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 median 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/mm² or 1000mg/m²) does not offer an efficacy advantage over the currently approved 500mg/m² dose for either western or Japanese patient populations.

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), thromboembolism (4 pts; 0 with Gr 4), skin toxicity (8 pts), thrombus (1 pt) and pneumonia (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.

A randomised phase II study comparing two schedules of the 21-day regimen of Gemcitabine and Carboplatin in advanced NSCLC

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Background: Carboplatin AUC 5 d1-Gemcitabine 1250 mg/m² d1, 8 is an approved standard regimen in advanced NSCLC. Hematologic toxicity is however frequent; thrombocytopenia is found in more than 40 % of cases, neutropenia in 20%. Aim: To investigate in two equally dose-dense regimens, whether the toxicity of the Gemcitabine-Carboplatin combination could be reduced by administering Carboplatin on day 8 instead of day 1 and without change in response rate.

Methods: Patients in arm A are treated with Gemcitabine (1250 mg/m² days 1,8) and Carboplatin (AUC 5 day 1) Patients in arm B are treated with Gemcitabine (1250 mg/m²/days 1,8) and Carboplatin (AUC 5 day 8.) Drugs are administered over a 21-day cycle, on an outpatient basis. Toxicity and response are evaluated weekly and every second cycle, respectively.

Statistics: The hypothesis of the study protocol is that regimen B shows a decrease in toxicity of 50% without loss of response rates. Toxicity is defined as a thrombocytopenia and/or neutropenia grade 1. The Bryan and Day design allows to consider both response and toxicity as primary endpoint. With an alpha of 0.10 and a power of 90% the sample size was estimated to be 67 patients in each arm. An interim analysis was performed after 54 included patients, 27 in each arm.

Results: A total of 71 patients were enrolled between April 2004 and March 2006, before the study was prematurely stopped because data showed a statistical significant difference in toxicity. Patient and disease characteristics for the 69 eligible patients are summarized in Table 1. Toxicity and response are reported in Table 2.