Tislelizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy as First-line Therapy in Patients With Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (G/GEJ) Adenocarcinoma: RATIONALE 305

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Background: Fluoropyrimidine- and platinum (plat)-based combination chemotherapy is first-line standard of care in patients with locally advanced or metastatic G/GEJ adenocarcinoma. Despite improved chemotherapy regimens, outcomes remain poor and survival is low. Tislelizumab, an investigational humanized IgG4 monoclonal antibody with high affinity and binding specificity for PD-1, was engineered to minimize binding of FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. Previous reports from early phase studies suggested tislelizumab, as a single agent and combined with chemotherapy, was generally well tolerated and had antitumor activity in patients with advanced solid tumors, including G/GEJ cancer.

Trial Design: This actively enrolling, randomized, placebo-controlled, phase 3 study (NCT03777657) is designed to evaluate plat/fluoropyrimidine + tislelizumab vs plat/fluoropyrimidine + placebo as first-line therapy for patients with locally advanced or metastatic G/GEJ adenocarcinoma. Patients (n≈720) from ~160 centers will be randomized 1:1 to receive tislelizumab (200 mg IV Q3W) or placebo in combination with chemotherapy. Oxaliplatin (130 mg/m² IV Q3W) + capecitabine (1000 mg/m^2 orally BID for 2 weeks) or cisplatin (80 mg/m² IV Q3W) + 5-fluorouracil (800 mg/m^2/day IV on Days 1-5 Q3W) will be used as backbone chemotherapy on an individual basis. Chemotherapy will be administered for up to 6 cycles; capecitabine maintenance therapy is optional for patients who received capecitabine and oxaliplatin. The VENTANA™ PD-L1 (SP263) assay will be used for PD-L1 expression analysis. Progression-free survival and overall survival are primary endpoints of the study. Secondary endpoints will include overall response rate, duration of response, quality-of-life outcomes, as well as the safety/tolerability profile of combination therapy. Exploratory endpoints include time to response and an analysis of potential predictive biomarkers (eg, PD-L1 expression).