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

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Abstract:

Introduction: Patients with programmed death-ligand 1 positive (PD-L1+), locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC) have a poor prognosis and treatment options are limited. Sitravatinib, a selective tyrosine kinase inhibitor, reduces the number of myeloid-derived suppressor cells and regulatory T cells, promotes the 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 report results from patients with PD-L1+, non-squamous NSCLC.

Methods: This was an open-label, non-randomized study. Eligible patients had PD-L1+, locally advanced or metastatic, non-squamous NSCLC without prior systemic treatment in the metastatic setting and without prior exposure to immunotherapy (anti-PD-1/PD-L1, anti-CTLA-4, anti-OX40 and anti-CD137). Patients were required to have a documented wild-type *EGFR* status; patients with *ALK/ROS1* rearrangements or *BRAF* mutations were ineligible. Patients received sitravatinib 120 mg orally once daily and 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 November 7, 2019 and December 23, 2020, 22 patients were enrolled. All patients were included in the safety analysis set, and 21 patients in the efficacy evaluable analysis set. The median age was 60.5 years (range: 41–78), and 68.2% of patients were male. Median study follow-up was 11.8 months (range: 0.9–17.9). At the data cut-off (November 8, 2021) treatment-emergent adverse events (TEAEs) of any Grade/≥ Grade 3 were reported in 100.0%/59.1% of patients. Serious TEAEs were observed in 45.5%, and the most common ≥ Grade 3 TEAE was hypokalemia (18.2%). A total of two TEAEs, death (death unexplained) and multiple organ dysfunction syndrome, led to death and were considered treatment related. In total, 72.7%/59.1% patients required dose modification of sitravatinib/tislelizumab due to TEAEs, respectively. Treatment-related AEs (TRAEs) of any Grade/≥ Grade 3, were observed in 95.5%/50.0% of patients. Serious TRAEs were reported in 36.4% of patients, and the most common ≥ Grade 3 TRAE was hypertension (13.6%). Confirmed ORR was 57.1% (95% confidence interval [CI]: 34.0, 78.2) with all 12 patients achieving partial response. DCR was 85.7% (95% CI: 63.7, 97.0), median PFS was 11.1 months (95% CI: 5.5, not estimable [NE]), and median OS was 17.4 months (95% CI: 11.8, NE).

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