**RATIONALE 306: A Randomized, Placebo-Controlled, Double-Blind Trial in Progress of 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 suggested 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.

**Trial Design** This phase 3, randomized, placebo-controlled, double-blind study (NCT03783442/ CTR2018013) is designed to evaluate the efficacy and safety of tislelizumab in combination with chemotherapy as first-line treatment of unresectable, locally advanced recurrent or metastatic ESCC. Adult patients with histologically confirmed unresectable ESCC that was stage IV disease at first diagnosis, or locally advanced recurrent/metastatic disease with a ≥6 month treatment-free interval, are eligible; palliative radiation administered >4 weeks from start of the study was allowed. Patients were ineligible if they had received prior anti-PD-(L)1, anti-PD-L2, or prior first-line therapy. Patients (n≈480) will be randomized 1:1 to receive tislelizumab 200 mg IV Q3W or placebo plus investigator-chosen chemotherapy. Chemotherapy 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, safety, and health-related quality of life.