of Æ-941 demonstrated in the Lewis lung cancer model, the excellent clinical safety profile and the preliminary dose trend observed, it is proposed to evaluate the effect of Æ-941 on survival in a randomized double-blind placebo-controlled clinical study in patients with locally advanced disease receiving induction chemotherapy and radiotherapy.

993 POSTER

Phase II study of gemcitabine (G) and cisplatin (P) in advanced nsclc. Focus on quality of life (QoL)

J. Jassem[1], M. Krzakowski[2], K. Roszkowski[3], B. Basinska[1], B. Mozejko-Pastewka[4], J. Lis[4], K. Miracki[4]. *[1]Medical University, Gdansk; [2]Institute of Oncology, Warsaw; [3]Institute of Tuberculosis and Lung Diseases, Warsaw; [4]Eli Lilly, Poland*

The combination of G and P has been shown to be active in advanced NSCLC but the impact of this regimen on QoL is not well established. Aim of study was to evaluate this regimen in terms of both, toxicity, activity and its effect on QoL Eighty pts with advanced NSCLC (68 men and 12 women, median age 61 years, range 40–75, median PS 80, range 60–100, 40 stage IIIB and 40 stage IV) received G (1000 mg/m^2, d. 1, 8 and 15) and P (100 mg/m^2, d. 2); q 28 d. QoL was assessed with the EORTC QLQ-30 and LC-13 questionnaires. Total number of 416 courses was administered (median 6, range 1–9). The main toxicity was myelosuppresion; grade 3/4 neutropenia, thrombocytopenia and anemia occurred in 55%, 53% and