First-line pembrolizumab plus chemotherapy may benefit patients with advanced biliary tract cancers

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The addition of pembrolizumab (Keytruda) to gemcitabine and cisplatin improved overall survival in patients with untreated metastatic or

unresectable biliary tract cancer, according to results from the phase III KEYNOTE-966 clinical trial, which were presented at the AACR Annual Meeting 2023, held April 14–19. The research is also published in *The Lancet*.

Biliary tract cancers are rare malignancies arising in the gallbladder, bile ducts, and the ampulla of Vater and are associated with poor patient outcomes.

"The median overall survival for people with advanced biliary tract cancers treated with the standard chemotherapy regimen of gemcitabine plus cisplatin is less than a year, and treatment options after progression are limited," said presenting author Robin "Katie" Kelley, MD, a professor of clinical medicine at the Helen Diller Family Comprehensive Cancer Center at University of California, San Francisco.

"There is an urgent need for more effective treatments and combinations for biliary tract cancers," she added.

Kelley and colleagues conducted the multinational KEYNOTE-966 phase III clinical trial to determine whether adding the immune checkpoint inhibitor pembrolizumab to standard chemotherapy would impact survival outcomes for patients with advanced stages of biliary tract cancer.

The trial enrolled 1,069 patients with metastatic or unresectable biliary tract cancers who had not received prior systemic therapy for their cancers. Patients were randomly assigned to receive either pembrolizumab (533 patients) or placebo (536 patients) in combination with gemcitabine and cisplatin. The primary endpoint was overall survival. Secondary endpoints were progression-free survival, objective response rate, and duration of response.

Patients in the pembrolizumab arm had a median overall survival of 12.7 months, as compared with 10.9 months among those in the placebo arm. After a median follow-up of 25.6 months, patients treated with pembrolizumab had a 17% lower risk of death than patients who received chemotherapy alone.

While objective response rates did not differ between the arms, patients in the pembrolizumab arm experienced a longer duration of response (median 9.7 months vs. 6.9 months); however, Kelley noted that the prolonged duration of response should be considered descriptive, as comparative statistical analyses were not performed. In addition, patients treated with pembrolizumab had a 14% lower risk of disease progression or death after a median follow-up of 13.6 months, but this difference did not meet the study's prespecified requirements for statistical significance. Median progression-free survival was 6.5 months and 5.6 months for the pembrolizumab and placebo arms, respectively.

Grade 3–5 adverse events were observed at similar rates between treatment arms (85.3% in the pembrolizumab arm vs. 84.1% in the placebo arm). Among patients who received pembrolizumab plus chemotherapy, 1.5% experienced a drug-related grade 5 adverse event, compared with 0.6% of those treated with placebo and chemotherapy. Potentially immune-mediated events and infusion reactions were observed in 22.1% of the pembrolizumab arm and 12.9% of the placebo arm.

"These data reinforce that patients with advanced biliary tract cancer may have durable immune responses and prolonged survival when an immune checkpoint inhibitor, such as pembrolizumab, is combined with first-line gemcitabine plus cisplatin chemotherapy," said Kelley. "The durability of responses and proportion of patients with prolonged survival are really meaningful in this difficult-to-treat family of cancers."

In September 2022, another immune checkpoint inhibitor, durvalumab (Imfinzi), was approved in combination with chemotherapy as a first-line therapy for patients with advanced biliary tract cancers. The approval was based on results from the TOPAZ-1 clinical trial.

"The KEYNOTE-966 and the TOPAZ-1 studies both mark significant advances in the field and together validate the role of immune checkpoint inhibition in combination with chemotherapy as first-line therapy to improve survival and achieve prolonged durations of response for patients with advanced stages of biliary tract cancers," said Kelley, adding that the KEYNOTE-966 trial included a larger sample size with more patients enrolled from non-Asian countries.

"Another key difference between the two studies was that patients in the TOPAZ-1 trial discontinued chemotherapy after six months but continued durvalumab or placebo as maintenance therapy, while patients in the KEYNOTE-966 trial were permitted to continue gemcitabine with pembrolizumab or placebo beyond six months, which reflects different treatment practices in many parts of the world," Kelley added.

A limitation of the KEYNOTE-966 study is that patients with intrahepatic bile duct cancers were overrepresented in the study population compared with the incidence of the disease in the general population, resulting in smaller sample sizes of patients with extrahepatic and gall bladder sites of origin.

More information: Robin Kate Kelley et al, Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial, *The Lancet* (2023). DOI: 10.1016/S0140-6736(23)00727-4