RATIONALE 302: A PHASE 3, RANDOMIZED, OPEN-LABEL STUDY TO COMPARE THE EFFICACY OF TISLELIZUMAB VS CHEMOTHERAPY AS SECOND-LINE THERAPY FOR ADVANCED UNRESECTABLE/METASTATIC ESOPHAGEAL SQUAMOUS CELL CARCINOMA: A TRIAL-IN-PROGRESS

RATIONALE TRIAL PROGRAM

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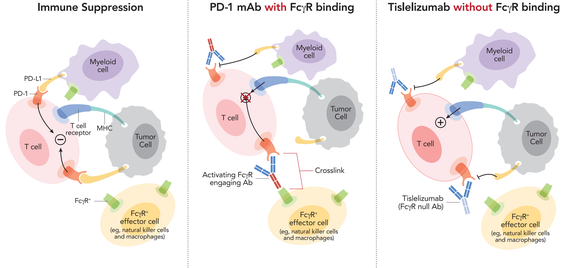
BACKGROUND

- Approximately 40% of patients with esophageal cancer are diagnosed with advanced unresectable or metastatic disease, which progresses rapidly, having a 5-year survival rate of less than 5%[1,2]
- The availability of high efficacy and generally tolerable treatment options is limited for those with advanced or metastatic disease who have failed first-line treatment[3–5]
- Inhibition of programmed cell death protein-1 (PD-1) has demonstrated antitumor activity and was generally well tolerated in patients with advanced unresectable or metastatic ESCC[6,7]
- Tislelizumab (also known as BGB-A317) is a humanized IgG4 monoclonal antibody with a high affinity and specificity for PD-1
- Tislelizumab was specifically engineered to minimize binding to FcγR on macrophages, thereby abrogating antibody-dependent T-cell clearance, a potential mechanism of resistance to anti-PD-1 therapy (Figure 1)
- A first-in-human study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and had preliminary antitumor effects in patients with advanced solid tumors, including ESCC.[8,9] Phase 2 and 3 studies in patients with advanced solid tumors are ongoing[10–12]
- The recommended dose of tislelizumab is 200 mg, given intravenously (IV) every 3 weeks (Q3W)

Figure 1: Lack of FcγR Binding Prevents Macrophage-Mediated T-Cell Clearance



Adapted from Dahan, et al. *Cancer Cell*. 2015;28:285–295.

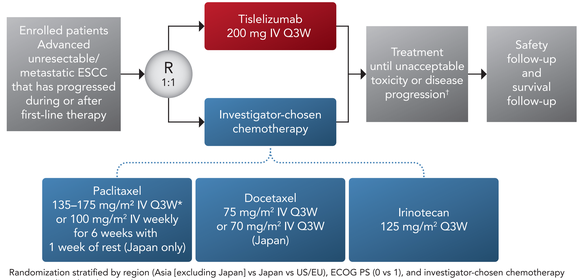
Abbreviations: Ab, antibody; CD, cluster of differentiation; FcγR, Fc-gamma receptor; mAb, monoclonal antibody; MHC, major histocompatibility complex; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1.

METHODS

Overall Design and Study Objectives

- RATIONALE 302 is a phase 3, randomized, controlled, open-label study (NCT03430843) was designed to evaluate the efficacy and safety of tislelizumab compared with investigator-chosen chemotherapy for second-line treatment of advanced unresectable/metastatic ESCC (Figure 2)
- The primary objective will be to compare overall survival (OS) for tislelizumab with that for chemotherapy
- Secondary objectives will include a comparison of tislelizumab versus chemotherapy for objective response rate (ORR), progression-free survival (PFS), and duration of response (DoR), along with health-related quality of life, and safety and tolerability
- Approximately 450 patients will be enrolled globally

Figure 2: Study Design



Randomization stratified by region (Asia [excluding Japan] vs Japan vs US/EU), ECOG PS (0 vs 1), and investigator-chosen chemotherapy option (paclitaxel vs docetaxel vs irinotecan).

*Paclitaxel may also be given in doses of 80–100mg/m² IV on a weekly schedule, according to local and/or country specific guidelines for standard of care.

