RATIONALE 305: TISLELIZUMAB PLUS CHEMOTHERAPY VERSUS PLACEBO PLUS CHEMOTHERAPY AS FIRST-LINE THERAPY IN PATIENTS WITH GASTRIC OR GASTROESOPHAGEAL JUNCTION (G/GJE) ADENOCARCINOMA

Rui-Hua Xu,1,2 Tobias Arkenau,3,4 Yung-Jue Bang,3,4 Crystal S. Denlinger,3,6 Ken Kato,7 Josep Tabernero,7,8 Jin Wang,9 Jiang Li,9 Yanyan Li,10 Markus Moehler11
1Sun Yat-sen University Cancer Center, Guangzhou, China; 2Sarah Cannon Research Institute, UK, London, United Kingdom; 3Seoul National University Hospital, Seoul, Korea; 4Fox Chase Cancer Center, Philadelphia, PA, USA; 5Hospital de la Santa Creu i de la Sant Pau, Barcelona, Spain; 6BeiGene (Beijing) Ltd., Beijing, China; 7Seoul National University Hospital, Seoul, Korea; 8Institute of Oncology (WRO), Warsaw, Poland; 9Barcelona Tumor Institute, Barcelona, Spain; 10Biostatistics and Medical Economics, Beijing, China; 11Medical University of Munich, Munich, Germany

Poster: P-026 World Congress on Gastrointestinal Cancer 1-4 July 2020 Virtual Congress

BACKGROUND

• Gastric cancer is the third most common cause of cancer-related death worldwide, posing a major clinical challenge due to limited treatment options.
• For patients with locally advanced or metastatic gastric or gastroesophageal junction (G/GJ) adenocarcinoma, the main treatment options include surgery, chemoradiotherapy, and platinum-based combination chemotherapy regimens.
• Immune checkpoint inhibitors, such as monoclonal antibodies against programmed cell death protein-1 (PD-1), have demonstrated promising antitumor activity across multiple malignancies, including G/GJ adenocarcinoma.
• Expression of programmed death-ligand 1 (PD-L1) increases further for nivolumab (Figure 1), compared with pembrolizumab and nivolumab, and shows greater potential for longer duration of response (DoR). The BC, CC', C'D, and FG loops of PD-1 are colored in blue, pink, yellow, and orange, respectively. The BC, CC', C'D, and FG loops of PD-1 are colored in blue, pink, yellow, and orange, respectively.

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

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

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

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 180 centers with approximately 980 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/GJ adenocarcinoma (Figure 3).
• The primary endpoint is overall survival (OS) of patients treated with tislelizumab plus chemotherapy versus patients treated with placebo plus chemotherapy.
• Secondary endpoints include progression-free survival (PFS), overall response rate (ORR), duration of response (DoR), disease control rate, clinical benefit rate, and time to response as assessed by investigators per RECIST v1.1 criteria.
• Additional secondary endpoints include quality-of-life outcome measures (e.g., 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.

An exploratory objective is PFS after next line of treatment, assessed by investigators per RECIST v1.1 criteria.

Study Population

• Adult patients with histologically confirmed unresectable or metastatic G/GJ adenocarcinoma, an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2 and adequate organ function and at least one measurable or non-measurable lesion according to RECIST v1.1, are eligible.
• Patients may not have received prior systemic therapy for locally advanced unresectable or metastatic G/GJ adenocarcinoma.
• Patients must be able to provide either a fresh or archival tumor tissue for assessment of biomarkers (e.g., 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/GJ adenocarcinoma are ineligible.
• Patients will also be excluded if they have a history of GI perforation and/or surgery within 6 months prior to randomization, clinically significant bleeding from the GI tract within 1 month 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 every 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/m2 IV Q3W (Day 1 of every 21-day cycle) plus capecitabine 1000 mg/m2 orally twice (Days 1-15 of every 21-day cycle), or
  - Cisplatin 80 mg/m2 IV Q3W (Day 1 of every 21-day cycle) plus 5-FU 800 mg/m2 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 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.
• Overall survival will be assessed using the Kaplan-Meier method; the stratified log-rank test will compare OS between Arm A and Arm B; treatment effect will be estimated by the stratified Cox proportional hazard model.
• Overall survival is defined as the time from date of randomization to the date of death due to any cause.
• One interim analysis of OS will be performed for efficacy using the O'Brien-Fleming boundary.
• 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, as every cycle through Cycle 6, and then every other cycle thereafter until progressive disease, and at the end of treatment visit.

REFERENCES


ACKNOWLEDGMENTS

The authors wish to acknowledge the investigative center study staff and to recognize those from BeiGene, Ltd. who have substantially contributed to the development of this presentation. This study was sponsored by BeiGene, Ltd. Writing and editorial assistance was provided by Agnieszka Laskowski, PhD, and Elizabeth Hermens, PhD (OPEN Health Medical Communications, Chicago, IL), and funded by the study sponsor.

Please address any questions or comments regarding this poster to Clinicaltrials@beigene.com