Safety and Efficacy of Sitravatinib + Tislelizumab in Patients with PD-L1+, Locally Advanced/Metastatic, Squamous NSCLC

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Abstract:

Introduction: Patients with programmed death-ligand 1 positive (PD-L1+), locally advanced or metastatic, squamous non-small cell lung cancer (NSCLC) have a poor prognosis and more effective treatments with better tolerability profiles are needed. Sitravatinib, a selective tyrosine kinase inhibitor, reduces the number of myeloid-derived suppressor cells and regulatory T cells, which promotes expansion and migration of antitumor cytotoxic T cells, and increases the ratio of M1/M2-polarized macrophages. Tislelizumab, an anti-programmed cell death protein 1 (PD-1) antibody engineered to minimize binding to FcγR on macrophages, has shown clinical activity in patients with advanced solid tumors, including NSCLC. This Phase 1b study assessed safety, tolerability, and antitumor activity of sitravatinib and tislelizumab in advanced solid tumors (NCT03666143). We present results from patients with PD-L1+, squamous NSCLC.

Methods: This was an open-label, non-randomized study. Eligible patients had PD-L1+, locally advanced or metastatic, squamous NSCLC without prior systemic treatment in the metastatic setting and without prior exposure to immunotherapy, including anti-PD-1/PD-L1, anti-CTLA-4, anti-OX40 and anti-CD137. Patients with a documented *EGFR* mutation, *ALK/ROS1* rearrangement, or *BRAF* mutation were not eligible. Patients received sitravatinib 120 mg orally once daily plus tislelizumab 200 mg intravenously every three weeks until unacceptable toxicity, withdrawal, or death. The primary endpoint was safety/tolerability. Secondary and exploratory endpoints included investigator-assessed objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and PD-L1 expression and the association with clinical benefit. Tumor response was assessed using RECIST v1.1. PD-L1+ was defined as PD-L1 staining on ≥ 1% of tumor cells (VENTANA SP263 immunohistochemistry assay).

Results: Between May 12, 2020 and February 10, 2021, 24 patients were enrolled. All patients were included in the safety analysis set, and 23 patients in the efficacy evaluable analysis set. The median age was 65.0 years (range: 56–71), and 91.7% of patients were male. Median study follow-up was 9.5 months (range: 0.4–16.2). At the data cut-off (November 8, 2021) treatment-emergent adverse events (TEAEs) of any Grade/≥ Grade 3 were reported in 95.8%/66.7% of patients. Serious TEAEs were observed in 50.0%, and the most common ≥ Grade 3 TEAE was hypertension (16.7%). A total of two TEAEs led to death, death and pneumonia and were not considered to be treatment related. In total, 70.8%/41.7% patients required dose modification of sitravatinib/tislelizumab due to TEAEs, respectively. Treatment-related AEs (TRAEs) of any Grade/≥ Grade 3, were observed in 91.7%/62.5% of patients. Serious TRAEs were reported in 37.5% of patients, and the most common ≥ Grade 3 TRAE was hypertension (16.7%). Confirmed ORR was 30.4% (95% confidence interval [CI]: 13.2, 52.9), with all seven patients achieving partial response. DCR was 78.3% (95% CI: 56.3, 92.5), median PFS was 5.4 months (95% CI: 2.8, 8.6), and median OS was not reached (95% CI: 6.7, not estimable).

Conclusion: Sitravatinib plus tislelizumab demonstrated a manageable safety and tolerability profile as well as antitumor activity in patients with PD-L1+, locally advanced or metastatic squamous NSCLC who had not received prior systemic treatment in the metastatic setting.