LEAP-014: AN OPEN-LABEL, RANDOMIZED, PHASE 3 STUDY OF FIRST-LINE LENVATINIB PLUS PEMBROLIZUMAB PLUS CHEMOTHERAPY IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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BACKGROUND

- Recent data from the KEYNOTE-590 study demonstrated the superiority of pembrolizumab + 5-fluorouracil and cisplatin (FP) compared with FP as first-line treatment for locally advanced unresectable or metastatic esophageal cancer or Siewert type 1 gastroesophageal junction cancer[1]
- Prior data also suggest promising antitumor activity of lenvatinib + pembrolizumab in advanced solid tumors[2,3]
- LEAP-014 (NCT04949256) is a randomized, 2-part, open-label, phase 3 study that will evaluate the efficacy and safety of first-line lenvatinib + pembrolizumab + chemotherapy versus pembrolizumab + chemotherapy in patients with metastatic esophageal squamous cell carcinoma (ESCC)

OBJECTIVES

Primary

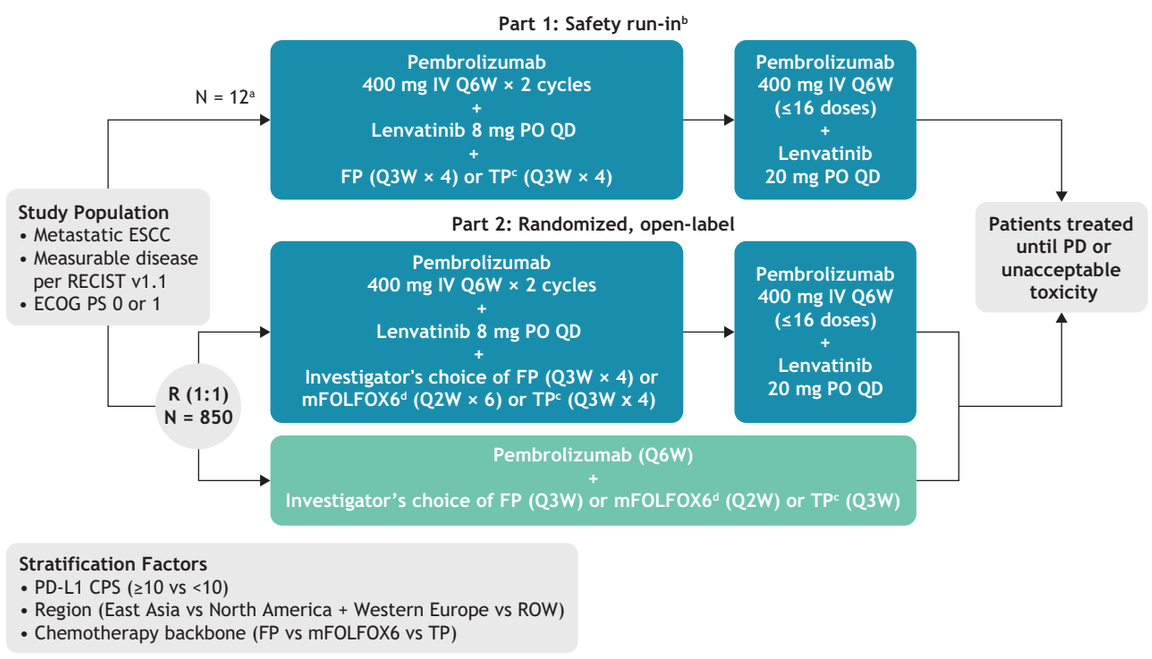
- To evaluate the safety and tolerability of treatment with lenvatinib + pembrolizumab + chemotherapy (part 1)
- To compare overall survival (OS) between lenvatinib + pembrolizumab + chemotherapy and pembrolizumab + chemotherapy (part 2)
- To compare progression-free survival (PFS) by blinded independent central review (BICR) per RECIST v1.1 between lenvatinib + pembrolizumab + chemotherapy and pembrolizumab + chemotherapy (part 2)