†Treatment beyond the initial investigator-assessed disease progression will be permitted in the tislelizumab arm if pseudo progression is suspected or there is reasonable belief that the patient could derive benefit from the treatment.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; EU, European Union; IV, intravenously; Q3W, once every 3 weeks; R, randomization; US, United States.

Study Population

- Adult patients, aged ≥18 years, will be enrolled if they had the following:
  - Histologically confirmed ESCC that has progressed during or after first-line therapy for unresectable/metastatic disease
  - At least one measurable/evaluable lesion by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
  - An Eastern Cooperative Oncology performance status score of 0 or 1
- Patients will be excluded from the study if they had the following:
  - Ineligible for any of the treatments of protocol-specified chemotherapy (paclitaxel/ docetaxel/irinotecan)
  - Received two or more prior systemic treatments for advanced/metastatic unresectable ESCC
  - Had palliative radiation treatment for ESCC within 14 days of study treatment initiation
  - A history of gastrointestinal perforation and/or fistula or aorto-esophageal fistula within 6 months of randomization
  - Apparent tumor invasion into organs located adjacent to the esophageal disease site that are at an increased risk of fistula
  - Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage
  - Active hepatitis C, untreated chronic hepatitis B, or if they are carriers of chronic hepatitis B virus (HBV) whose HBV DNA is higher than 500 IU/mL

TREATMENT

- Patients will be randomized 1:1 to receive either tislelizumab 200 mg IV Q3W (Day 1 of each 21-day cycle) or investigator-chosen chemotherapy:
  - Paclitaxel 135–175 mg/m² IV Q3W (Day 1 of each 21-day cycle) or 100 mg/m² IV weekly for 6 weeks with 1 week of rest (Japan only); or
  - Docetaxel 75 mg/m² or 70 mg/m² (Japan only) IV Q3W (Day 1 of each 21-day cycle); or
  - Irinotecan 125 mg/m² IV Q3W (Day 1, Day 8 of each 21-day cycle)
- Randomization will be stratified by region, ECOG performance status, and chemotherapy option
- Treatment will be administered until disease progression, intolerable toxicity, or treatment discontinuation for other reasons. Patients on the tislelizumab arm will be permitted to continue tislelizumab treatment beyond radiological progression if clinical benefit is observed per investigator's discretion
- There will be no dose reduction of tislelizumab in this study; dose delays or interruption of less than 12 weeks will be permitted
- A maximum of two dose reductions will be permitted for each chemotherapeutic agent. Chemotherapy-related toxicities (with the exception of alopecia or grade 2 fatigue) must have resolved to baseline or grade 0–1 prior to administration of the next chemotherapy dose

STUDY ASSESSMENTS AND STATISTICAL ANALYSIS

- The primary endpoint will be OS for tislelizumab versus investigator-chosen chemotherapy, with analysis performed using a two-sided, stratified log-rank test with a significance level of 0.05; data will be presented as Kaplan–Meier survival probability plots
  - An interim analysis of OS is planned
- The secondary endpoints of ORR (the proportion of patients with complete response or partial response), PFS, and DoR will be assessed by the investigator using RECIST v1.1 criteria
  - Tumor assessments will occur at baseline, every 6 weeks (±7 days) for 6 months, then every 9 weeks (±7 days) until disease progression
  - ORR will be analyzed using a Cochran-Mantel-Haenszel test, adjusting for selected stratification factors, and PFS will be assessed using the Kaplan–Meier method
- Health-related quality of life will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 index, the EORTC QLQ esophageal cancer module OES18, and the generic health state instrument EuroQol 5D
  - Assessment will occur at baseline, on Day 1 of Cycles 1 through 6, and at the safety follow-up visit
  - Results will be presented using descriptive statistics to show changes from baseline for each treatment arm
- Safety/tolerability will be assessed by monitoring adverse events (AEs) occurring up to 30 days after the last dose of the study drug, monitoring immune-related AEs occurring up to 90 days after the last dose of the study drug, and through physical examinations, vital signs, and electrocardiograms

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