BGB-A317-LBL-007-202: A Phase-2, Randomized, Active-Controlled, Open-Label Study to Evaluate the Efficacy and Safety of LBL-007 (Anti-LAG-3) in Combination With Tislelizumab (TIS; Anti-PD-1) Plus Chemotherapy (chemo) as First-Line (1L) Treatment in Patients With Unresectable Locally Advanced/Metastatic Esophageal Squamous Cell Carcinoma (ESCC)

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Summary

BGB-A317-LBL-007-202 (NCT06010303) is a phase 2 trial evaluating the efficacy and safety of LBL-007 (anti-lymphocyte activation gene-3, anti-LAG-3) in combination with tislelizumab (anti-programmed cell death protein-1, anti-PD-1) and chemotherapy versus tislelizumab and chemotherapy as a first-line treatment in patients with unresectable locally advanced or metastatic esophageal squamous cell carcinoma (ESCC).

The trial is currently being conducted at approximately 46 sites across Asia, including mainland China, Taiwan, South Korea, and Thailand.

Enrollment is ongoing.

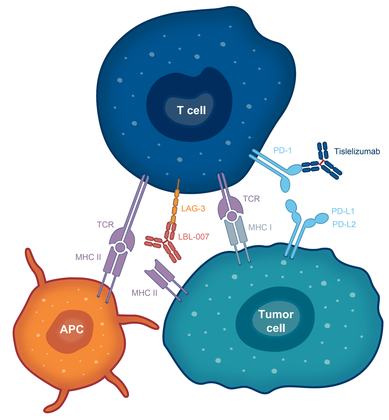
Background

- Esophageal cancer is the seventh most common cancer in terms of incidence and the sixth most common cause of cancer-related deaths worldwide,[1] and approximately 85% of esophageal cancers are esophageal squamous cell carcinoma (ESCC)[2]
- Patients with locally advanced/metastatic ESCC have poor clinical outcomes, with a 5-year survival rate of 5.6% for patients with distant metastases[3]
- First-line treatment with inhibitors of programmed cell death protein-1 (PD-1) combined with platinum-based chemotherapy has become the new standard of care for advanced ESCC[4]
- Despite recent advances, the limited efficacy of these treatments underscores the need for improved treatment outcomes for patients with locally advanced/metastatic ESCC[5]

Investigational Agents

- **LBL-007** is a novel fully humanized anti-lymphocyte activation gene-3 (anti-LAG-3) IgG4 monoclonal antibody (mAb) (**Figure 1**)
  - LAG-3 is an inhibitory immune checkpoint receptor that is frequently upregulated in tumor-infiltrating T cells, and negatively regulates T-cell activation[5]
  - LBL-007 blocks the interaction of LAG-3 with ligands on tumor cells and antigen-presenting cells to restore T-cell activity and enhance anti-tumor immunity
- **Tislelizumab** is a humanized IgG4 anti-PD-1 mAb that blocks the PD-1/programmed death-ligand 1 (PD-L1) immune checkpoint, resulting in T-cell activation (**Figure 1**)
  - Tislelizumab was designed to minimize binding to Fcγ receptor (FcγR) on macrophages, reducing antibody-dependent macrophage-mediated killing of T cells[6]
  - Tislelizumab is approved in China as monotherapy in patients with locally advanced or metastatic ESCC who have disease progression or are intolerant to first-line standard chemotherapy,[7] and in combination with chemotherapy as first-line treatment in patients with unresectable locally advanced, recurrent, or metastatic ESCC.[8]
  - It is approved in the European Union as monotherapy for the treatment of adult patients with unresectable, locally advanced or metastatic ESCC after prior platinum-based chemotherapy.[9]
  - It is approved in the United States as monotherapy for the treatment of adult patients with unresectable or metastatic ESCC after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.[10]

