Grade 3/4 AEs occurred in 40.6% (gefitinib) and 81.6% (docetaxel) of patients. The incidence of interstitial lung disease (ILD) was 5.7% (n=14) and 2.9% (n=7) with gefitinib and docetaxel, respectively. There were four deaths due to AEs in the gefitinib arm (three possibly treatment-related due to ILD; one due to pneumonia that was not considered treatment-related), and none in the docetaxel arm. Biomarker data will also be reported.

Conclusions: Non-inferiority in overall survival between gefitinib and docetaxel was not demonstrated according to predefined criteria. However, there was no statistically significant difference in survival between the two groups. Imbalances in the proportion and type of post-study treatments in both arms have complicated interpretation of survival results. The secondary endpoints are largely unaffected by subsequent therapy and provide further evidence of the clinical efficacy of gefitinib in Japanese patients. AEs were consistent with those previously observed for both treatments.

B3-02 **Molecular Targeted Therapy: EGFR Inhibitors, Tue, 13:45 - 15:30**

Randomized, double-blind, multicenter, parallel-group, Phase II study of gefitinib (IRESSA) plus best supportive care (BSC) versus placebo plus BSC in chemotherapy-naïve patients with advanced non-small-cell lung cancer and poor performance status (INSTEP)

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Background: It is estimated that 30-40% of patients with advanced non-small-cell lung cancer (NSCLC) have a poor performance status (PS); however, there is no consensus on the best treatment approach for such patients (Gridelli et al, Ann Oncol 2004;15:419-426). In a large randomized four arm, Phase III study, the median survival for PS2 patients treated with combination chemotherapy was 3.9 months (Schiller et al, NEJM 2002;346:92-98). Single-agent chemotherapy is also an option for PS2 patients (Gridelli et al, Lung Cancer 2002;38: S37-S41) but there is a need for effective treatment alternatives for patients considered unfit for chemotherapy or who refuse chemotherapy. A retrospective review of 198 chemotherapy-naïve patients (20% PS2 and 3) with advanced NSCLC who received gefitinib (IRESSA) within a compassionate use program in the USA, reported a median survival of 6 months and objective response rate of 6.3% (Govindan et al. Lung Cancer 2006;53:331-337). The Phase II, randomized, double-blind, multicenter, parallel-group study reported here compared gefitinib plus BSC to placebo plus BSC in patients with advanced NSCLC and poor PS (IRESSA NSCLC Trial Evaluating Poor PS patients [INSTEP]).

Methods: This study planned to recruit approximately 200 patients. Following written, informed consent, patients (≥18 years) with locally advanced or metastatic (stage IIIB or IV) NSCLC who were chemotherapy-naïve, had a poor PS (WHO PS 2 or 3) and were considered unfit for chemotherapy were randomized to gefitinib (250 mg/day orally) plus BSC or placebo plus BSC. The primary objective of this study was to compare progression-free survival (PFS) between the two treatment groups. Secondary endpoints were objective response rate (assessed every 6 weeks using RECIST criteria), overall survival, patient-reported functionality and quality of life (via the Functional Assessment of Cancer Therapy-Lung [FACT-L] trial outcome index and total score, respectively), pulmonary symptom improvement (as measured by the pulmonary items of the FACT-L lung cancer subscale), and tolerability (frequency and severity of adverse events [via CTC version 3.0] and laboratory parameters). An exploratory endpoint was to correlate the efficacy of gefitinib with epidermal growth factor receptor (EGFR) gene copy number. A proportional hazards model (presenting a hazard ratio and its associated 95% confidence intervals) will be used to compare PFS between treatment groups, with gender, PS, histology, smoking history, and stage as covariates. While median PFS on BSC is expected to be in the region of 4 weeks, there are no data upon which to accurately anticipate the effectiveness of gefitinib in this setting. With 200 patients recruited, this study would have greater than 90% power to detect a 75% improvement in PFS and 81% power to detect a 50% improvement in PFS.

Results: Between September 2004 and December 2006, 201 patients were randomized from 5 countries and 37 centers. Efficacy, quality of life, safety and EGFR gene copy number results will be available for presentation at this meeting.

Conclusions: To be completed once data are available.

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B3-03 **Molecular Targeted Therapy: EGFR Inhibitors, Tue, 13:45 - 15:30**

A randomized multicenter phase III study of cetuximab (Erbitux®) in combination with Taxane/Carboplatin versus Taxane/Carboplatin alone as first-line treatment for patients with advanced/metastatic Non-small cell lung cancer (NSCLC)

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Background: Cetuximab (Erbitux®) is a chimeric monoclonal IgG1 antibody targeting the epidermal growth factor receptor (EGFR) thereby blocking ligand-receptor interaction, promoting receptor internalization, cell cycle arrest and apoptosis. Several phase II studies with cetuximab in combination with platinum based chemotherapy have shown encouraging anti-tumor activity in patients with advanced/metastatic NSCLC. This randomized phase III study was conducted to determine the efficacy of adding cetuximab to taxane/platinum chemotherapy in patients with recurrent or metastatic NSCLC in a randomized controlled setting.

