BACKGROUND

Esophageal squamous cell carcinoma (ESCC) is a common cancer type in China that is associated with a poor prognosis.

- At initial diagnosis, half of the patients present with locally advanced disease and many are unfit for surgery.
- An accepted alternative to surgery is concurrent chemoradiotherapy (cCRT).

Tislelizumab is an investigational monoclonal antibody with high affinity and specificity for PD-1.

Tislelizumab was specifically engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent T-cell clearance and potential off-rate, respectively.

Antibodies targeting PD-1 have demonstrated antitumor activity in patients with advanced esophageal cancers.

PD-1 inhibition in combination with chemoradiotherapy has demonstrated synergistic antitumor activity in both preclinical models and in clinical trials.

Tislelizumab is an investigational monoclonal antibody with high affinity and specificity for PD-1.

Tislelizumab was specifically engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent T-cell clearance and potential off-rate, respectively (Figure 1).

METHODS

Overall Design and Study Objectives

- This phase 3, randomized, double-blind, placebo-controlled study (NCT03957590) is being conducted in approximately 316 patients from 35 centers; the study is designed to compare the efficacy of tislelizumab versus placebo in combination with cCRT (Figure 3).

- The primary objective is to compare progression-free survival (PFS) between tislelizumab and placebo in combination with cCRT in the intent-to-treat (ITT) population.

- An Independent Data Monitoring Committee (IDMC) safety review will occur when the first 20 patients (i.e., 10 patients per treatment arm) have had at least 6 weeks of follow-up after the last dose of radiotherapy; monitoring across the study will occur at regular intervals (at least every 6 months) thereafter.

- Secondary objectives include:
  - Evaluation of the overall response rate (ORR) and duration of response (DoR), assessed by the BIRC per RECIST v1.1, in patients treated with tislelizumab or placebo in combination with cCRT in the ITT population.
  - Comparison of the overall survival (OS) between tislelizumab plus cCRT and placebo plus cCRT in the ITT population.
  - Evaluation of the safety/tolerability profile of tislelizumab in combination with cCRT.

Study Population

- Adult patients (aged 18-75 years) with histologically confirmed localized ESCC with an Eastern Cooperative Oncology Group (ECOG) performance status ≤1 for whom cCRT is suitable and surgery is unsuitable/declined are being enrolled.

- Patients who receive prior chemotherapy (no more than three cycles) without radiotherapy can be enrolled.

- Patients will be excluded if:
  - History of surgery for esophageal cancer.
  - History of fistula due to primary tumor invasion, a high risk of fistula, or sign of perforation.
  - Evidence of distant metastases.
  - Intolerable or resistant to protocol-specified chemotherapy, or have received prior radiotherapy or therapies targeting PD-1, PD-L1, PD-L2, or other immune-oncology therapies.

Figure 1. Lack of FcγR Binding May Help Prevent Macrophage-Mediated T-Cell Clearance

Arm A: Tislelizumab + cCRT (2 cycles) or placebo + cCRT (2 cycles)
Arm B: Tislelizumab + cCRT (2 cycles) or placebo + cCRT (2 cycles)

Figure 2. 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 yellow, respectively.

Figure 3. Study Design

Study Assessments and Statistical Analysis

- Tumor assessments will occur at baseline, every 9 weeks for the first 54 weeks, and every 12 weeks thereafter until radiographic disease progression or death.

- The primary endpoint, PFS per BIRC assessment, will be compared between tislelizumab in combination with cCRT (Arm A) and placebo with cCRT (Arm B).

- Response endpoints (e.g., ORR, DoR) will be assessed by the BIRC per RECIST v1.1. OS will be estimated using the Kaplan-Meier method.

- Safety/tolerability of tislelizumab or placebo in combination with cCRT will be assessed by the incidence and severity of treatment-emergent adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 criteria.

Tislelizumab versus Placebo in Combination with Concurrent Chemoradiotherapy in Patients with Localized Esophageal Squamous Cell Carcinoma: A Phase 3 Trial in Progress

Acknowledgments

The authors wish to acknowledge the investigative centers’ staff and study patients, 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 Regina Switzer, PhD, and Elizabeth Herrmans, PhD (OPEN Health Medical Communications, Chicago, IL), and funded by the study sponsor.

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from the author of this poster.