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08

Phase 3 KEYNOTE-937: adjuvant pembrolizumab versus placebo in patients with hepatocellular carcinoma and complete radiologic response after surgical resection or local ablation

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INTRODUCTION

- Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide[1,2]
  - Global burden of HCC is expected to reach 22 million by 2038[3]
- Surgical resection and local ablation are potentially curative options for patients with HCC[4]; however, tumor recurrence is not uncommon, with 5-year recurrence rates of 50%-80%[5,6]
- The lack of a standard-of-care adjuvant therapy for HCC highlights an urgent therapeutic need to
  - Prevent disease recurrence
  - Increase survival in the postresection/postablation setting
- Pembrolizumab, a potent humanized immunoglobulin G4 monoclonal antibody that blocks the interaction between the PD-1 receptor and its ligands, PD-L1 and PD-L2, is approved for the treatment of patients with HCC who were previously treated with sorafenib[7]
  - KEYNOTE-224 (phase 2; NCT02702414): patients with advanced HCC previously treated with sorafenib[8]
    - Manageable safety
    - Meaningful clinical efficacy: objective response rate (ORR), 17%; median progression-free survival (PFS), 4.9 months; median overall survival (OS), 12.9 months
  - KEYNOTE-240 (phase 3; NCT02702401): patients with previously treated, advanced HCC[9]
    - Improved OS (hazard ratio [HR], 0.78; 1-sided *P* = 0.0238) and PFS (HR, 0.78; 1-sided *P* = 0.0209) compared with placebo
      - Differences did not meet statistical significance per prespecified criteria
    - Improved ORR (16.9%; 95% CI, 12.7-21.8) compared with placebo (2.2%; 95% CI, 0.5-6.4) (nominal 1-sided *P* = 0.00001)
    - Durable responses (median duration of response [DOR], 13.8 months [range, 1.5-23.6+])
- No direct evidence of PD-1 inhibition benefit in adjuvant HCC is available; data from other indications suggest a favorable benefit-risk profile[10,11]
  - KEYNOTE-054 (phase 3; NCT02362594): patients with resected stage III melanoma
    - Adjuvant pembrolizumab prolonged recurrence-free survival (RFS) compared with adjuvant placebo (HR for recurrence or death, 0.57; 98.4% CI, 0.43-0.74; *P* < 0.001)[10]
  - Pembrolizumab maintained health-related quality of life (QoL) compared with placebo[12]

AIM

- KEYNOTE-937 (NCT03867084) is phase 3 study being conducted to evaluate the safety and efficacy of pembrolizumab compared with placebo as adjuvant therapy in patients with HCC and radiologic complete response (CR) after surgical resection or local ablation

METHOD

Objectives

Primary

- To compare the following between pembrolizumab and placebo
  - RFS by blinded independent central review (BICR)
  - OS

Key Secondary

- To compare the following between pembrolizumab and placebo
  - Safety and tolerability (adverse events [AEs], discontinuation because of AEs)
  - Time to deterioration and change from baseline using global health status/QoL scales (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 [EORTC QLQ-C30], European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-HCC18 [EORTC QLQ-HCC18])
  - Characterize health utilities using EuroQol 5-dimension, 5-level questionnaire (EQ-5D-5L)

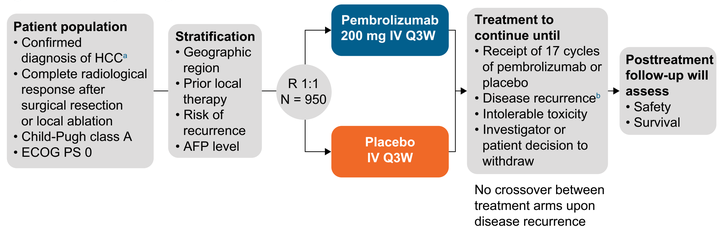
Exploratory

- To compare the following between pembrolizumab and placebo
  - Time to distant metastasis-free survival and time to recurrence assessed by BICR
  - Molecular (genomic, metabolic, and/or proteomic) biomarkers

Study Design

- KEYNOTE-937 is a randomized, placebo-controlled, double-blind, phase 3 trial (Figure 1)

Figure 1. Study Design



AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; Q3W, every 3 weeks; R, randomization.

[a]Diagnosis to be documented radiologically by AASLD criteria[13] (patients undergoing ablation without a previous biopsy) and/or pathologically (patients undergoing ablation and not meeting AASLD criteria and patients undergoing surgical resection).
[b]Investigator assessed, verified by BICR.