Secondary

- To evaluate objective response rate (ORR) by BICR per RECIST v1.1 between lenvatinib + pembrolizumab + chemotherapy and pembrolizumab + chemotherapy (part 2)
- To evaluate duration of response (DOR) by BICR per RECIST v1.1 between lenvatinib + pembrolizumab + chemotherapy and pembrolizumab + chemotherapy (part 2)
- To compare OS and PFS, ORR, and DOR by BICR per RECIST v1.1 between lenvatinib + pembrolizumab + chemotherapy and pembrolizumab + chemotherapy in patients with PD-L1–positive (combined positive score [CPS] ≥10) tumors (part 2)
- To evaluate the safety and tolerability profile of lenvatinib + pembrolizumab + chemotherapy versus that of pembrolizumab + chemotherapy (part 2)
- To compare health-related quality-of-life outcomes using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and Quality of Life Questionnaire-Esophageal Cancer Module between lenvatinib + pembrolizumab + chemotherapy and pembrolizumab + chemotherapy (part 2)

METHODS

Study design and patients



DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; mFOLFOX6, oxaliplatin + 5-FU + leucovorin; PD, progressive disease; PO, by mouth; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; QD, once daily; R, randomization; ROW, rest of world; TP, paclitaxel plus cisplatin.

[a]~6 patients will be treated for induction with a chemotherapy regimen of FP and ~6 patients in China, Hong Kong, Republic of Korea, and Taiwan will be treated for induction with a chemotherapy regimen of TP.
[b]Patients will be closely monitored for 21 days after the first dose of study drug intervention for DLTs.
[c]TP chemotherapy may only be administered to patients in China, Hong Kong, Republic of Korea, and Taiwan. A maximum of 10% of patients enrolled in the study are permitted to receive TP chemotherapy.
[d]Acceptable safety run-in data from LEAP-015 for pembrolizumab + lenvatinib + mFOLFOX6 support the inclusion of mFOLFOX6 in part 2 of the study.

Patient eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • Histologically or cytologically confirmed metastatic ESCC • Measurable disease per RECIST v1.1 as determined by the local site investigator/ radiology assessment • ECOG PS of 0 or 1 assessed ≤3 days before randomization • Tumor tissue sample for PD-L1 analysis before randomization • Adequately controlled BP with or without antihypertensive medications • Adequate organ function	• Previous therapy for locally advanced unresectable or metastatic esophageal cancer • Locally advanced esophageal carcinoma • Metastatic adenocarcinoma of the esophagus • Direct invasion into adjacent organs, such as the aorta or trachea (T4b disease) • Radiographic evidence of >90° encasement of a major blood vessel or of intratumoral cavitation • Perforation risks or significant GI bleeding • Uncontrollable pleural effusion, pericardial effusion, or ascites necessitating frequent drainage or medical intervention • GI obstruction, poor oral intake, or difficulty taking oral medication • Major surgery, open biopsy, or significant traumatic injury ≤3 weeks before the first dose of study drug • Prior radiotherapy ≤2 weeks before start of study drug • Prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent or an agent directed to another TCR • Prior therapy with anti–VEGF TKI or anti–VEGF mAb • Known active CNS metastases and/or carcinomatous meningitis • Known history of HIV, hepatitis B infection, or hepatitis C infection • Clinically significant cardiovascular disease ≤12 months from first dose of study drug • Current pneumonitis/interstitial lung disease or history of (noninfectious) pneumonitis/interstitial lung disease that necessitated use of steroids • Active autoimmune disease that has necessitated systemic treatment in the past 2 years • Active infection necessitating systemic therapy • Poorly controlled diarrhea • Weight loss of >20% in the past 3 months

BP, blood pressure; CNS, central nervous system; GI, gastrointestinal; HIV, human immunodeficiency virus; mAb, monoclonal antibody; TCR, T-cell antigen receptor; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Assessments

- In part 1, DLTs will be assessed for 21 days after the first dose of study drug in cycle 1
  - If ≥3 DLTs occur during the FP safety run-in period, enrollment for part 2 may be delayed to further evaluate safety data and consider study design changes

Dose-limiting toxicities

Toxicity category	NCI CTCAE v5.0 toxicity grade
Hematologic	• Grade 4 neutropenia lasting for ≥7 days • Grade 3 or 4 febrile neutropenia[a] • Grade 3 thrombocytopenia with bleeding or grade 4 thrombocytopenia • Grade 4 anemia
Other nonhematologic toxicity	• Any other grade 4 or 5 toxicity • Grade 3 toxicity lasting >3 days, excluding – Nausea, vomiting, and diarrhea controlled by medical intervention within 72 hours – Grade 3 rash in the absence of desquamation and with no mucosal involvement, no need for steroids, and resolution to grade 1 by the next scheduled dose of pembrolizumab • Grade 3 hypertension that cannot be controlled by medication • Grade ≥3 GI perforation • Grade ≥3 wound dehiscence necessitating medical or surgical intervention • Any-grade thromboembolic event
	• Any grade 3 nonhematologic laboratory value if – Medical intervention is necessary to treat the patient – The abnormality leads to hospitalization

ANC, absolute neutrophil count; CTCAE v5.0, Common Terminology Criteria for Adverse Events, version 5.0; NCI, National Cancer Institute.

