recent phase III study has shown efficacy of pemetrexed (Pem) as a maintenance therapy. This is a prospective multicenter study of Pem combined with carboplatin (Cb) as an induction therapy followed by Pem maintenance. Trial sponsor is Eli Lilly Japan K.K. (ClinicalTrials.gov identifier NCT01020786).
Materials and Methods: Eligible patients (pts) had chemo-naïve, unresectable stage IIIB, IV or postoperative recurrent non-squamous NSCLC, and ECOG Performance Status (PS) of 0−1. Pts received Cb AUC 6 and Pem 500 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles as induction therapy. Pts who achieved CR/PR/SD by the end of induction phase, could continue on Pem as maintenance therapy until PD or unacceptable toxicity. Written informed consent was obtained from all enrolled pts.
Results: Pem and Cb were administered as induction therapy to 109 pts. Patients backgrounds were; median age 63 years (range 38−78), male/female (63%/37%), PS 0/1 (34%/66%), and stage IIIB/IV/recurrent disease (30%/66%/4%). Seventy-five pts (69%) were completed induction therapy, and 60 pts (55%) entered into the maintenance therapy.
In the induction phase, dose reduction was required in 20% of pts, and dose delay in 68%. The relative dose intensities for Pem and Cb were 89% and 90%, respectively. The most frequently reported grade $\geqslant$ 3 toxicity was neutropenia (54%). Other grade $\geqslant$ 3 toxicities were also hematologic, including thrombocytopenia (41%) and anemia (28%). Red blood cells transfusion, platelet transfusion and G-CSF administration were required in 10%, 7% and 9% of the pts. Serious adverse events including thrombocytopenia, anemia, or gastric ulcer were reported in 12 pts (11%). There were no treatment related deaths.
Of 109 pts evaluable for response, 42 pts (38.5%) achieved a partial response (including unconfirmed) in the induction phase.
Conclusions: This prospective multicenter study suggested that Pem plus Cb combination chemotherapy was well tolerated and more than half of pts could be received maintenance therapy. This combination is active as a first-line treatment for advanced non-squamous NSCLC. Overall safety and efficacy results will be presented at the conference.

9129 POSTER

Safety Profile and Efficacy of Erlotinib in a Japanese Post-marketing Surveillance Study of 10,708 Non-small-cell Lung Cancer (NSCLC) Patients (pts) − Interim Analyses From the First 3,488 Pts

Y. Ohe[1], M. Fukuoka[2], S. Kudoh[3], K. Nakagawa[4], T. Johkoh[5], M. Ando[6], N. Yamazaki[7], S. Takemoto[8], A. Seki[8]. *[1]National Cancer Center Hospital East, Thoracic Oncology, Kashiwa, [2]Kinki University and Izumi Municipal Hospital, Kinki University (Professor Emeritus) and Director of Cancer Center Izumi Municipal Hospital, Isumi, [3]Double-Barred Cross Hospital Japan Anti-Tuberculosis Association and Nippon Medical School, Nippon Medical School (Professor Emeritus), Kiyose, [4]Kinki University School of Medicine, Medical Oncology, Osaka, [5]Kinki Central Hospital of Mutual Aid Association of Public School Teachers, Radiology, Hyogo, [6]Kyoto University, Centre for Student Health, Kyoto, [7]National Cancer Center Hospital, Dermatology, Tokyo, [8]Chugai Pharmaceutical Co Ltd, Pharmacovigilance, Tokyo, Japan*

