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Pembrolizumab in combination with gemcitabine and cisplatin for the treatment of advanced biliary tract cancer: phase 3 KEYNOTE-966 trial in progress

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INTRODUCTION

- Biliary tract cancer (BTC), which includes intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer, is an aggressive malignancy with limited treatment options[1]
  - Most patients present with advanced or unresectable disease
- The current first-line standard-of-care treatment for metastatic and unresectable BTC is chemotherapy with gemcitabine + cisplatin, as well as S-1 therapy in Japan[1,2]
  - The prognosis for patients with unresectable, recurrent, or metastatic BTC is poor; median survival is approximately 12 months after chemotherapy[3]
- Pembrolizumab is a potent, high-affinity PD-1 inhibitor[4]
  - Pembrolizumab is a treatment option for patients with unresectable or metastatic, microsatellite instability–high or mismatch repair deficient tumors, including BTCs, although data are limited in this setting[1,4]
- The phase 2 KEYNOTE-158 study showed preliminary evidence suggestive of durable antitumor activity with pembrolizumab monotherapy in patients with advanced BTC who experienced disease progression on or who were not candidates for standard therapy[5]
  - The objective response rate (ORR) was 5.8% (6/104; all partial responses), and the median duration of response (DOR) was not reached (range, 6.2-26.6+ months)
  - Toxicity was manageable
- The efficacy and safety of adding pembrolizumab to chemotherapy has been demonstrated in other tumor types, such as metastatic non–small cell lung cancer and incurable locally recurrent or metastatic head and neck squamous cell carcinoma[6-8]

AIM

- KEYNOTE-966 (NCT04003636) is an international, randomized, double-blind, phase 3 study that will evaluate pembrolizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin in patients with metastatic and/or unresectable locally advanced BTC

METHOD

Objectives

Dual Primary

- To compare progression-free survival (PFS) assessed by blinded independent central review (BICR) per RECIST v1.1 and overall survival (OS) for pembrolizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin

Secondary

- To evaluate the following for pembrolizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin
  - ORR assessed by BICR per RECIST v1.1
  - DOR assessed by BICR per RECIST v1.1
  - Safety and tolerability

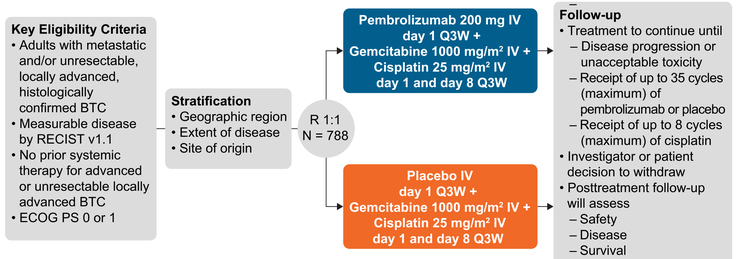
Exploratory

- To evaluate the following for pembrolizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin
  - Disease control rate assessed by BICR per RECIST v1.1
  - Health-related quality of life (EuroQol 5-dimension, 5-level questionnaire [EQ-5D-5L], European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 [QLQ-C30], and EORTC Quality of Life Questionnaire Cholangiocarcinoma and Gallbladder Cancer [QLQ-BIL21])
  - Molecular and genetic biomarkers

Study Design and Patients

- Approximately 788 patients will be randomly assigned 1:1 to receive pembrolizumab or placebo in combination with gemcitabine + cisplatin (**Figure 1**)

Figure 1. Study Design



ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomization.

Patient Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years • Histologically confirmed advanced (metastatic) and/or unresectable (locally advanced) BTC (intrahepatic or extrahepatic cholangiocarcinoma or gallbladder cancer) • Measurable disease based on RECIST v1.1, as determined by the site investigator • Past or ongoing HCV infection or controlled HBV infection in participants who meet protocol-specified criteria • ECOG PS 0 or 1 • Adequate organ function • Tumor tissue for biomarker analysis	• Past systemic therapy for advanced (metastatic) or unresectable (locally advanced) BTC (intrahepatic or extrahepatic cholangiocarcinoma or gallbladder cancer) • Ampullary cancer, small cell cancer, neuroendocrine tumors, lymphoma, sarcoma, and/or mucinous cystic neoplasms • Active autoimmune disease necessitating systemic treatment in the past 2 years • Past major surgery with ongoing grade >1 toxicity and/or complications • 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, CD137)

CTLA-4, cytotoxic T-lymphocyte–associated protein 4; HBV, hepatitis B virus; HCV, hepatitis C virus.

Assessments and Follow-Up

- Responses will be assessed by imaging of the chest, abdomen, and pelvis every 6 weeks through week 54 and every 12 weeks thereafter as assessed by BICR per RECIST v1.1 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 for 30 days during the follow-up period (90 days for serious AEs) and will be graded according to the Common Terminology Criteria for Adverse Events, v5.0
- Patient-reported outcomes (EQ-5D-5L, QLQ-C30, and QLQ-BIL21) will be collected before AE evaluation, disease status notification, and dosing on day 1 of each treatment cycle for the first 10 treatment cycles, every 2 cycles thereafter to cycle 18, at the end of treatment, and at the 30-day safety follow-up visit

Analyses

Efficacy

- Efficacy end points (except DOR) 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 responder population (ie, those who achieve complete or partial response)
  - The nonparametric Kaplan-Meier method will be used to estimate PFS and OS, 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 will be used for comparison of ORRs between treatment arms, with the same stratification factors for randomization applied in the analysis

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

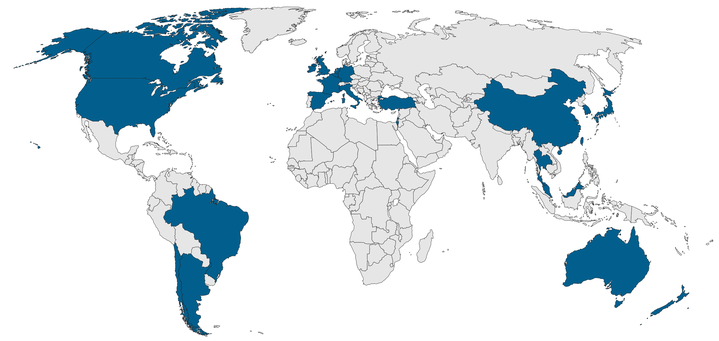
Patient-Reported Outcomes

- Analyses will be based on a quality of life–related full analysis set population that includes all randomly assigned participants who received ≥1 dose of study drug and completed ≥1 PRO assessment

STATUS

- Countries participating in KEYNOTE-966 are Argentina, Australia, Belgium, Brazil, Canada, Chile, China, France, Germany, Hong Kong, Ireland, Israel, Italy, Japan, Malaysia, Netherlands, New Zealand, South Korea, Spain, Taiwan, Thailand, Turkey, United Kingdom, and United States (**Figure 2**)

Figure 2. Countries Participating in KEYNOTE-966 (in blue)



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