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

RATIONALE TRIAL PROGRAM

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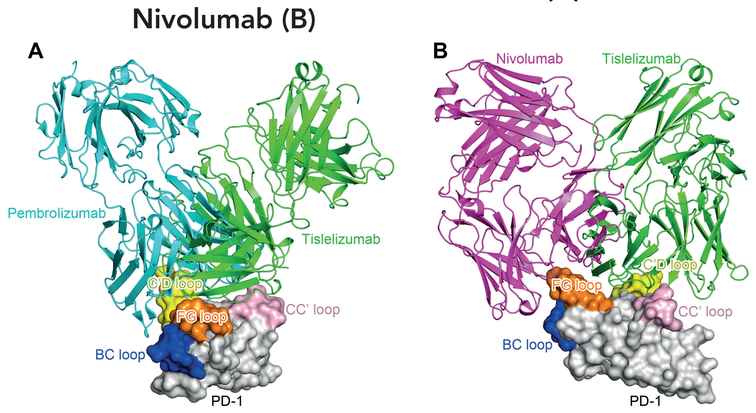
BACKGROUND

- Gastric cancer is the third most common cause of cancer-related death worldwide, posing a major clinical challenge due to limited treatment options[1]
- For patients with locally advanced or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma, the main treatment options include irinotecan, taxane, fluoropyrimidine, and platinum-based combination chemotherapy regimens[2]
- Immune checkpoint inhibitors, such as monoclonal antibodies against programmed death-1 receptor (PD-1), have demonstrated promising antitumor activity across multiple malignancies, including G/GEJ adenocarcinoma[3]
- Expression of programmed death ligand-1 (PD-L1) increases after gastrointestinal (GI) cancer cell lines are treated with 5-fluorouracil (5-FU), suggesting that the PD-1/PD-L1 axis may play a role in resistance to chemotherapy[4]
- Tislelizumab is an investigational monoclonal antibody with high affinity and specificity for PD-1
  - Tislelizumab has shown higher affinity to PD-1 than pembrolizumab and nivolumab with an ~100- and 50-fold slower off-rate, respectively[5]
- Tislelizumab has a different binding orientation to PD-1 compared with pembrolizumab and nivolumab; the binding surface on PD-1 for tislelizumab partially overlaps with that for pembrolizumab, but differs significantly from that for nivolumab (**Figure 1**)[5]

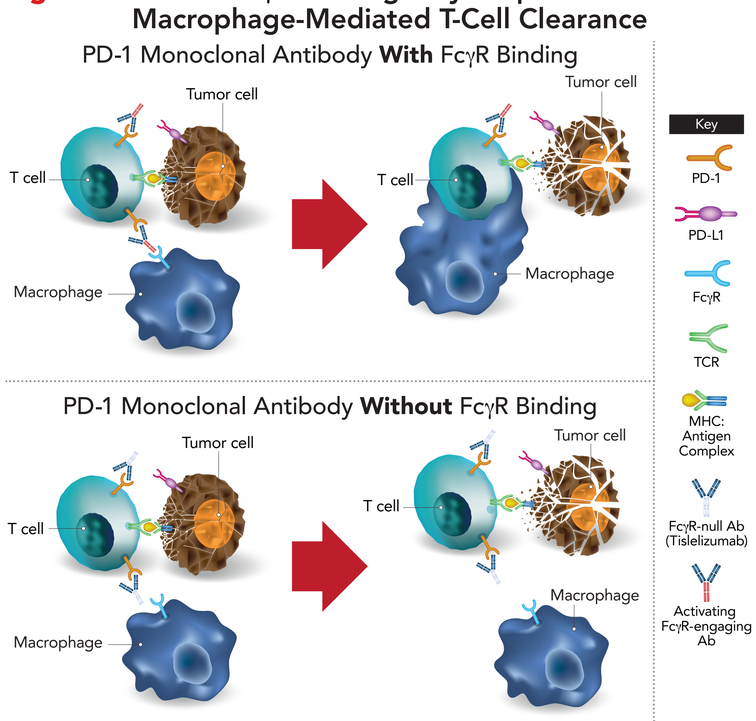
Figure 1: Tislelizumab Binds to PD-1 in an Orientation Different From Pembrolizumab (A) and Nivolumab (B)



PD-1, tislelizumab, pembrolizumab, and nivolumab are colored in gray, green, cyan, and magenta, respectively. The BC, CC', C'D, and FG loops of PD-1 are colored in blue, pink, yellow, and orange, respectively.
Abbreviation: PD-1, programmed death-1 receptor.

