**BACKGROUND**

- The programmed death 1 (PD-1) pathway is commonly altered in cancer, leading to inhibition of active T-cell–mediated immune surveillance of tumors (Figure 1).
- Pembrolizumab (Merck) is a highly selective, humanized monoclonal anti–PD-1 antibody designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2 (Figure 1).
- Pembrolizumab has demonstrated robust antitumor activity and a favorable safety profile in multiple tumor types and is currently approved in more than 50 countries for one or more advanced malignancies.

**Figure 1. Pembrolizumab and the PD-1 Pathway**

**DESIGN**

- In KEYNOTE-181, ~600 patients will be randomly assigned in a 1:1 ratio to receive 1 of the following (Figure 2):
  - Pembrolizumab 200 mg every 3 weeks (Q3W)
  - Investigator’s choice of 1 of 3 standard chemotherapy regimens, determined before randomization:
    - Paclitaxel 85-150 mg/m² on days 1, 8, and 15 every 4 weeks (Q4W)
    - Docetaxel 75 mg/m² Q3W
    - Irinotecan 180 mg/m² every 2 weeks (Q2W)
- Patients are to be stratified by tumor histology (squamous vs adenocarcinoma) and geographic region (Asia vs rest of world).
- Treatments are to continue until disease progression, unacceptable toxicity, patient withdrawal of consent, investigator decision to withdraw the patient, or completion of 35 cycles (pembrolizumab only)
- Patients in the pembrolizumab and control arms are to have their determined complete response (CR) may consider stopping trial treatment after receiving at least 8 treatments (6 months) of pembrolizumab and having had at least 2 treatments with pembrolizumab beyond initial CR.
- Patients who discontinue pembrolizumab because of CR or those who stop after receiving 35 treatments (>2 years) may be eligible for an additional 17 treatments (>1 year) after experiencing radiographic progressive disease if they meet the criteria for retreatment and the study is ongoing.

**Figure 2. Study Design**

**OBJECTIVES**

**Primary**
- Compare progression-free survival (PFS) per RECIST v1.1 achieved by central imaging vendor review in patients with biomarker-positive (determined by intratumoral gene expression analysis) esophagogastric carcinoma and in all enrolled patients.
- Compare overall survival (OS) in patients with biomarker-positive esophageal carcinoma and in all enrolled patients.

**Secondary**
- Evaluate ORR per RECIST v1.1 assessed by central imaging vendor review in patients with biomarker-positive esophageal carcinoma and in all enrolled patients.
- Evaluate safety and tolerability of pembrolizumab in patients with biomarker-positive esophageal carcinoma and in all enrolled patients.

**Exploratory**
- Evaluate time to progression per RECIST v1.1 assessed by central imaging vendor review in patients with biomarker-positive esophageal cancer and in all enrolled patients.
- Evaluate PFS per immune-related (iRECIST) assessed by central imaging vendor review in patients with biomarker-positive esophageal cancer and in all enrolled patients.
- Explore the relationship between PD-L1 expression by immunohistochemistry and response to treatment.
- Explore the concordance of gene expression profiles in archival compared with newly obtained tumor tissue.
- Explore the relationship between genetic variation and response to treatment.
- Evaluate health-related quality of life assessed using the EORTC QLQ-C30 and EORTC QLQ-GSE18.
- Evaluate health outcome utilities assessed using the EuroQOL EQ-5D questionnaire.

**Analyses and Follow-Up**

- Intratumoral expression levels of select immune-related genes will be analyzed using an analytically validated platform analysis, such as the NANOLuc® nCounter Analysis System.
- Association between an immune-related expression profile and response to pembrolizumab has been established in melanoma and head and neck, bladder, gastric, ovarian, esophageal, and other cancers.
- Tumor imaging will be performed at baseline and every 9 weeks thereafter.
- Imaging will be performed by computed tomography (CT), strongly preferred, or by magnetic resonance imaging when CT is contraindicated or for imaging in the brain.
- Response will be assessed per RECIST v1.1 by central imaging vendor review.
- Adverse events (AEs), including serious AEs and predefined AEs of clinical interest, will be monitored throughout the study and for 30 days thereafter (90 days for serious AEs) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
- After confirming disease progression or start of new antitumor agent therapy, patients will be contacted by telephone every 9 months to monitor survival.

**Status**

- Enrollment in KEYNOTE-181 is ongoing at 160 sites in 31 countries in Asia, Australia, Europe, North America, and South America (Figure 3).

**Figure 3. Countries With Sites of Enrollment for KEYNOTE-181 (shown in green)**

**References**

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Please contact Dr. Doi at tdoi@east.ncc.go.jp for questions or comments.