Phase III study of pemetrexed plus cisplatin versus gemcitabine plus cisplatin in chemonaive patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)

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Background: Platinum-based doublet chemotherapy is the standard of care for first-line treatment of locally advanced or metastatic NSCLC, and gemcitabine + cisplatin (GC) is an active, widely used doublet in this setting. In phase II studies, efficacy of pemetrexed-platinum doublets was comparable with other active platinum-doublets. Pemetrexed + cisplatin (PC) has several potential advantages including a more conveniently administered schedule.

Methods: Chemonaive patients with stage IIIB or IV NSCLC and ECOG PS of 0–1 were randomized to receive PC (P 500 mg/m^2 d1 + C 75 mg/m^2 d1) or GC (G 1250 mg/m^2 d1, 8 + C 75 mg/m^2 d1) Q3 weeks for up to 6 cycles. Both arms received dexamethasone prophylaxis, folic acid, and vitamin B_{12} supplementation. The primary endpoint of this non-inferiority study was overall survival. Using the Cox proportional hazards model and a two-tailed 95% CI for the hazard ratio (HR), rejection of the H_0 occurs when the upper-bound of the HR 95% CI is <1.176, with an 80% probability of rejecting H_0.

Results: 1725 pts were randomized to PC (n = 862) or GC (n = 863) from 7/04 to 12/05. Both arms were well balanced for known prognostic factors: median age 61 years, 70% male, 78% Caucasian, 64% PS 1, 15% never smokers and 76% stage IV NSCLC. Over 200 formalin-fixed paraffin-embedded tissue samples were collected for mRNA, protein expression and analysis of correlations between biomarker expression and clinical outcomes. Overall survival for pts randomized to PC was non-inferior to those on GC (10.3 vs 10.3 mo [HR 0.94, CI 0.84–1.05]), with the entire CI for HR well below the 1.176 non-inferiority margin. The CI further implies that PC retains at least 83% of GC survival benefit. Progression free survival and response rates showed similarly robust non-inferiority for PC vs GC (4.8 vs 5.1 mo [HR 1.04, CI 0.94–1.15] and 31% vs 28%). Hematologic grade 3/4 drug-related toxicities were significantly ($p \leqslant 0.001$) lower for PC; neutropenia (15% vs 27%), anemia (6% vs 10%), and thrombocytopenia (4% vs 13%). Febrile neutropenia (grade 3/4, 1% vs 4%, $p = 0.002$) and alopecia (12% vs 21%) were significantly less for PC ($p < 0.001$). Less grade 3/4 nausea (7% vs 4%, $p = 0.004$) and anorexia (2% vs 1%, $p = 0.009$) were observed for GC. However there was no significant difference in weight loss (any grade) between arms.

Conclusion: For first-line treatment of advanced NSCLC, PC provides similar efficacy with better tolerability and more convenient administration than GC.