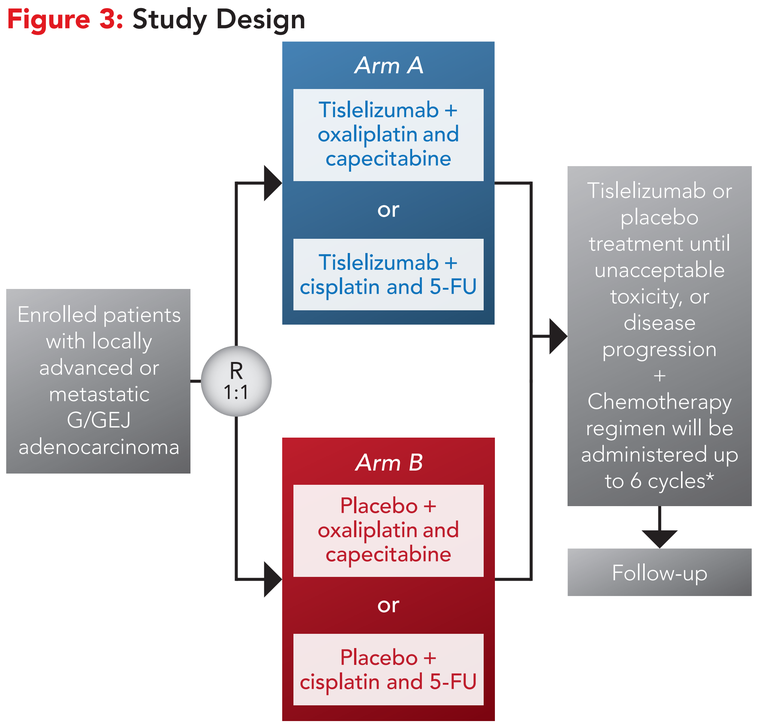
- Tislelizumab was specifically engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy (**Figure 2**)[6,7]
- Early phase studies (NCT02407990; NCT03469557) have reported that tislelizumab, as a single agent and in combination with chemotherapy, was generally well tolerated and had encouraging antitumor activity in patients with G/GEJ adenocarcinoma[8-10]

Figure 2: Lack of FcγR Binding May Help Prevent Macrophage-Mediated T-Cell Clearance



Abbreviations: Ab, antibody; MHC, major histocompatibility complex; PD-1, programmed death-1 receptor; PD-L1, programmed death ligand-1; TCR, T-cell receptor.

Figure 3: Study Design



Randomization stratified by regions of enrollment, PD-L1 expression, presence of peritoneal metastasis, and investigator's choice of chemotherapy.
*Capecitabine as maintenance therapy is optional only for oxaliplatin and capecitabin regimen and may be administered until disease progression, intolerable toxicity, or another treatment discontinuation criterion is met.
Abbreviations: 5-FU, 5-fluorouracil; G/GEJ, gastric or gastroesophageal junction; R, randomized.

METHODS

Overall Design and Study Objectives

- RATIONALE 305 (NCT03777657) is a currently enrolling, global, double-blind, placebo-controlled, randomized, phase 3 study being conducted in 160 centers with approximately 720 patients that is designed to compare tislelizumab plus platinum/fluoropyrimidine versus placebo plus platinum/fluoropyrimidine as first-line therapy for patients with locally advanced or metastatic G/GEJ adenocarcinoma (**Figure 3**)
- Primary endpoints are to compare progression-free survival (PFS) and overall survival (OS) of patients treated with tislelizumab plus chemotherapy versus patients treated with placebo plus chemotherapy
- Secondary endpoints include overall response rate (ORR) and duration of response (DoR), as assessed by blinded independent review committee per RECIST v1.1 criteria, quality-of-life outcome measures (eg, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC] Gastric Cancer Module QLQ-STO22 Score, EORTC of Life Questionnaire-Core 30 Score, and European Quality of Life 5-Dimensions [EQ-5D] 5-Levels Health Questionnaire Score), as well as safety/tolerability profile of combination therapy
- Exploratory objectives, including independent review of disease control rate (DCR), clinical benefit rate (CBR), and time to response, as well as PFS, ORR, DoR, DCR, CBR, and time to response, were assessed by the investigator