Background: Erlotinib is approved in Japan for the treatment of nonresectable, recurrent and advanced NSCLC, following failure of at least one prior chemotherapy regimen. A large scale surveillance study has been implemented to investigate erlotinib safety and efficacy in Japanese pts, focusing on the incidence of interstitial lung disease (ILD), which had been highlighted in previous studies as an adverse drug reaction (ADR) of particular concern in this population.
Methods: Enrolment: Dec 2007–Oct 2009; observation period: 12 months. ADRs were defined as adverse events (AEs) where causality to erlotinib could not be ruled out and all events resembling ILD were assessed by an independent committee. Overall survival (OS) and progression-free survival (PFS) were also assessed. These interim data are for pts registered prior to 30 Jun 2008.
Results: From a total of 10,708 enrolled pts, 3743 were enrolled by 30 Jun 2008 and data were available for 3488 (255 pts unavailable for CRF or not treated with erlotinib or registered more than once). Baseline characteristics included: male (51%), median age (65 years), any smoking history (52%), adenocarcinoma (83%), ECOG PS 0−1 (74%), patients who received more than three lines of treatment (56%). Previous first-line chemotherapy included platinum-based doublets (73.2%), of which the majority were carboplatin based (52.9%; predominantly carboplatin/paclitaxel, 39%), non-platinum single agents (20.7%), and non-platinum doublets (2.8%). Gefitinib, mainly second line, had been received by 55%. ADRs were reported in 82% of pts and the most common were skin disorders (69%), including rash (63%), and gastrointestinal disorders (32%), including diarrhoea (24%). 189 pts experienced 'ILD-like' events and ILD was confirmed by the independent ILD review committee in 158 pts (4.5% of population), with a mortality rate of 1.6%. Smoking status (hazard ratio [HR]= 3.0), history of ILD (HR = 4.1), history of lung infection (HR = 2.0) and ECOG PS 2−4 (HR = 1.6) were identified as risk factors for ILD by multivariate analysis. No new safety signals were identified. Median OS and PFS were 260 days and 64 days, respectively. Data collection and analysis are continuing.
Conclusions: Interim data from this large surveillance study in Japanese pts with recurrent and advanced NSCLC are favourable towards the risk/benefit balance for the use of erlotinib and provide further information on the risk of ILD and the treatment profile of this population.

9130 POSTER

The Prognostic Role of Myeloid-derived Suppressor Cells Related Markers in Peripheral Blood From Advanced Non-small Cell Lung Cancer Patients

R. Sirera[1], E. Jantus-Lewintre[1], E. Caballero[1], A. Artigot[1], E. Sanmartin[1], M. Uso[1], R. Rosell[1], S. Gallach[1], C. Camps[1]. *[1]Hospital General Universitario, Molecular Oncology, Valencia, Spain*

Background: Myeloid-derived suppressor cells (MDSC) are found in most patients with advanced cancers, and are potent inhibitors of innate and adaptive immunity. Marker genes associated with the presence of MDSC are CD11b, CD18, CD115, GR1, IL-4Rα and IL-13. The aim of this study was to determine the expression level of these genes by qRT-PCR in patients with advanced non-small cell lung cancer (NSCLC) and to correlate them with clinico-pathological and prognostic variables.
Methods: RNA was isolated from peripheral blood collected from NSCLC patients (n = 50) and controls (n = 54). qRT-PCR was performed to analyze the expression of CD11b, CD18, CD115, GR1, IL-4Rα and IL-13. Relative expression was normalized by endogenous genes (GAPDH and β-actin) using the Pfaffl formulae. Statistical analyses were considered significant at $p < 0.05$.
Results: We found significant differences in the expression levels of 3 analyzed genes (CD115, GR1 and IL4a) and in other two differences were borderline (CD11b, $p = 0.061$; and IL13, $p = 0.068$) between patients and controls. Pair-matched samples comparing pre and post-treatment expression levels of CD18, GR1 and IL4Ra showed that they were significantly reduced after chemotherapy. Lower levels of expression of CD11b were related with progressive disease ($p = 0.005$). The prognostic impact of the studied variables was assessed by Cox univariate analysis (see Table) and Kaplan–Meier plots. We found that those patients with baseline CD11b expression below the median had significant worse progression-free ($p = 0.005$) and overall survival ($p = 0.013$).
Conclusion: This study shows that it is possible to detect and quantified MDSC-related markers in peripheral blood samples of advanced NSCLC patients. The expression of the analyzed genes, especially CD11b, could have prognostic value in advanced NSCLC.
This work was supported in part, by a grant [RD06/0020/1024] from Red Temática de Investigación Cooperativa en Cáncer, RTICC, Instituto de Salud Carlos III (ISCIII), Spanish Ministry of Science and Innovation & European Regional Development Fund (ERDF) "Una manera de hacer Europa".

