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

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Background: Gastric cancer is the second most common cause of cancer-related deaths worldwide and poses a major clinical challenge due to limited treatment options. Fluoropyrimidine- and platinum-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. New therapies have focused on targeting the immune system, including the programmed death-1 receptor/programmed death-ligand 1 (PD-1/PD-L1) axis. Tislelizumab, a humanized 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, either alone or in combination with chemotherapy, was generally well tolerated and demonstrated antitumor activity in patients with advanced solid tumors, including G/GEJ cancer. The recommended dosing for tislelizumab has been established as 200 mg IV every three weeks (Q3W).

Trial Design: This global, double-blind, placebo-controlled, randomized, phase 3 study (NCT03777657) is designed to evaluate platinum/fluoropyrimidine plus tislelizumab versus platinum/fluoropyrimidine plus placebo as first-line therapy for patients with locally advanced or metastatic G/GEJ adenocarcinoma. Adult patients (n≈720) from ~160 centers will be randomized 1:1 to receive tislelizumab (200 mg IV Q3W) or placebo in combination with chemotherapy. Randomization will be stratified by region, PD-L1 expression assessed by a central laboratory, presence of peritoneal metastasis, and investigator's choice of chemotherapy. Patients with histologically confirmed G/GEJ adenocarcinoma, an Eastern Cooperative Oncology Group performance status score of ≤1, adequate organ function, and ≥1 measurable/evaluable lesion per RECIST v1.1 will be eligible. Patients may have received prior neoadjuvant/adjuvant therapy if completed ≥6 months prior to study entry (without disease recurrence/progression), but are ineligible if they received previous systemic therapy for locally advanced unresectable or metastatic G/GEJ adenocarcinoma. Oxaliplatin (130 mg/m² IV Q3W) plus capecitabine (1000 mg/m^2 orally twice daily for 2 weeks) or cisplatin (80 mg/m² IV Q3W) plus 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 six cycles; capecitabine maintenance therapy is optional for patients receiving capecitabine and oxaliplatin. The VENTANA PD-L1 (SP263)

assay will be used for PD-L1 expression analysis. Progression-free and overall survival are primary endpoints of the study. Secondary endpoints will include the safety/tolerability profile of combination therapy, overall response rate and duration of response (as assessed by blinded independent review committee per RECIST v1.1 criteria), and quality-of-life outcome measures (eg, European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Gastric Cancer Module QLQ-STO22 Score, EORTC Quality of Life Questionnaire-Core 30 Score, and European Quality of Life 5-Dimensions 5-Levels Health Questionnaire Score). Exploratory endpoints include disease control rate, clinical benefit rate, time to response, and an analysis of potential predictive biomarkers including, but not limited to, PD-L1 expression. This trial is currently enrolling.