Figure 1. LBL-007 + Tislelizumab Proposed Mechanism of Action



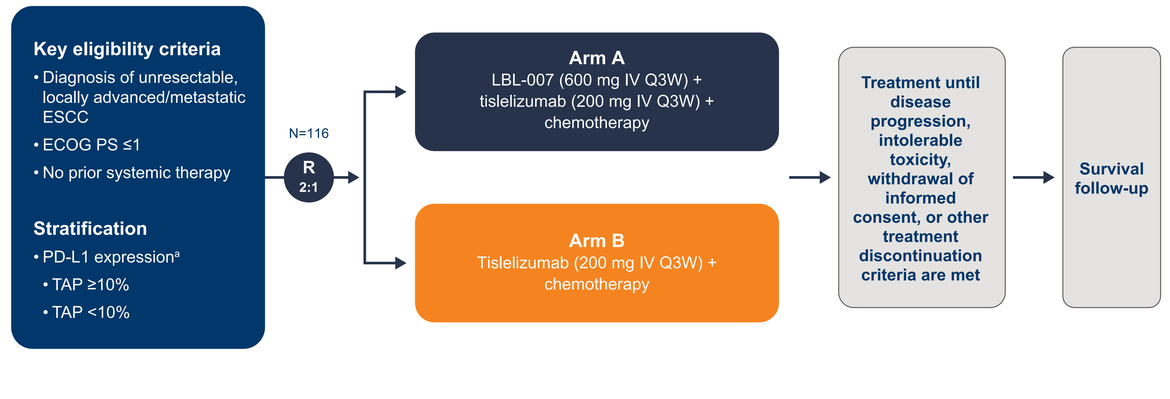
APC, antigen presenting cell; LAG 3, lymphocyte activation gene 3; MHC, major histocompatibility complex; PD 1, programmed cell death protein 1; PD L1, programmed death ligand 1; PD L2, programmed death ligand 2; TCR, T cell receptor.

Methods

Trial Design and Treatments

- BGB-A317-LBL-007-202 (NCT06010303) is a phase 2, randomized, active-controlled, open-label trial evaluating the efficacy and safety of LBL-007 in combination with tislelizumab and chemotherapy versus tislelizumab and chemotherapy as first-line treatment in patients with unresectable locally advanced or metastatic ESCC (**Figure 2**)
- Approximately 116 patients will be randomized 2:1 to:
  - **Arm A:** LBL-007 + tislelizumab + chemotherapy doublet
  - **Arm B:** tislelizumab + chemotherapy doublet
- The chemotherapy doublet will consist of either cisplatin + 5-fluorouracil, or cisplatin + paclitaxel
  - Selection of the chemotherapy regimen will be determined by the investigator before randomization
  - Crossover between treatment arms or between 5-fluorouracil and paclitaxel during the treatment period is not permitted
- Randomization will be stratified by baseline PD-L1 expression status (tumor area positivity score ≥10% or <10%)
- The objective response rate (ORR) for anti-PD-1 combined with chemotherapy is approximately 50% to 65%[11,12]; the ORR in the control arm is considered as 55%, and the ORR difference as 20% (increase from 55% to 75%)

Figure 2. Trial Design



[a]PD-L1 expression will be assessed centrally by the Ventana PD-L1 (SP263) assay.
ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; IV, intravenous; PD-L1, programmed death-ligand 1; Q3W, once every 3 weeks; R, randomization; TAP, tumor area positivity.

Trial Population

Eligibility criteria include the following:

- Aged ≥18 years
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤1
- Pathologically confirmed diagnosis of metastatic or unresectable, locally advanced ESCC
- An archival or newly obtained tumor sample for PD-L1 testing and retrospective biomarker assessment
- At least 1 measurable lesion as defined per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)
- No prior systemic therapy for advanced or metastatic ESCC
- No prior therapies targeting PD-1, PD-L1, PD-L2, LAG-3, or other immune-oncological drugs
- Eligible for treatment with either protocol-specified chemotherapy regimen

Endpoints and Assessments

- The primary endpoint is the ORR, assessed by investigators per RECIST v1.1
- Secondary and exploratory endpoints are listed in **Table 1**
- On-treatment tumor assessments are conducted every 6 weeks for the first 48 weeks, then every 9 weeks
- Safety is assessed through monitoring of the incidence and severity of adverse events (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0), laboratory results, vital signs, ECOG PS changes, and other examinations

Table 1. Trial Endpoints

Primary endpoint	Investigator-assessed ORR per RECIST v1.1
Secondary endpoints	Investigator-assessed PFS, DoR, and DCR per RECIST v1.1
	Incidence and severity of adverse events per CTCAE v5.0
Exploratory endpoints	Overall survival
	Evaluation of predictive, prognostic, and pharmacodynamic biomarkers
	Evaluation of pharmacokinetics of LBL-007 and tislelizumab
	Immunogenic responses to LBL-007 and tislelizumab

CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DoR, duration of response; LAG-3, lymphocyte activation gene-3; ORR, objective response rate; OS, overall survival; PDL-1, programmed death-ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

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Presenter disclosures

Dr Shahidi is employed by BeiGene and may hold stock or other ownership.

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