9131 POSTER

Relative Expression of Regulatory T-lymphocyte Associated Markers Inperipheral Blood Samples From Advanced NSCLC − Analysis of the Prognostic Role

R. Sirera[1], E. Jantus-Lewintre[1], A. Artigot[1], E. Sanmartin[1], M. Uso[1], E. Caballero[1], S. Gallach[1], R. Rosell[1], C. Camps[1]. *[1]Hospital General Universitario, Molecular Oncology, Valencia, Spain*

Background: T-cell tolerance is an important mechanism for tumour escape. An imbalance of regulatory T-lymphocytes (Treg) could promote peripheral immune tolerance to tumour cells. Marker genes associated with the presence of Treg are CD127, CD8a, Foxp3, CD4, CD25 and TGF-β1. The aim of this study was to determine the expression level of these marker genes by qPCR in patients with non-small cell lung cancer (NSCLC) in advanced stages and to correlate them with clinic-pathological and prognostic variables.
Methods: 54 control individuals and 50 patients with advanced-NSCLC (IIIB-IV) treated with cisplatin and docetaxel were studied. Blood samples were collected at baseline and after 3 cycles of chemotherapy in PAXgene Blood RNA Tubes and stored at −80ºC until RNA isolation. mRNA was reverse transcribed and RT-PCR was performed to analyze the expression of CD127, CD8a, Foxp3, CD4, CD25 and TGF-β1. Relative expression was normalized by endogenous genes (GAPDH and β-actin) using the Pfaffl formulae. Statistical analyses were considered significant at $p < 0.05$.
Results: The characteristics of the studied patients were: median age: 57.8 years [37.7–75.1], 89% males, 55% adenocarcinomas. We found significant differences in the expression levels of CD4 ($p < 0.0001$), CD8

($p = 0.019$), CD25 ($p = 0.003$), CD127 ($p = 0.031$), Foxp3 ($p < 0.0001$) and TGF-β1 ($p < 0.0001$) between patients and controls. Pairmatched samples comparing pre and post-treatment expression of TGF-β1 showed that it was significantly reduced after chemotherapy. Additionally, patients with higher ratios (baseline/post-treatment) of CD4 and TGF-β1 were associated with local metastasis and progression, respectively. Survival analysis revealed that patients with combined high expression of CD25 and low expression of CD127 (reflecting a Treg phenotype), had significantly reduced TTP (median 2.40 months *vs* 5.47 months, $p = 0.001$) and a trend in OS (median 3.87 months *vs* 9.80 months, $p = 0.078$).

Conclusion: Based on gene expression analysis, it seems that the presence of a "Treg profile" in peripheral blood is associated with a poor prognosis in patients with advanced NSCLC.

This work was supported in part, by a grant [RD06/0020/1024] from Red Temática de Investigación Cooperativa en Cáncer, RTICC, Instituto de Salud Carlos III (ISCIII), Spanish Ministry of Science and Innovation & European Regional Development Fund (ERDF) "Una manera de hacer Europa".

9132 POSTER

Efficacy Outcomes in First-line Treatment of Advanced NSCLC With Gefitinib (G) vs Carboplatin/paclitaxel (C/P) by Epidermal Growth Factor Receptor (EGFR) Gene-copy Number Score and by Most Common EGFR Mutation Subtypes − Exploratory Data From IPASS

J. Yang[1], Y.L. Wu[2], N. Saijo[3], S. Thongprasert[4], D.T. Chu[5], Y.M. Chen[6], E. Duffield[7], Y. Rukazenkov[8], T.S.K. Mok[9], M. Fukuoka[3]. *[1]Taiwan University Hospital & College of Medicine, National Taiwan University, Taipei, Taiwan; [2]Guangdong General Hospital, Guangdong Lung Cancer Institute Guangdong Academy of Medical Sciences, Guangzhou, China; [3]Kinki University School of Medicine, Department of Oncology, Osaka-Sayama, Japan; [4]ChiangMai University, Maharaj Nakorn ChiangMai Hospital, ChiangMai, Thailand; [5]Chinese Academy of Medical Sciences, Cancer Institute and Hospital, Beijing, China; [6]Taipei Veterans General Hospital, Chest Department, Taipei, Taiwan; [7]AstraZeneca, Biostatistics, Macclesfield, [8]AstraZeneca, Research and Development, Macclesfield, United Kingdom; [9]The Chinese University of Hong Kong, State Key Laboratory in Oncology in South China Sir YK Pao Center for Cancer Department of Clinical Oncology, Hong Kong, China*