[a]Febrile neutropenia grade 3 (defined as ANC <1000/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour) or grade 4 (defined as ANC <1000/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour, with life-threatening consequences and urgent intervention necessary).

- In part 2, tumor imaging will be conducted by computed tomography (CT; preferred) or magnetic resonance imaging of the abdomen and pelvis and CT of the chest at baseline, Q6W from the date of randomization for 1 year, then every 9 weeks thereafter
- Tumor response and disease progression will be assessed by BICR per RECIST v1.1
- Electronic patient-reported outcome (ePRO) questionnaires will be administered Q6W
- Adverse events (AEs) graded per NCI CTCAE v5.0 will be monitored continuously throughout the study up to 30 days after the last dose (up to 90 days for serious AEs)

Key efficacy analyses (part 2)[a]

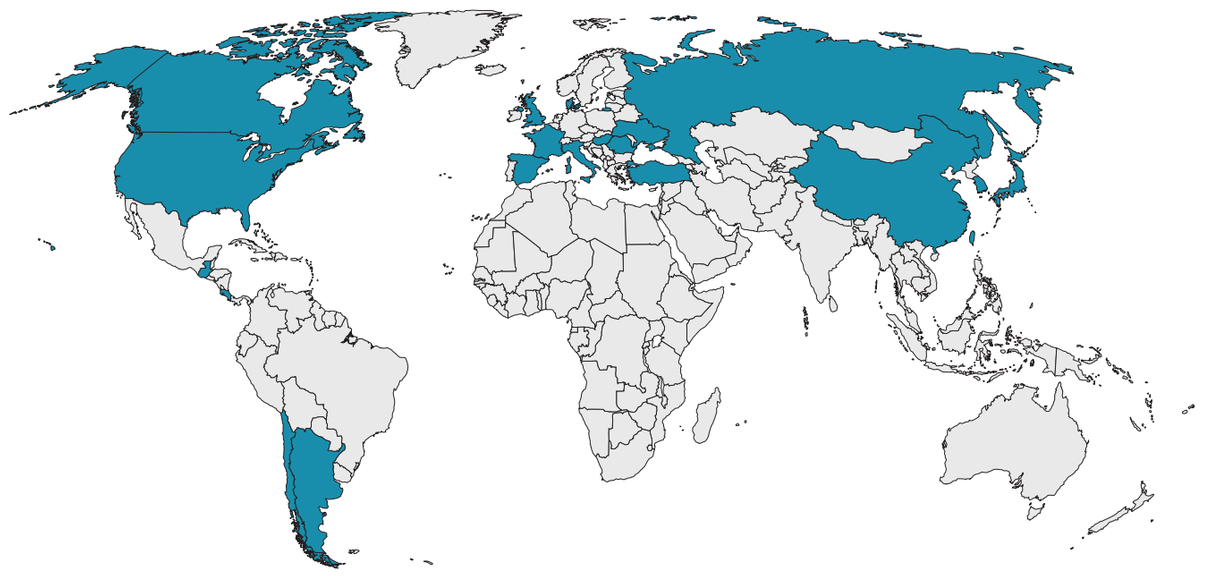
End point	Statistical method
Coprimary end points	
OS	Testing: stratified log-rank test Estimation: stratified Cox proportional hazards model with the Efron method of tie handling
PFS per RECIST v1.1 by BICR	
Key secondary end points	
ORR per RECIST v1.1 by BICR	Testing: Miettinen and Nurminen method Estimation: Miettinen and Nurminen method with strata weighted by sample size

[a]Evaluated in the intention-to-treat population, which comprises all randomly assigned patients.

- In part 1, safety will be assessed in all patients who received ≥1 dose of study drug and will be reported as descriptive summary statistics
- In part 2, safety will be assessed in all randomly assigned patients who received ≥1 dose of study drug and will be reported as descriptive summary statistics
  - For tier 2 parameters, 95% CIs will be provided for between-treatment differences in the percentage of patients who experienced events, determined using the Miettinen and Nurminen method
- In part 2, ePROs will be assessed in all randomly assigned patients who have received ≥1 dose of study drug and completed ≥1 ePRO assessment

STATUS

Sites of enrollment (blue)



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