First-Line Chemotherapy With or Without Tislelizumab for Extensive-Stage Small Cell Lung Cancer: RATIONALE-312 Phase 3 Study

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Introduction: Tislelizumab, an anti-programmed cell death protein 1 monoclonal antibody, in combination with chemotherapy, showed promising antitumor activity in patients with extensive-stage small-cell lung cancer (ES-SCLC) receiving first-line treatment in the phase 2 BGB-A317-206 study. Here, we present the final analysis of the

randomized, double-blind, placebo-controlled, phase 3 RATIONALE-312 study (NCT04005716), which compared efficacy and safety of tislelizumab plus chemotherapy with placebo plus chemotherapy as first-line treatment in patients with ES-SCLC.

Methods: Eligible patients in China with previously untreated ES-SCLC were randomized 1:1 to receive 4 cycles of tislelizumab 200 mg or placebo with etoposide plus carboplatin or cisplatin intravenously every 3 weeks, followed by tislelizumab 200 mg or placebo as maintenance until disease progression, loss of clinical benefit, unacceptable toxicity, or withdrawal of consent. The primary endpoint was overall survival (OS) in the intent-to-treat analysis set. Key secondary endpoints included investigator-assessed progression-free survival (PFS), objective response rate (ORR), and duration of response (DoR) per RECIST v1.1, and safety outcomes.

Results: Between July 22, 2019 and April 22, 2021, 457 patients were randomized (tislelizumab arm, n=227; placebo arm, n=230). Baseline demographics were generally well balanced between treatment arms. Higher tumor burden was observed at baseline in the tislelizumab arm compared with the placebo arm; more patients had advanced disease (AJCC Stage IV: 91.2% vs 87.4%) and ≥3 metastatic lesions (80.6% vs 71.3%), respectively. Median (range) study follow-up at the final data cutoff (April 19, 2023) was 14.2 months (0.1-44.9). Tislelizumab plus chemotherapy demonstrated a statistically significant OS benefit compared with placebo plus chemotherapy (stratified hazard ratio [HR]=0.75 [95% confidence interval (CI): 0.61, 0.92]; *P*=0.0035; median OS: 15.5 [95% CI: 13.5, 17.1] vs 13.5 months [95% CI: 12.1, 14.9], respectively). OS rates at 1, 2, and 3 years were 62.7%, 33.2%, and 25.0%, respectively, in the tislelizumab arm and 58.4%, 22.4%, and 9.3%, respectively, in the placebo arm. Treatment with tislelizumab plus chemotherapy significantly improved PFS compared with placebo plus chemotherapy (stratified HR=0.63 [95% CI: 0.51, 0.78]; *P*<0.0001; median PFS: 4.8 [95% CI: 4.3, 5.5] vs 4.3 months [95% CI: 4.2, 4.4], respectively). Further, improved confirmed ORR (68.3% vs 61.7%) and more durable responses (median DoR 4.3 vs 3.7 months) were observed in the tislelizumab compared with the placebo arm, respectively. In the tislelizumab arm, 59.9% of patients received ≥1 subsequent systemic anticancer therapy vs 73.9% in the placebo arm. In the safety analysis set, 85.5% of patients in the tislelizumab arm vs 86.0% in the placebo arm had ≥grade 3 treatment-related treatment-emergent adverse events (TRAEs), with the most common (≥10% of patients) being hematologic toxicities in both arms. Serious TRAEs occurred in 31.3% of patients in the tislelizumab arm vs 17.9% in the placebo arm. Incidence of immune-mediated adverse events (imAEs) was 38.3% in the tislelizumab arm and 17.9% in the placebo arm. Most imAEs were manageable with systemic steroids or hormone therapies.

Conclusions: Tislelizumab in combination with chemotherapy as first-line treatment for patients with untreated ES-SCLC demonstrated significant clinical benefit and a manageable safety profile compared with placebo plus chemotherapy.