Editorial Commentary

Beyond chemotherapy in biliary tract cancer: a closer look at the updated long-term follow-up data of the TOPAZ-1 trial

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Biliary tract cancers (BTCs) arise from the biliary tree and present as a biologically and clinically heterogeneous group of tumours. BTCs encompass cholangiocarcinomas (CCAs) further divided into intrahepatic, perihilar or distal CCAs, as well as gallbladder carcinoma and ampulla of Vater cancer (1). Importantly, these anatomical subtypes are not only morphologically diverse but also defined by unique molecular and genetic alterations, as highlighted in recent genomic profiling studies (2). Unfortunately, most patients are diagnosed with advanced stages of disease. Currently, the only curative treatment option is surgical resection, or, within the framework of studies, liver transplantation. However, these curative options can only be offered to up to 25% of patients (3). Furthermore, BTCs show high tumour recurrence rates of up to 60% (4). Therefore, a majority of patients requires palliative systemic treatment.

For more than 10 years, the combination of two cytotoxic chemotherapeutic agents with gemcitabine and cisplatin has represented the standard first-line treatment. In the ABC-02 trial [2010], this regimen demonstrated a modest survival benefit, with median overall survival (OS) extending to 11.7 months compared to 8.1 months with gemcitabine monotherapy (5). A median OS below 12 months underscored the urgent need for therapeutic innovation.

Recently, the phase III TOPAZ-1 trial set a new benchmark for first-line systemic therapy in BTC patients introducing a combination therapy of anti-PD-L1-antibody durvalumab, an immune checkpoint inhibitor, together with the established chemotherapy regimen of gemcitabine and cisplatin (Gem/Cis) compared to placebo with Gem/Cis. The interim analysis of theTOPAZ-1 trial showed an improved median OS of 12.8 months [hazard ratio (HR), 0.8; 95% confidence interval (CI): 0.66–0.97] for the combined treatment of Gem/Cis and durvalumab *vs.* 11.5 months in the control arm without durvalumab (6).

Notably, the 2-year OS rate was 24.9% with durvalumab *vs.* 10.4% in the control arm. Objective response rates (ORRs) were 26.7% *vs.* 18.7%, and disease control rates were similarly high in both groups (85.3% *vs.* 82.6%). Progression-free survival (PFS) was 7.2 months with durvalumab compared to 5.7 months with placebo (HR, 0.75; 95% CI: 0.63–0.89) (6).

Importantly, the addition of immune checkpoint therapy did not result in a relevant increase in toxicity. Grade 3 or 4 adverse events (AEs) were observed in 75.7% of durvalumab-treated patients *vs.* 77.8% in the placebo

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group. Hematologic toxicity [anaemia (48.2% *vs.* 44.7%), neutropenia] and nausea (40.2% *vs.* 34.2%) were the most common. Immune-related AEs occurred in 12.7% of durvalumab-treated patients *vs.* 4.7% in the placebo group, with grade 3 or 4 events being rare (2.4% *vs.* 1.5%). Treatment discontinuation due to AEs occurred in 13% of patients receiving durvalumab and 15.2% in the placebo group, with treatment-related mortality reported at 3.6% and 4.1%, respectively (6). The results of the trial led to widespread approval by regulatory authorities of this new first-line therapy regimen.

Updated trial results have recently been published by Oh *et al.* with a special focus on patients who survived at least 18 months after randomization [long-term survivors (LTS)] and revealed an expanded survival advantage over time (7). In the updated analysis (median follow-up: 23.4 months), the median OS with durvalumab was confirmed at 12.9 *vs.* 11.3 months with an HR of 0.76 (95% CI: 0.64–0.91). Additionally, the updated data allowed to assess long-term survival: the initial survival rate difference of 54.3% in the durvalumab group *vs.* 47.1% in the placebo group after 12 months increased over time with survival rates of 34.8% *vs.* 24.1% after 18 months and 23.6% *vs.* 11.5% after 24 months, respectively (7). Recently, the 3-year follow-up data were published, reaffirming a median OS of 12.9 *vs.* 11.3 months with a HR of 0.74 (95% CI: 0.63–0.87) and an OS rate of 14.6% in the interventional *vs.* 6.9% in the control arm (8).

A typical feature of immunotherapy trials is the delayed separation of survival curves. Indeed, Kaplan-Meier analysis showed overlapping curves for the first 6 months (HR, 0.91), which were then followed by a significant separation (HR, 0.71), underscoring a more durable effect of immune checkpoint inhibition. The updated data demonstrates that the separation of the survival curves became more pronounced over time among patients who achieved at least a partial response (PR), with OS rates of 31.9% in the immunotherapy arm compared to 15.6% in the control arm. In contrast, no significant difference in survival was observed among patients with progressive disease (PD) (8).