Study Population

- Adult patients with histologically confirmed unresectable or metastatic G/GEJ adenocarcinoma, an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤1 and adequate organ function and at least one measurable/evaluable lesion according to RECIST v1.1, are eligible
- Patients may not have received prior systemic therapy for locally advanced unresectable or metastatic G/GEJ adenocarcinoma
- Patients must be able to provide either a fresh or archival tumor tissue for assessment of biomarkers (eg, PD-L1)
  - PD-L1 expression will be assessed in a central laboratory using the VENTANA PD-L1 (SP263) assay
- Patients with squamous cell, undifferentiated, or other histological type of GC or a diagnosis of HER2-positive G/GEJ adenocarcinoma are ineligible
- Patients will also be excluded if they have a history of GI perforation and/or fistulae within 6 months prior to randomization, clinically significant bleeding from the GI tract within 3 months prior to randomization, or clinically significant bowel obstruction, have any other active malignancy ≤2 years before randomization, or received prior therapy with a drug specifically targeting T-cell co-stimulation or checkpoint pathways

Treatment

- Patients will be randomized 1:1 to receive either tislelizumab 200 mg IV every 3 weeks (Q3W; Day 1 of each 21-day cycle; *Arm A*) or placebo IV Q3W (*Arm B*) plus investigator-chosen chemotherapy
  - Randomization will be stratified by region, PD-L1 expression, presence of peritoneal metastasis, and investigator's choice of chemotherapy
- Investigators can choose from two chemotherapy options:
  - Oxaliplatin 130 mg/m^2 IV Q3W (Day 1 of each 21-day cycle) plus capecitabine 1000 mg/m^2 orally twice daily (Days 1-15 of every 21-day cycle); **or**
  - Cisplatin 80 mg/m^2 IV Q3W (Day 1 of each 21-day cycle) plus 5-FU 800 mg/m^2 IV continuously for 24 hours (Days 1-5 of each 21-day cycle)
- Tislelizumab or placebo will be administered until disease progression, intolerable toxicity, withdrawal of consent, or until another treatment discontinuation criterion is met
- The chemotherapy regimen will be administered for up to six cycles; capecitabine as maintenance therapy is optional only for the oxaliplatin and capecitabine regimen

Study Assessments and Statistical Analysis

- Tumor assessments will occur at baseline, every 6 weeks for 48 weeks, then every 9 weeks until disease progression
- Primary endpoints, PFS and OS, will be assessed using the Kaplan-Meier method; the stratified log-rank test will be used to assess between group differences in PFS and OS; treatment effect will be estimated by the stratified Cox proportional hazard model
  - Progression-free survival is defined as the time from date of randomization to the date of the first objectively documented tumor progression
  - Overall survival is defined as the time from date of randomization to the date of death due to any cause
  - Interim analysis of OS will be performed at the time of final PFS analysis
- Safety/tolerability of tislelizumab or placebo plus chemotherapy will be assessed by the incidence and severity of adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for AEs v5.0 criteria, physical examinations, vital signs, electrocardiogram, ECOG scores, and laboratory test results up to 30 days after the last dose of study drug
  - Immune-related AEs will be collected up to 90 days after the last dose of study drug
  - Safety and tolerability assessments will be performed in the safety analysis set, which will consist of all subjects who receive ≥1 dose of the assigned study drug
- Quality-of-life assessments will be performed at baseline, at every cycle through Cycle 6, then every other cycle thereafter until progressive disease, and at the end of treatment visit

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