**Tislelizumab Plus Chemotherapy as First-line Treatment for Unresectable, Locally Advanced Recurrent/Metastatic Esophageal Squamous Cell Carcinoma**

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**Background** Esophageal squamous cell carcinoma (ESCC) is the predominant histological subtype of esophageal cancer, particularly in Asian countries. Inhibition of the PD-1/PD-L1 axis has demonstrated antitumor activity in patients with advanced unresectable or metastatic ESCC. Tislelizumab, an investigational humanized IgG4 monoclonal antibody with high affinity and binding specificity for PD-1, was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. Results from early phase clinical studies suggest tislelizumab, as a single agent or in combination with chemotherapy, was generally well tolerated and had antitumor activity in patients with solid tumors, including ESCC.

**Methods** This global, phase 3, randomized, placebo-controlled, double-blind study (NCT03783442) is designed to evaluate the efficacy and safety of tislelizumab plus chemotherapy as first-line treatment of unresectable, locally advanced recurrent or metastatic ESCC. Adult patients with histologically confirmed unresectable ESCC, or locally advanced recurrent/metastatic disease with a ≥6 month treatment-free interval, are eligible; palliative radiation administered >4 weeks from study initiation is allowed. Patients who received prior anti-PD-(L)1, anti-PD-L2, or first-line therapy are ineligible. Patients (n≈480) will be randomized 1:1 to receive tislelizumab 200 mg IV every 3 weeks (Q3W) plus investigator-chosen chemotherapy (ICC) or placebo plus ICC. ICC options include: platinum (plat; cisplatin 60-80 mg/m$^2$ or oxaliplatin 130 mg/m$^2$ IV Q3W) + 5-FU 750-800 mg/m$^2$ by continuous IV infusion over 24 hours for 5d Q3W; or plat + capecitabine 1000 mg/m$^2$ orally BID for 14d Q3W; or plat + paclitaxel 175 mg/m$^2$ IV Q3W. Progression-free and overall survival are primary endpoints; secondary endpoints include objective response rate, duration of response, and health-related quality of life. Safety will be assessed by monitoring adverse events, physical examinations, vital signs, and electrocardiograms. This study is actively enrolling.