This observation is supported by the higher proportion of patients achieving long-term survival following initial combination therapy. A *post-hoc* analysis identified a subgroup of LTS, defined as patients who survived ≥18 months post-randomization (7). Twenty-two percent of all participants were identified as LTS (26% durvalumab; 19% placebo). In the latest analysis, another subgroup of extended LTS (eLTS) were defined as patients who survived ≥30 months post randomization. In total 12.8% of all patients were eLTS with 17% in the immunotherapy group and 8.7% in the control group. In both treatment arms the proportion of patients that reached complete response (CR) or PR was higher in the eLTS subgroup compared to the whole study population with 55.2% *vs.* 26.7% (durvalumab) and 40% *vs.* 18.7% (placebo) (8). The baseline characteristics of this subgroup was similar to the overall cohort indicating that no distinct clinical subgroup solely accounts for this effect. However, those in the durvalumab group more often had recurrent disease, lower neutrophil/lymphocyte ratios (<3), and showed cancer antigen 19-9 levels less than 500 U/mL and carcinoembryonic antigen levels less than 5 ng/mL. While detailed surrogate parameters for tumour biology and anti-tumour immunogenicity are missing, it could be speculated that the LTS subgroup within the durvalumab-treated population may have harboured tumours with a lower tumour burden and potentially altered tumour-immune microenvironment rendering them more responsive to durvalumab. Furthermore, the proportion of patients achieving CR or PR in the LTS subgroup was notably higher with 44% *vs.* 27% in the durvalumab arm, and 34% *vs.* 19% in the control arm (7).

Eventually, more than 50% of the patients in both treatment groups received one or more subsequent anticancer therapy regimens after discontinuation of study treatment. The most common subsequent therapy was cytotoxic chemotherapy. In the durvalumab group, 12% were rechallenged with cisplatin and 8% with gemcitabine. Immunotherapy post-progression was administered in 2.6% of the durvalumab treated patients and 7% in the placebo arm. The ORR in the overall population was 27% (durvalumab) *vs.* 19% (placebo), increasing to 44% and 34%, respectively, among LTS. The median duration of treatment was 7.3 months for durvalumab *vs.* 5.8 months for placebo, and among LTS, treatment extended to 11.3 and 9.7 months, respectively (7). Moreover, neither the use of subsequent immune-based therapies nor extended follow-up treatments appeared to influence long-term survival outcomes (7).

The safety profile remained consistent in the updated analysis. Grade 3 and 4 AEs occurred in 75%. The most frequent toxicities were hematologic and gastrointestinal, similar to the previous published results (6).

In the eLTS subgroup, the proportion of severe AEs (sAEs) was interestingly lower with 32.8% *vs.* 48.8% in the durvalumab group and 36.7% *vs.* 44.4% in the placebo group (8).

Patient reported outcome assessed with the Quality of

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Life Questionnaire core 30 (QLQ-C30) and Quality of Life Questionnaire-Cholangiocarcinoma and Gallbladder Cancer (QLQ-BIL21) showed no significant difference when durvalumab was added to the standard chemotherapy. Interestingly, the survival curves for deterioration of quality of life (QOL) or global health status separated already after 1 month for patients reaching at least PR, indicating that QOL measurement could be an early indicator of clinical benefit (9).

Discontinuation due to AEs occurred in 15% of patients, without increased discontinuation rates or deaths related to durvalumab and occurred even less in the eLTS subgroup, suggesting also higher levels of QOL (8). No additional death was considered to be causal to treatment related adverse effects. Immune-related AEs occurred more frequently in the durvalumab arm (15%), but grade 3 and 4 AEs were rare with only 8 cases compared to 5 cases in the placebo group.

Real-world evidence has substantiated the results of the TOPAZ-1 trial. Observational studies confirm the efficacy and safety of immunochemotherapy in broader, more diverse patient populations, including those typically underrepresented or excluded from clinical trials (10-12). Notably, long-term outcomes in real-world settings appear comparable to clinical trial data, supporting the rationale for early integration of immunotherapy.

Apart from the TOPAZ-1 trial, the KEYNOTE-966 study has provided additional evidence for a benefit of immunotherapy in first-line treatment of BTCs. This phase III trial evaluated the anti-PD-1 antibody pembrolizumab in combination with gemcitabine and cisplatin, demonstrating comparable efficacy and safety. The median OS was 12.7 *vs.* 10.9 months in the control arm (HR, 0.86), underscoring the benefit of adding immune checkpoint inhibition to standard chemotherapy (13).