Background: IPASS (NCT00322452) demonstrated significantly improved progression-free survival (PFS) and objective response rate (ORR) with first-line G *v* C/P. EGFR mutation was a strong predictive biomarker for PFS benefit and tumour response to first-line G *v* C/P. PFS was prolonged for G *v* C/P in both common activating mutation subtypes. Here we report exploratory analyses of PFS and ORR in patients (pts) with high EGFR gene-copy number (high gene polysomy or gene amplification), and overall survival (OS) by most common EGFR activating mutation subtypes (Exon 19 deletion; L858R point mutation).

Methods: EGFR gene-copy number was determined by fluorescence in-situ hybridisation. High EGFR gene-copy number was defined as high gene polysomy (score 5; $\geqslant$4 copies in $\geqslant$40% of cells) or gene amplification (score 6; gene:chromosome $\geqslant$2, or $\geqslant$15 copies per cell in $\geqslant$10% cells). For each of these groups, hazard ratios (HRs; G:C/P) and 95% CIs were estimated for PFS using a Cox proportional hazards model adjusted for WHO PS (0, 1 *v* 2), smoking history (never *v* light ex-smoker) and gender. Odds ratios (ORs) and 95% CIs were estimated for ORR using a logistic regression model adjusted for the same covariates. EGFR mutations were detected using an amplification mutation refractory system with an EGFR detection kit. For pts with Exon 19 deletion or L858R mutation, HRs and 95% CIs were estimated for OS using a Cox proportional hazards model adjusted for the same covariates as PFS.

Results: 406 (of 1217 randomised) pts had known EGFR-gene-copy number biomarker status: 83 with gene amplification; 166 with high gene polysomy. PFS and ORR outcomes for G *v* C/P in pts with gene amplification: PFS HR 0.46, 95% CI 0.28–0.77; ORR OR 4.46, 95% CI 1.57–12.68; and in pts with high gene polysomy: PFS HR 0.77, 95% CI 0.53–1.11; ORR OR 1.46, 95% CI 0.79–2.71. Incidence of co-existing EGFR mutation was higher with gene amplification (86.7%) than high gene polysomy (71.1%). 261 pts had EGFR mutation-positive tumours: 140 with Exon 19 deletion; 111 with L858R. HRs for OS were 0.79 (95% CI 0.54–1.15) for Exon 19 deletion and 1.44 (95% CI 0.90–2.30) for L858R mutation.

Conclusions: PFS and ORR were improved with G *v* C/P in both gene-copy number score groups, with greater benefit with G in the gene amplification group. This was probably driven by an overlap with co-existing EGFR mutation, a known predictive biomarker for improved PFS and ORR with G in this setting.

9133 POSTER

Association Between TS, DHFR, and GARFT mRNA Expression and Efficacy of Pemetrexed in Advanced Non-small Cell Lung Cancr Patients

T. Shimizu[1], Y. Nakanishi[2], Y. Nakagawa[1], T. Sugane[1], I. Tsujino[1], T. Oinuma[2], N. Takahashi[1], S. Hashimoto[1], N. Nemoto[2]. *[1]Nihon University School of Medicine, Respiratory Medicine, Tokyo, [2]Nihon University School of Medicine, Pathology, Tokyo, Japan*

Background: Pemetrexed (PMT), a multitargeted antifolate drug, inhibits three key folate enzymes: thymidylate synthetase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT). PMT is effective in non-small-cell lung cancer (NSCLC) patients with non-squamous cell carcinoma. TS expression is lower in adenocarcinoma compared with squamous cell carcinoma. The relationship between clinical effectiveness of PMT and expression of folate enzymes in lung cancer cells is unknown. The purpose of this study is to determine whether TS, DHFR, and GARFT expression affect therapeutic efficacy of PMT.

