the end of 1st line CT, at the initiation and completion of second line CT and 12 and 18 months post baseline.

**Results:** 975 patients were enrolled between April 2003 and September 2004, with observations completed in March 2006. Median age was 65 yrs (32-90) with 28.3% of pts aged ≥ 70 yrs; 71.3% were male; 65.2% had stage IV disease. 487 pts experienced weight loss, 172 lost >10% body weight in 4 weeks prior to the start of CT (79 pts, 15.3% unknown). Overall baseline WHO PS was 0 (21.1%), 1 (65.1%), 2 (10.0%), 3 (3.3%), 4 (0.5%). After 2 cycles of CT, WHO PS was unchanged for 57.6% (562) of pts (missing 99 pts); analysis by baseline WHO PS showed no change for 90 (44.3%) of pts with PS 0, 423 (67.6%) PS 1, 32 (33.3%) PS 2, 14 (43.8%) PS 3 and 3 pts (60.0%) with baseline PS 4. Median duration of first line CT was 3.0 months. At the end of 1st line chemotherapy PS was unchanged from baseline for 41.2% of pts (missing 223 pts, 22.9%). Analysis by baseline PS shows no change for 64 (31.5%) of pts with baseline PS 0, 313 (50.0%) PS 1, 14 (14.6%) PS 2, 9 (28.1%) PS 3, 2 (40%) PS 4. Improvement in PS during 1st line CT was seen in 66 (10.5%) of pts with baseline PS 1, 30 (31.3%) PS 2, 5 (15.6%) PS 3, 2 (40%) PS 4. 285 pts were intended to receive 2nd line CT. At initiation of 2nd line CT, overall WHO PS was 0 (11.3%), 1 (67.5%), 2 (17%), 3 (9.9%), 4 (0.4%). Median duration of 2nd line CT was 2.5 months. At the end of 2nd line CT, 254 patients had WHO PS 0 (10%), 1 (56.2%), 2 (17%), 3 (14.5%), 4 (5.5%) (no data 19 pts).

**Conclusion:** The administration of CT to patients with PS 0 - 4 was recorded in this first large-scale observational study of pts with advanced NSCLC. The majority of patients maintain PS after two cycles of 1st line CT. In those pts who received second line CT, a trend toward deteriorating PS is seen. The assessment of WHO PS is subjective. Maintenance or change in WHO PS may be driven by the impact of the cancer, chemotherapy treatment and/or any pre-existing co-morbidities.

**PD4-3-3 Cytotoxic Chemotherapy II, Tue, 16:00 - 17:30
Phase II trial of carboplatin plus docetaxel combined with a selective cyclooxygenase-2 inhibitor (meloxicam) in first-line treatment of patients with advanced unresectable non-small cell lung cancer: anti-tumor effect and cyclooxygenase-2 expression**

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**Background:** Preclinical and clinical studies showed that selective cyclooxygenase-2 (COX-2) inhibitor (celecoxib or rofecoxib) might improve efficacy of treatment of advanced NSCLC. Meloxicam is a non-steroidal anti-inflammatory drug (NSAID), and selectively inhibits COX-2. Comparing with coxibs, meloxicam shows less cardiovascular toxicity; however, anti-tumor efficacy has not been proved in clinical settings. The correlation between overexpression of COX-2 and chemotherapeutic response is also still controversial.

**Methods:** Eligibility criteria included stage IIIB/IV histologically or cytologically confirmed non-small cell lung cancer, no prior chemotherapy, no current use of NSAIDs, PS = 0-1, and no urgent symptoms.

**Results:** 975 patients were enrolled between April 2003 and September 2004, with observations completed in March 2006. Median age was 65 yrs (32-90) with 28.3% of pts aged ≥ 70 yrs; 71.3% were male; 65.2% had stage IV disease. 487 pts experienced weight loss, 172 lost >10% body weight in 4 weeks prior to the start of CT (79 pts, 15.3% unknown). Overall baseline WHO PS was 0 (21.1%), 1 (65.1%), 2 (10.0%), 3 (3.3%), 4 (0.5%). After 2 cycles of CT, WHO PS was unchanged for 57.6% (562) of pts (missing 99 pts); analysis by baseline WHO PS showed no change for 90 (44.3%) of pts with PS 0, 423 (67.6%) PS 1, 32 (33.3%) PS 2, 14 (43.8%) PS 3 and 3 pts (60.0%) with baseline PS 4. Median duration of first line CT was 3.0 months. At the end of 1st line chemotherapy PS was unchanged from baseline for 41.2% of pts (missing 223 pts, 22.9%). Analysis by baseline PS shows no change for 64 (31.5%) of pts with baseline PS 0, 313 (50.0%) PS 1, 14 (14.6%) PS 2, 9 (28.1%) PS 3, 2 (40%) PS 4. Improvement in PS during 1st line CT was seen in 66 (10.5%) of pts with baseline PS 1, 30 (31.3%) PS 2, 5 (15.6%) PS 3, 2 (40%) PS 4. 285 pts were intended to receive 2nd line CT. At initiation of 2nd line CT, overall WHO PS was 0 (11.3%), 1 (67.5%), 2 (17%), 3 (9.9%), 4 (0.4%). Median duration of 2nd line CT was 2.5 months. At the end of 2nd line CT, 254 patients had WHO PS 0 (6.8%), 1 (56.2%), 2 (17%), 3 (14.5%), 4 (5.5%) (no data 19 pts).

