Lung cancer II

9007 ORAL

Randomized, double-blind phase IIIb study of first-line paclitaxel (P) plus carboplatin (C) in combination with vorinostat or placebo in patients with advanced non-small-cell lung cancer (NSCLC)

C. Belani1, S. Ramalingam2, G. Kalemkerian3, T. Mok4, R. Rosell5, M.J. Ahn6, L. Sun7, M. Gates8, G.M. Lubiniecki6, R. Govindan9, 1Penn State Cancer Institute, Penn State College of Medicine, Hershey PA, USA; 2Emory Winship Cancer Institute, Hematology and Medical Oncology, Atlanta PA, USA; 3University of Michigan Health System, Internal Medicine, Ann Arbor MI, USA; 4Chinese University of Hong Kong, Clinical Oncology, Shatin Hong Kong, China; 5Catalan Institute of Oncology, Medical Oncology Services, Barcelona, Spain; 6Samsung Medical Center, Hematology and Oncology, Seoul, Korea; 7Merck Research Laboratories, Late Development Statistics, Upper Gwynedd PA, USA; 8Merck Research Laboratories, Oncology Clinical Research, Upper Gwynedd PA, USA; 9Washington University School of Medicine, St. Louis MO, USA

Background: Preclinical and phase I clinical data suggest that vorinostat (Zolinza®), a potent histone deacetylase inhibitor, may potentiate antitumor activity of P and C. This study assessed whether vorinostat added to P and C provides clinical benefit in first-line treatment of patients with advanced NSCLC.

Material and Methods: Patients ≥18 years with Stage IIIb (wet)/Stage IV NSCLC; ECOG performance status ≤1, and no prior systemic chemotherapy (except adjuvant therapy for NSCLC) were randomized to receive P 200 mg/m2 and C AUC 6 on Day 1 and either vorinostat 400 mg or placebo control on Days −4−10 of Cycle 1 (25-day cycle) and Days 1−14 of each subsequent 21-day cycle for ≤6 cycles. Primary endpoints were overall survival (OS) and safety. Secondary endpoints were progression-free survival (PFS) and objective response rate (ORR), as assessed by independent radiological review. P values were one-sided and interpreted to favor placebo if p<0.05.

Results: 253 patients were randomized. Patients’ characteristics were balanced between the arms except for age and sex, both favoring the control arm. Median OS favored patients in the control arm vs. the vorinostat arm (14.0 vs. 11.0 months, respectively, HR 1.18, 95% CI 0.86 to 1.63, p = 0.86). ORR was also higher in the control arm vs. the vorinostat arm (29.3% vs. 22.4%, p = 0.899). In 248 patients evaluable for safety, relevant grade 3−5 adverse experiences (vorinostat vs. control) included febrile neutropenia (9% vs. 5%), thrombocytopenia (19% vs. 2%), diarrhea (4% vs. 2%), asthenia (6% vs. 2%), and fatigue (6% vs. 5%). Median exposure to P and C was 4 cycles in the vorinostat arm and 6 cycles in the control arm. Study discontinuation during cycles 1 and 2 was 35% vs. 23% (vorinostat vs. control).

Conclusions: Based on recommendations of an independent data safety monitoring board at the second interim analysis, this study was terminated as the pre-specified proof-of-concept criterion (p < 0.10 for the test of treatment effect on PFS based on the first 100 PFS events) to go to phase III was not met. The addition of vorinostat on this dose and schedule, despite the baseline demographic imbalance, does not improve clinical efficacy obtained with P and C in patients with previously untreated NSCLC. Ongoing studies of vorinostat with chemotherapy in NSCLC patients may provide more information.