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LEAP-012: a randomized, double-blind, phase 3 study of pembrolizumab plus lenvatinib in combination with transarterial chemoembolization in patients with intermediate-stage hepatocellular carcinoma not amenable to curative treatment

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INTRODUCTION

- Hepatocellular carcinoma (HCC) is a common cause of death globally, and limited treatment options are available for patients with incurable nonmetastatic disease[1]
- A recommended treatment for patients with localized disease (ie, no macrovascular disease) who are ineligible for curative treatment is locoregional therapy with transarterial chemoembolization (TACE)[2]
- Lenvatinib, a potent multikinase inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor α, RET, and KIT, is approved as a first-line treatment option for patients with unresectable HCC[3]
- Pembrolizumab, a humanized monoclonal antibody against PD-1, is approved as a second-line treatment option for advanced HCC[4]
- In a phase 1b trial (NCT03006926) of patients with unresectable intermediate-stage HCC not amenable to TACE, lenvatinib + pembrolizumab demonstrated promising antitumor activity and a manageable safety profile[5]
  - Objective responses per Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1 were achieved in 36 of 100 (36%) patients with unresectable HCC receiving lenvatinib + pembrolizumab and per modified RECIST (mRECIST; independent imaging review) in 46 of 100 (46%) patients

AIM

LEAP-012 (NCT04246177) is a randomized, double-blind, phase 3 trial investigating lenvatinib + pembrolizumab + TACE compared with placebo + TACE in patients with incurable nonmetastatic HCC

METHOD

Objectives

Dual Primary

- To compare the following for lenvatinib + pembrolizumab + TACE and placebo + TACE in patients with intermediate-stage HCC
  - Progression-free survival (PFS) and overall survival (OS)
    - PFS will be assessed by blinded independent central review (BICR) per RECIST v1.1

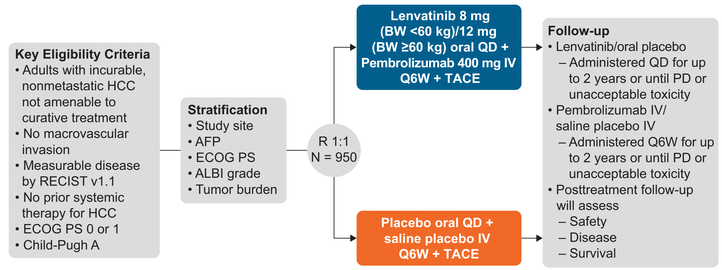
Secondary and Exploratory

- To compare the following for lenvatinib + pembrolizumab + TACE and placebo + TACE in patients with intermediate-stage HCC
  - PFS per mRECIST for HCC assessed by BICR
  - Objective response rate (ORR), disease control rate (DCR), duration of response (DOR), and time to progression (TTP) assessed by BICR per mRECIST and RECIST v1.1
  - Safety and tolerability
  - PFS, ORR, DCR, DOR, and TTP assessed by the investigator per RECIST v1.1
  - Biomarker analyses
  - Patient-reported outcomes (PROs; European Organisation for Research and Treatment of Cancer [EORTC] Questionnaire Core 30 [QLQ-C30], EORTC Quality of Life Questionnaire Hepatocellular Cancer [QLQ-HCC18], and EuroQol 5-dimension, 5-level questionnaire [EQ-5D-5L])

Study Design

- Approximately 950 patients will be randomly assigned 1:1 to receive lenvatinib + pembrolizumab + TACE or placebo + placebo + TACE (**Figure 1**)

Figure 1. Study Design



AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BW, body weight; cTACE, conventional TACE; DEB-TACE, drug-eluting bead TACE; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; PD, progressive disease; QD, once-daily; Q6W, every 6 weeks; R, randomization; TACE, transarterial chemoembolization..

Patient Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years • HCC confirmed by radiology, histology, or cytology • HCC localized to the liver without portal vein thrombosis and not amenable to curative treatment • ≥1 measurable HCC lesion based on RECIST v1.1, confirmed by BICR • ECOG PS 0 or 1 • Amenable to TACE + chemotherapy agent prespecified at the study site: all lesions treatable with TACE • Adequate organ function	• Extrahepatic disease • Eligible for liver transplantation • Esophageal or gastric variceal bleeding in the past 6 months; or clinically diagnosed hepatic encephalopathy in the past 6 months unresponsive to therapy; or uncontrolled, clinically apparent ascites • Past systemic chemotherapy, including anti–VEGF therapy, or any systemic investigational anticancer agents for HCC • Past therapy with an anti–PD-1, anti-PD-L1, or anti–PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, or CD137) • Past locoregional therapy to liver, including TACE, transarterial embolization, TARE, hepatic arterial infusion, or radiation. Past use of ablation and resection permitted if it occurred >4 weeks before first dose of study intervention

CTLA-4, cytotoxic T-lymphocyte–associated protein 4; TARE, transarterial radioembolization with yttrium-90.

Assessments and Follow-Up

- Responses will be assessed by computed tomography or magnetic resonance imaging every 9 weeks per RECIST v1.1 by BICR until disease progression, start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first
- Adverse events (AEs) will be monitored throughout the study and up to 90 days (120 days for serious AEs) after the last dose or 30 days after the last dose if the participant initiates new anticancer therapy, whichever is sooner during the follow-up period, and will be graded according to the Common Terminology Criteria for Adverse Events, v5.0
- PROs (QLQ-C30, QLQ-HCC18, and EQ-5D-5L) will be collected on day 1 of cycles 1, 3, and 5 and then on day 1 of every other cycle up to cycle 35

Analyses

Efficacy

- Efficacy end points are based on the intention-to-treat population, which includes all randomly assigned participants analyzed according to randomized treatment group; DOR is based on the population of responders
  - The nonparametric Kaplan-Meier method will be used to estimate PFS and OS, the hypothesis of treatment difference in PFS and OS will be tested by a rerandomization test based on the stratified log-rank test, and a stratified Cox proportional hazards model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference
  - The stratified Miettinen and Nurminen method with weights proportional to the stratum size will be used for comparison of ORRs between the treatment arms

Safety

- Safety analyses will be conducted in the as-treated population (all randomly assigned participants who received ≥1 dose of study drug) according to the study intervention received

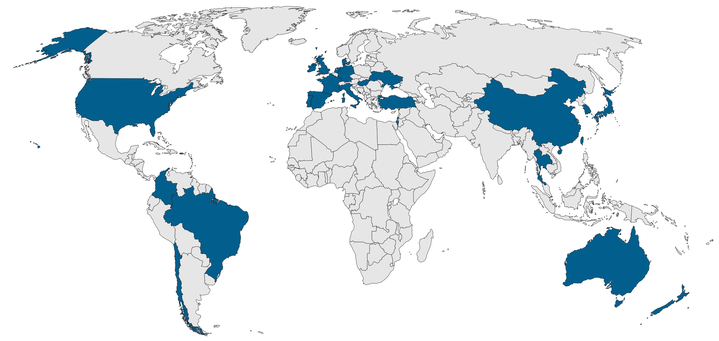
Patient-Reported Outcomes

- Analyses will be based on a PRO full analysis set population that includes participants who received ≥1 dose of study drug and completed ≥1 PRO assessment

STATUS

- Recruitment began in April 2020 at 165 sites in 24 countries and 1 territory (**Figure 2**)
- Countries (and 1 territory) participating in LEAP-012 are Australia, Brazil, Chile, China, Colombia, Denmark, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Portugal, Puerto Rico, South Korea, Spain, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, and United States

Figure 2. Countries Participating in LEAP-012 (in blue)



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