Patient Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years • Confirmed diagnosis of HCC[a] • Complete radiologic response after surgical resection and intermediate, high, or very high risk of recurrence per AJCC 8th edition[14] and pathology report • Complete radiologic response after local ablation and intermediate, high, or very high risk of recurrence[b] • No radiologic evidence of disease before enrollment (investigator assessed; verified by BICR at screening) • ECOG PS 0 ≤7 days before first study dose • Child-Pugh class A liver score ≤7 days before first study dose • AFP concentration <400 ng/mL ≤28 days before first study dose • May have past or ongoing HCV infection[c] • May have controlled HBV if prespecified criteria met • Adequate organ function	• Additional malignancy: progressing or necessitated antineoplastic treatment or surgery (preceding 3 years) • Esophageal or variceal bleeding (preceding 6 months) • Clinically apparent ascites by physical examination • Clinically diagnosed hepatic encephalopathy (preceding 6 months) • Received local therapy to liver ablation[d] • Pneumonitis or history of (noninfectious) pneumonitis necessitating steroid therapy • Active infection necessitating systemic therapy • Known history of HIV infection • Systemic chemotherapy or investigational anticancer agents for HCC – Or previous therapy with anti–PD-1, anti–PD-L1, or anti–PD-L2 agent – Or agent directed to another stimulatory or coinhibitory T-cell receptor • Active autoimmune disease with systemic treatment (past 2 years) • Allogeneic tissue/solid organ transplant • Pregnant or breastfeeding

AJCC, American Joint Commission on Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

[a]Diagnosis to be documented radiologically by AASLD criteria[13] (patients undergoing ablation without a prior biopsy) and/or pathologically (patients undergoing ablation and not meeting AASLD criteria and patients undergoing surgical resection).
[b]Intermediate risk for solitary tumor ≥2 cm and ≤3 cm. High risk for 2-4 tumors all ≤3 cm or one solitary tumor >3 cm and ≤5 cm. Very high risk for 2-4 tumors with at least one >3 cm and all ≤5 cm. If screening AFP ≥100 ng/mL, intermediate upstaged to high risk.
[c]Must have completed treatment ≥1 month before cycle 1 day 1.
[d]Other than radiofreqency or microwave ablation.

Assessments and Follow-Up

- Tumor imaging: until BICR-verified intrahepatic/extrahepatic disease recurrence on study and at treatment discontinuation
- Posttreatment imaging: until investigator-documented, BICR-verified extrahepatic disease recurrence
  - Tumor imaging continued as if patients were still on study if they discontinued for reasons other than BICR-verified extrahepatic disease
- AEs per Common Terminology Criteria for Adverse Events, v4.0[15] (randomization to ≤30 days after last study dose)
- Serious AEs: 90 days after last study dose; 30 days if new cancer therapy initiated
- EuroQol EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-HCC18 questionnaires
  - Questionnaires were completed electronically in the order mentioned above at regular intervals during treatment, at the end of treatment, at the 30-day safety follow-up, and at posttreatment imaging visits
- Blood and tumor samples collected for biomarker analysis

Analyses

Efficacy

- Efficacy analysis was conducted on the intention-to-treat population (defined as all randomly assigned patients)
- RFS and OS were estimated separately for each treatment group using the nonparametric Kaplan-Meier method; differences were tested using the stratified log-rank test and a stratified Cox proportional hazards model with the Efron method of tie handling
  - HRs and 95% CIs will be reported

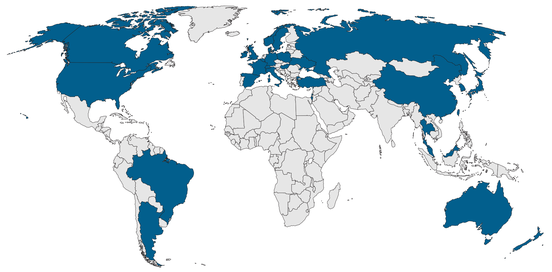
Safety

- Safety and tolerability analyses were conducted on the as-treated population (defined as all randomly assigned patients who received ≥1 dose of study medication)
  - Clinical review was performed on all relevant parameters, including AEs, laboratory tests, vital signs, and electrocardiography measurements

STATUS

- Enrollment is underway in 29 countries in Asia, Australia, Europe, North America, and South America (Figure 2)

Figure 2. Countries With Sites of Enrollment for KEYNOTE-937 (in blue)



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