Durvalumab Plus Chemotherapy: A New First-Line Option for Advanced Biliary Tract Cancer?

Written by The Life Science Feed Editorial Team · Published 27 August 2026 · Edited by Mara Voss

For over a decade, the standard first-line treatment for advanced biliary tract cancer has remained unchanged, leaving patients with a poor prognosis. New research from the TOPAZ-1 trial investigates whether adding the immune checkpoint inhibitor durvalumab to standard chemotherapy can improve outcomes for these patients.

KEY TAKEAWAYS

- The Pivot: Durvalumab combined with gemcitabine and cisplatin significantly improved overall survival compared to chemotherapy alone in advanced biliary tract cancer.
- The Data: The 24-month overall survival rate was 24.9% with durvalumab plus chemotherapy versus 10.4% with placebo plus chemotherapy.
- The Action: This combination therapy represents a potential new first-line treatment option for patients with unresectable or metastatic biliary tract cancer.

The Challenge of Advanced Biliary Tract Cancer

Biliary tract cancer (BTC) is a group of aggressive cancers originating in the bile ducts, gallbladder, or ampulla of Vater. Patients diagnosed with advanced, unresectable, or metastatic BTC face a particularly grim prognosis, with limited treatment options. For more than 10 years, the first-line standard of care has been a combination of gemcitabine and cisplatin chemotherapy. Despite its established role, the survival benefits offered by this regimen are modest, highlighting an urgent need for more effective therapies to improve patient outcomes and extend survival in this challenging disease setting.

Investigating Immunotherapy in BTC: The TOPAZ-1 Study Design

The TOPAZ-1 trial was a global, double-blind, placebo-controlled, phase 3 study designed to evaluate the efficacy and safety of adding durvalumab, a PD-L1 immune checkpoint inhibitor, to standard gemcitabine and cisplatin chemotherapy. The study enrolled patients with previously untreated, unresectable or metastatic BTC, or recurrent disease. Participants were randomly assigned in a 1:1 ratio to receive either durvalumab or placebo, in combination with gemcitabine and cisplatin, for up to eight cycles. Following the chemotherapy phase, patients continued to receive durvalumab or placebo monotherapy until disease progression or unacceptable toxicity. The primary objective of the study was to assess overall survival (OS), with key secondary endpoints including progression-free survival (PFS), objective response rate (ORR), and safety. The trial was registered on ClinicalTrials.gov (NCT03875235) and funded by AstraZeneca1.

Durvalumab Significantly Extends Overall Survival

The TOPAZ-1 trial randomized 685 patients, with 341 assigned to the durvalumab group and 344 to the placebo group. At the data cutoff, 198 patients (58.1%) in the durvalumab group and 226 patients (65.7%) in the placebo group had died. The study found that the addition of durvalumab to chemotherapy significantly improved overall survival compared to chemotherapy alone. The hazard ratio (HR) for overall survival was 0.80 (95% confidence interval [CI], 0.66 to 0.97; P=0.021), indicating a 20% reduction in the risk of death with the durvalumab combination. The estimated 24-month overall survival rate was 24.9% (95% CI, 17.9 to 32.5) for the durvalumab group, more than double the 10.4% (95% CI, 4.7 to 18.8) observed in the placebo group1.

Improvements in Progression-Free Survival and Response Rates

Beyond overall survival, the durvalumab combination also demonstrated significant improvements in prespecified secondary endpoints. The hazard ratio for progression-free survival was 0.75 (95% CI, 0.63 to 0.89; P=0.001), suggesting a 25% reduction in the risk of disease progression or death. The objective response rate (ORR) was also higher in the durvalumab arm, with 26.7% of patients achieving an objective response compared to 18.7% in the placebo arm. Importantly, the safety profiles of both treatment groups were similar. The incidences of grade 3 or 4 adverse events were 75.7% in the durvalumab group and 77.8% in the placebo group, indicating that the addition of durvalumab did not substantially increase the rate of severe adverse events beyond that seen with chemotherapy alone1.

Clinical Implications for Practice

The findings from the TOPAZ-1 trial suggest that durvalumab in combination with gemcitabine and cisplatin represents a meaningful advance in the first-line treatment of advanced biliary tract cancer. The significant improvement in overall survival, coupled with a manageable safety profile, offers a new therapeutic strategy for a patient population with historically limited options. This study provides a strong evidence base for incorporating immunotherapy into the initial treatment paradigm for BTC.

Why this matters for clinical practice today: For clinicians managing patients with advanced biliary tract cancer, these results offer a much-needed new first-line option. The fact that durvalumab significantly extends overall survival without a substantial increase in severe adverse events compared to chemotherapy alone is a critical consideration. This data supports a shift in standard practice, potentially allowing more patients to benefit from a combination therapy that includes an immune checkpoint inhibitor, thereby improving long-term outcomes in a disease where prognosis has long been poor.

Limitations and Future Directions

While the TOPAZ-1 trial provides compelling evidence, it is important to consider its limitations. The study focused on a broad population of advanced BTC, and further research may be needed to identify specific subgroups of patients who might derive the greatest benefit from this combination therapy. Biomarker analysis could help in patient selection and personalize treatment approaches. Additionally, while the 24-month survival data is encouraging, longer-term follow-up will be valuable to fully understand the durability of the benefit. Future studies could also explore optimal sequencing or combination with other emerging therapies to further enhance outcomes for patients with advanced biliary tract cancer.

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REFERENCES

1. 1. Oh DY, Ruth He A, Qin S, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evid. 2022;1(8):EVIDoa2200015. doi:10.1056/EVIDoa2200015

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