Methods: Patients with previously untreated stage IIIB (malignant pleural effusion) or stage IV NSCLC were eligible for this study. Patients on arm A received cetuximab (400 mg/m^2 IV on day 1 followed by 250 mg/m^2 weekly) combined with either paclitaxel (225 mg/m^2 IV q3 weeks) or docetaxel (75mg mg/m^2 IV q3 weeks) and carboplatin (AUC 6 IV q3 weeks). Patients on Arm B received the same chemo-

therapy regimen but without cetuximab. The choice of taxane was at the discretion of the investigator but had to be made before randomization since on-study taxane (paclitaxel or docetaxel), ECOG PS (0 vs. 1) and site were part of the stratification scheme. The primary endpoint was progression-free-survival (PFS) as determined by an Independent Radiology Review Committee. In order to have 90% power to detect a hazard ratio of 0.75 of the combination arm over the control arm 510 progression events were required. Secondary endpoints included response rate, time to response, duration of response, disease control rate, quality of life and overall survival (OS).

Results and Conclusions: From December 2004 until October 2006 676 patients were randomized at 97 centers in the US: 58.6% men, 41.4 % women with a median age of 65 years (range 34-87). Data on the primary and secondary objectives along with unblinded safety data will be presented at the meeting.

B3-04 **Molecular Targeted Therapy: EGFR Inhibitors, Tue, 13:45 - 15:30**

Gefitinib (IRESSA) versus vinorelbine in chemonaïve elderly patients with advanced non-small-cell lung cancer (INVITE): a randomized Phase II study

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Background: This Phase II, open-label, parallel-group study (INVITE [IRESSA in NSCLC vs Vinorelbine Investigation in The Elderly]) compared gefitinib (IRESSA) with vinorelbine in chemonaïve elderly patients with locally advanced or metastatic non small-cell lung cancer.

Methods: Patients (≥70 years; performance status ≤2) were randomized to gefitinib (250 mg/day orally) or vinorelbine (30 mg/m^2 infusion on Days 1 and 8 of a 21 day cycle). The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS), objective response rate (ORR; assessed by RECIST), quality of life (QoL; assessed by Functional Assessment of Cancer Therapy Lung [FACT-L] and improvement in the physical aspects of QoL as measured by the trial outcome index [TOI]), pulmonary symptom improvement (PSI; assessed by the 4 pulmonary items of the lung cancer symptoms subscale [LCS] of the FACT-L) and adverse event (AE) profile. Exploratory analysis included EGFR gene copy number by fluorescence in situ hybridization (FISH), EGFR protein expression and EGFR mutation analysis.

Results: 196 patients (75.5% male, 85.7% regular/ex smokers, 40.3% adenocarcinoma) from a total of 10 countries were randomized to gefitinib (n=97) or vinorelbine (n=99). Hazard ratios (HR) for PFS and OS were 1.19 (95% CI 0.85, 1.65) and 0.98 (95% CI 0.66, 1.47), respectively, for gefitinib vs vinorelbine. ORR and disease control rates were 3.1% and 43.3% (gefitinib) and 5.1% and 53.5% (vinorelbine), respectively. FACT-L QoL improvement rates were higher with gefitinib vs vinorelbine (24.3% vs 10.9%, respectively) as was the TOI (22.9% vs 6.3%, respectively). Symptom improvement rates appeared similar with gefitinib vs vinorelbine: 36.6% vs 31.0% for PSI and 42.9% vs 39.1% on the LCS. In the EGFR FISH-positive subgroup (n=54), HRs for gefitinib vs vinorelbine were 3.13 (95% CI 1.45, 6.76) for PFS and 2.88 (95% CI 1.21, 6.83) for OS. In the EGFR FISH-negative subgroup (n=104), HRs for gefitinib vs vinorelbine were 0.93 (95% CI 0.59, 1.46) for PFS and 0.79 (95% CI 0.46, 1.37) for OS. Few patients had tumor samples that were EGFR protein expression negative (13/157 [8.3%] patients) or EGFR mutation-positive (7/65 [10.8%] patients), precluding further analysis of these data. The gefitinib arm had fewer treatment-related grade 3-5 AEs compared with vinorelbine (12.8% vs 41.7%). The most common AEs were rash and diarrhea for gefitinib, and constipation, fatigue and neutropenia for vinorelbine. There were three treatment-related deaths in the vinorelbine arm, and none in the gefitinib arm.

Conclusions: Although the primary endpoint of demonstrating superior PFS for gefitinib relative to vinorelbine was not met, gefitinib was broadly similar to vinorelbine in terms of PFS, OS and ORR in this first-line study in elderly patients. Gefitinib was better tolerated than vinorelbine. Overall QoL improvement, including TOI, was increased with gefitinib compared with vinorelbine, while PSI and LCS was similar in both arms. The difference between gefitinib and vinorelbine in the small exploratory analyses of FISH positive patients requires further investigation.

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B3-05 **Molecular Targeted Therapy: EGFR Inhibitors, Tue, 13:45 - 15:30**

Meta-analysis comparing docetaxel and vinca-alkaloids in the first-line treatment of NSCLC. Comparison of results based on individual patient data, study report data, and published data

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Background: Meta-analyses based on data extracted from the literature rather than on individual patient data (IPD) must be interpreted with caution. We compare here results obtained with 3 sources: published data, study report data and IPD in analyzing randomized studies comparing docetaxel to vinca-alkaloïds in first line treatment of NSCLC.

Material and Methods: Study search and selection have been previously described [Douillard JY et al. Proc ASCO 2006]. Summary statistics to perform a meta-analysis of published data were either directly extracted (hazard ratio (HR) and 95% CI available) or derived from the number of deaths and log-rank p value [Parmar M et al. Stat Med 1998; 17: 2815-34]. Summary statistics of the study report data were either directly extracted, derived, or computed using life tables. All analyses were performed on an intention-to-treat basis when available. Logarithms of the HR were pooled by the inverse-variance weighting method. For IPD, the meta-analysis was performed by a log-rank test stratified for study.