**Conclusion:** The administration of CT to patients with PS 0 - 4 was recorded in this first large-scale observational study of pts with advanced NSCLC. The majority of patients maintain PS after two cycles of 1st line CT. In those pts who received second line CT, a trend toward deteriorating PS is seen. The assessment of WHO PS is subjective. Maintenance or change in WHO PS may be driven by the impact of the cancer, chemotherapy treatment and/or any pre-existing co-morbidities.

**PD4-3-4 Cytotoxic Chemotherapy II, Tue, 16:00 - 17:30
Correlation of pemetrexed (PEM) NSCLC exposure-response relationships (ERRs) to clinical study results from western and Japanese patient populations**

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**Background:** The efficacy of PEM 500mg/m² administered with vitamin B12 and folic acid (FS) in previously treated NSCLC has been established (Hanna 2004, N=571 [Study-W0]). The 500mg/m² dose used in that study was selected based on the MTD for single-agent PEM without FS. Subsequent phase I studies in both western and Japanese study populations showed that single-agent PEM with FS was tolerated at doses of 900-1000mg/m². The low toxicities in Study-W0 and the tolerability of higher doses in the more recently completed dose escalation studies with FS led to studies comparing PEM 500mg/m² to 900 mg/m² or 1000mg/m² to determine whether a higher dose would provide additional efficacy while maintaining an acceptable safety profile. This work examines PEM ERRs and clinical study results from trials conducted in western and Japanese patients.
Methods: Patients in a randomized phase III study conducted in western patients (Study-W1) received PEM 500mg/m² or 900mg/m² once every 3 weeks. Patients enrolled in a randomized phase II study conducted in Japan (Study-J1) received PEM 500mg/m² or 1000mg/m² once every 3 weeks. Eligible patients in each of the studies had a histologic or cytologic diagnosis of NSCLC and had been previously treated. An established pharmacokinetic model was used to estimate AUCs from CrCL for patients in Study-W0 that received PEM 500mg/m² (N=265) and for patients in Study-J1. AUC was evaluated as a predictor of clinical efficacy (survival, TTPD, PFS) to identify ERRs. The models included previously identified prognostic factors and inverse of mean daily AUC over the treatment period as covariates.

Results: Study-W1 did not show a survival advantage for the 900mg/m² (N=293) dose over the 500mg/m² (N=295) dose. Study-J1 showed PEM 500mg/m² (N=108) and 1000mg/m² (N=108) to have similar efficacy for Japanese patients with previously treated NSCLC. Of the efficacy ERRs evaluated for Study-W0 and Study-J1, AUC was independently significant only for TTPD in Study-W0 and was not significant for other ERRs in either study (ERRs were not evaluated for Study-W1). There is internal consistency between the Study-J1 clinical results and the lack of ERRs for that study and external consistency between the Study-W1 clinical results and the lack of survival ERR for Study-W0.

Conclusion: Based on results available from two large randomized clinical trials and the evaluation of exposure-response relationships from a third trial, high dose PEM (900mg/m² or 1000mg/m²) does not offer an efficacy advantage over the currently approved 500mg/m² dose for either western or Japanese patient populations.

PD4-3-5 Cytotoxic Chemotherapy II, Tue, 16:00 - 17:30

Phase I/II study of oral TS-1 and gemcitabine in elderly patients with advanced non-small-cell-lung cancer (NSCLC): Thoracic Oncology Research Group Study 0502

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Background: Optimal treatment for elderly patients with NSCLC has been under active investigation. This study evaluated the safety and initial efficacy of a novel combination regimen of oral fluoropyrimidine TS-1 plus gemcitabine (GEM) for elderly patients (pts) with advanced NSCLC.

Methods: A phase I/II trial in 11 centers examined TS-1 and GEM in pts with age ≥ 70, stage IIIIB/IV previously untreated NSCLC. The starting dose was 60 mg/day (day 1-14) for TS-1 and 800 mg/m² for GEM (day 8, 15). GEM was increased to 1000 mg/m² at dose level 2 and TS-1 was increased to 80 mg/day at dose level 3. Phase II portion of the study assessed the efficacy and tolerability of the combination regimen at the dose determined in the phase I portion. The primary endpoint was objective response rate.

Results: Twenty two pts were enrolled in the phase I portion: 6 pts on dose level 1, 10 on dose level 2 and 6 on dose level 3. Median age of this group was 75 yrs (range 70-85). Dose limiting toxicities included Gr. 4 neutropenia (2 pts) and Gr.3 skin toxicity (4 pts). The recommended dose (RD) was TS-1 160 mg/day and GEM 1000 mg/m², with which 20 pts were subsequently treated in the phase II portion. The median age of 30 pts treated with the RD was 76 yrs (range 70-85). Grade (Gr) 3/4 toxicities include neutropenia (12 pts; 7 with Gr 4), thrombocytopenia (4 pts; 0 with Gr 4), skin toxicity (8 pts), thrombus (1 pt) and pneumonitis (2 pts). Nine patients (30%, 95% confidence interval [CI] = 14 to 46%) had partial responses and 16 (53%, 95% CI = 35 to 71%) had stable disease.

Conclusion: Encouraging antitumor activity and safety of TS-1 plus gemcitabine support further development of this combination therapy for elderly patients with advanced NSCLC.