While the results of the trials were similar, it has to be mentioned that the therapy regimen in KEYNOTE-966 was slightly different to TOPAZ-1, as pembrolizumab was continued in combination with gemcitabine following the induction phase with 8 cycles. Whether extended gemcitabine maintenance in combination with durvalumab may improve survival even further has not been investigated and remains an open question (14).

The updated TOPAZ-1 trial results definitively strengthen the rationale for integrating immune checkpoint inhibition in first-line treatment of BTCs. However, a significant proportion of patients do not achieve meaningful clinical benefit. This highlights the urgent need to better understand mechanisms of primary and acquired resistance to immune checkpoint inhibitors. Current research efforts are focused on elucidating tumour-intrinsic factors (e.g., low tumour mutational burden, absence of neoantigens, immunosuppressive tumour microenvironment) as well as host-related factors that may contribute to immune evasion. This accompanying research might not only contribute to developing strategies to address resistance to immunotherapy but also to identify reliable biomarkers to predict which patients most likely benefit from immune checkpoint inhibition. The development of robust biomarkers—potentially integrating genomic, transcriptomic, and immunologic data—will be crucial for guiding treatment selection.

A detailed investigation of extraordinary treatment responses including both, cases of rapid disease progression with poor survival and long-term survivors achieving complete remission or durable responses upon re-treatment, may contribute to the identification of distinct biological subgroups with differential sensitivity to immunotherapy. Such insights could be applied to future strategies for patient selection and personalized treatment approaches (15).

As ever more patients receive immunotherapy in a first-line setting, data on effective second-line and salvage strategies are sparse. Prospective studies are needed to determine the best approach to subsequent treatment.

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References

1. Valle JW, Kelley RK, Nervi B, et al. Biliary tract cancer. Lancet 2021;397:428-44.
2. Roos E, Soer EC, Klompmaker S, et al. Crossing borders: A systematic review with quantitative analysis of genetic mutations of carcinomas of the biliary tract. Crit Rev Oncol Hematol 2019;140:8-16.
3. Banales JM, Marin JJG, Lamarca A, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol 2020;17:557-88.
4. Rizzo A, Carloni R, Frega G, et al. Intensive Follow-Up Program and Oncological Outcomes of Biliary Tract Cancer Patients after Curative-Intent Surgery: A Twenty-Year Experience in a Single Tertiary Medical Center. Curr Oncol 2022;29:5084-90.
5. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273-81.
6. Oh DY, Ruth He A, Qin S, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evid 2022;1:EVIDoa2200015.
7. Oh DY, He AR, Bouattour M, et al. Durvalumab or placebo plus gemcitabine and cisplatin in participants with advanced biliary tract cancer (TOPAZ-1): updated overall survival from a randomised phase 3 study. Lancet Gastroenterol Hepatol 2024;9:694-704.
8. Oh DY, He AR, Qin S, et al. Durvalumab plus chemotherapy in advanced biliary tract cancer: 3-year overall survival update from the phase III TOPAZ-1 study. J Hepatol 2025;S0168-8278(25)02201-9.
9. Burris HA 3rd, Okusaka T, Vogel A, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer (TOPAZ-1): patient-reported outcomes from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2024;25:626-35.
10. Rimini M, Fornaro L, Lonardi S, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer: An early exploratory analysis of real-world data. Liver Int 2023;43:1803-12.
11. Olkus A, Tomczak A, Berger AK, et al. Durvalumab Plus Gemcitabine and Cisplatin in Patients with Advanced Biliary Tract Cancer: An Exploratory Analysis of Real-World Data. Target Oncol 2024;19:213-21.
12. Mitzlaff K, Kirstein MM, Müller C, et al. Efficacy, safety and differential outcomes of immune-chemotherapy with gemcitabine, cisplatin and durvalumab in patients with biliary tract cancers: A multicenter real world cohort. United European Gastroenterol J 2024;12:1230-42.
13. Kelley RK, Ueno M, Yoo C, 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. Lancet 2023;401:1853-65.
14. Hyung J, Kim B, Yoo C, et al. Clinical Benefit of Maintenance Therapy for Advanced Biliary Tract Cancer Patients Showing No Progression after First-Line Gemcitabine Plus Cisplatin. Cancer Res Treat 2019;51:901-9.
15. Saner FAM, Herschtal A, Nelson BH, et al. Going to extremes: determinants of extraordinary response and survival in patients with cancer. Nat Rev Cancer 2019;19:339-48.

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