Methods: The subjects were advanced NSCLC patients who treated with PMT. Samples were gotten by tumour biopsy before treatment. We dissected cancer cells from formalin-fixed paraffin-embedded tissues by using a laser microdissection. TS, DHFR, and GARFT mRNA were analyzed by using real-time RT-PCR. We assessed the association between TS, DHFR, and GARFT mRNA expression and therapeutic efficacy of PMT.

Results: Twenty-nine patients were enrolled. The median age was 67 years. Seventy-two percent of patients had a previous treatment with chemotherapy. Overall response rates were 27.6% for PMT. Median progression free survival (PFS) was 22.5 weeks for PMT. TS mRNA levels ranged from 0.001 to 33.590 (mean 2.451). TS mRNA expression was significantly lower in response group (CR+PR) compared with non-response group (SD+PD) (0.223 ± 0.083 versus 3.195 ± 1.752, $p < 0.001$). DHFR and GARFT mRNA expression were not correlated with response rate. PFS was superior for lower DHFR and GARFT mRNA expression patients compared with higher DHFR and GARFT mRNA expression patients, which was not statistically significant. (DHFR 29.1 versus 16.6 weeks, $p = 0.158$, GARFT 30.7 versus 16.6 weeks, $p = 0.071$).

Conclusions: We could analyze TS, DHFR, and GARFT mRNA expression in lung cancer cells specifically from biopsy specimens by using a laser microdissection. TS mRNA expression affected therapeutic efficacy of PMT. TS mRNA expression may be usefull predictive biomarker for NSCLC patients received PMT.

9134 POSTER

Tumour Response, Skin Rash and Health-related Quality of Life (HRQoL) − Post-hoc Data From the IPASS Study

Y. Wu[1], M. Fukuoka[2], T.S.K. Mok[3], N. Saijo[2], S. Thongprasert[4], J.C.H. Yang[5], D.T. Chu[6], J.J. Yang[1], Y. Rukazenkov[7]. *[1]Guangdong General Hospital, Guangdong Lung Cancer Institute Guangdong Academy of Medical Sciences, Guangzhou, China; [2]Kinki University School of Medicine, Department of Oncology, Osaka-Sayama, Japan; [3]The Chinese University of Hong Kong, State Key Laboratory in Oncology in South China Sir YK Pao Center for Cancer Department of Clinical Oncology, Hong Kong, China; [4]Chiang Mai University, Faculty of Medicine Maharaj Nakorn ChiangMai Hospital, ChiangMai, Thailand; [5]National Taiwan University, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan; [6]Chinese Academy of Medical Sciences, Cancer Institute and Hospital, Beijing, China; [7]AstraZeneca, Research and Development, Macclesfield, United Kingdom*

Background: IPASS (NCT00322452) demonstrated significantly longer progression-free survival (PFS) with first-line gefitinib *v* carboplatin/paclitaxel in never/light ex-smokers with advanced pulmonary adenocarcinoma in Asia, in the overall intent-to-treat (ITT) population and *EGFR* mutation-positive subgroup. We investigated objective response rate (ORR) and HRQoL in patients treated with gefitinib (ITT; *EGFR* mutation-positive subgroup) to further characterise the clinical relevance of the PFS data.

Methods: Objective response was assessed (RECIST) 6-weekly. Median time to response was summarised, median duration of response calculated (from first confirmed response visit) and change in tumour size assessed (percentage change from baseline) post-hoc. Patients without an end date were censored at their last evaluable assessment. The percentage of patients with a deterioration in HRQoL (reduction in Functional Assessment of Cancer Therapy-Lung [FACT-L; $\geqslant$6 points], Trial Outcome Index [TOI; $\geqslant$6 points]) or symptoms (Lung Cancer Subscale [LCS; $\geqslant$2 points]) at 4 months post-randomisation (median time on carboplatin/paclitaxel) was analysed according to progression status (post-hoc logistic regression adjusted for gender [male *v* female], WHO performance status [PS 0, 1 *v* 2] and smoking history [never *v* light ex-smoker]).