A phase 2 study of sitravatinib in combination with tislelizumab versus chemotherapy in patients with locally advanced unresectable or metastatic esophageal squamous cell carcinoma that progressed on or after anti–PD-1/anti–PD-L1 antibody therapy

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ABSTRACT

Objective: There is no established standard of care for second- or later-line treatment of patients with locally advanced unresectable or metastatic esophageal squamous cell carcinoma (ESCC) whose disease progressed on or after anti–programmed cell death protein-1 (PD-1)/anti–programmed death ligand-1 (PD-L1) therapy. Sitravatinib (SITRA) is a selective tyrosine kinase inhibitor that may help to alter the tumor microenvironment to overcome resistance to PD-1/PD-L1 inhibitors and augment antitumor responses. Tislelizumab (TIS) is an anti–PD-1 monoclonal antibody designed to abrogate antibody-dependent phagocytosis, a potential mechanism of resistance. Combining TIS and SITRA could potentially reverse resistance to PD-1/PD-L1 inhibitors. The objective of this study was to investigate the efficacy and safety of TIS+SITRA in these patients.

Methods: This open-label, randomized, multicenter, phase 2 study (NCT05461794) enrolled adults with locally advanced unresectable or metastatic ESCC whose disease progressed on or after prior platinum-based chemotherapy doublet and anti–PD-1/anti–PD-L1 antibody therapy, and who received ≤2 lines of systemic anticancer therapy for advanced disease. Patients were randomized (2:1:2) to receive SITRA 100 mg orally once daily (QD) plus TIS 200 mg IV on Day 1 of every 21-day cycle (TIS+SITRA), SITRA 100 mg orally QD (SITRA), or investigator choice chemotherapy (ICC; docetaxel 75 mg/m^2 IV on Day 1 of every 21-day cycle or irinotecan 125 mg/m^2 IV on Days 1 and 8 of every 21-day cycle). Randomization was stratified by PD-L1 expression status (tumor area positivity [TAP] score ≥10% vs <10%). The primary endpoint was investigator-assessed overall response rate (ORR) per RECIST version 1.1 in the TIS+SITRA and ICC arms. Secondary endpoints included investigator-assessed disease control rate (DCR), clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), and safety.

Results: Overall, 96 patients were randomized (intent-to-treat [ITT] population: n=39, TIS+SITRA; n=19, SITRA; n=38, ICC); of these 92 patients were treated (safety analysis set: n=39, TIS+SITRA; n=19, SITRA; n=34, ICC). Median age was 59.0 years (range: 37-73), 92.7% were male, and 14.6% had high PD-L1 expression (TAP ≥10%). At the data cutoff of February 26, 2024 (median follow-up times of 4.2, 5.3, and 4.4 months for TIS+SITRA, SITRA, and ICC, respectively), investigator-confirmed ORRs were 10.3% (95% CI, 2.9-24.2), 21.1% (95% CI, 6.1-45.6), and 5.3% (95% CI, 0.6-17.7) with TIS+SITRA, SITRA, and ICC, respectively. There were no complete responses. DCR was 64.1% (95% CI, 47.2-78.8), 63.2% (95% CI, 38.4-83.7), and 42.1% (95% CI, 26.3-59.2) with TIS+SITRA, SITRA, and ICC, respectively. CBR was 17.9% (95% CI, 7.5-33.5), 26.3% (95% CI, 9.1-51.2), and 5.3% (95% CI, 0.6-17.7) with TIS+SITRA, SITRA, and ICC, respectively. Median PFS with TIS+SITRA, SITRA, and ICC was 3.4 (95% CI, 2.1-5.6), 5.6 (95% CI, 2.1 -not estimable [NE]), and 2.6 (95% CI, 1.5-3.8) months, respectively. Median OS with TIS+SITRA, SITRA, and ICC was 6.1 (95% CI, 3.4-7.5), 9.1 (95% CI, 6.5-NE), and 5.5 (95% CI, 4.7-6.6) months, respectively. All patients had ≥1 all-grade treatment-emergent adverse event (TEAE); increased aspartate aminotransferase was the most common in both the TIS+SITRA (41.0%) and SITRA (47.4%) arms and decreased white blood cell count was the most common in the ICC (73.5%) arm. 66.7% (TIS+SITRA), 73.7% (SITRA), and 70.6% (ICC) of patients had at least 1 grade ≥3 TEAE. 56.4%, 31.6%, and 44.1% of patients in the TIS+SITRA, SITRA, and ICC arms, respectively, had serious TEAEs; 33.3%, 42.1%, and 26.5% of patients in the TIS+SITRA, SITRA, and ICC arms, respectively, had TEAEs leading to treatment discontinuation. One (2.6%) patient in the TIS+SITRA arm had a TEAE leading to death (reported as unexplained death), which was unrelated to disease under study and study treatment as assessed by the investigator.

Conclusion: TIS+SITRA and SITRA monotherapy demonstrated numerically favorable tumor response in patients with ESCC who progressed on or after anti–PD-1/PD-L1 antibody therapy compared with ICC chemotherapy and were tolerable with acceptable safety profiles. The survival benefit of SITRA monotherapy or in combination with TIS remains to be determined.