Three-year survival and safety update from the Phase 3 TOPAZ-1 study of durvalumab plus chemotherapy in biliary tract cancer

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Objective

- Durvalumab plus gemcitabine and cisplatin (GemCis) significantly improved overall survival (OS) versus placebo plus GemCis in participants with advanced biliary tract cancer (BTC) with manageable safety at the primary analysis of TOPAZ-1. The objective of this analysis was to assess OS and safety approximately 3 years after the last participant was randomised

Conclusions

- Durvalumab plus GemCis continues to demonstrate consistent, clinically meaningful and durable survival benefit versus placebo plus GemCis with 3-year follow-up, the longest follow-up reported in this setting
- The safety profile of durvalumab plus GemCis was consistent with previous analyses, with no new signals identified
- These updated survival and safety data further support the use of durvalumab plus GemCis as standard of care in patients with locally advanced or metastatic BTC

Plain language summary

Why did we perform this research?

- The previous standard of care treatment for advanced BTC was a combination of chemotherapies called GemCis
- The TOPAZ-1 study found that treatment with a type of immunotherapy called durvalumab, when added to GemCis chemotherapy, helped patients with BTC to live longer than patients treated with chemotherapy alone. Now, durvalumab and chemotherapy is a standard of care treatment for people with advanced BTC
- Here, we conducted an updated analysis of TOPAZ-1 after participants had been observed for approximately 3 years from the date the last patient was assigned to a treatment group

How did we perform this research?

Participants were treated with either durvalumab plus GemCis or placebo plus GemCis. The length of time participants lived for and the serious side effects they experienced during the study were reported

What were the findings of this research?

Participants with advanced BTC who received durvalumab plus chemotherapy continued to live longer than participants who received placebo plus chemotherapy. The serious side effects were comparable for patients who received durvalumab plus chemotherapy and patients who received placebo plus chemotherapy, and were primarily associated with chemotherapy

What are the implications of this research?

These results continue to support durvalumab plus chemotherapy as a standard first-line treatment for people with advanced BTC

Where can I access more information?

Information about the medicines being used in this study and the people who could participate can be found here: https://clinicaltrials.gov/study/NCT03875235

Previous results from this study can be found here: https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200015

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Poster presented at the AMMF's Hybrid 2024 European Cholangiocarcinoma Conference by Juan W. Valle

Poster

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Poster presented at the AMMF's Hybrid 2024 European Cholangiocarcinoma Conference, 8–10 May

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Introduction

- Prior to the addition of durvalumab immunotherapy to GemCis chemotherapy in the Phase 3 TOPAZ-1 study (NCT03875235), GemCis was the standard of care for BTC for over a decade[1-3]
- At the primary analysis (data cut-off [DCO]: 11 August 2021) of TOPAZ-1, durvalumab plus GemCis significantly improved OS versus placebo plus GemCis (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.66–0.97; p=0.021, 2-sided, threshold for significance=0.03) and was associated with a manageable safety profile[3]
- Based on these results from the TOPAZ-1 study, durvalumab plus GemCis has become a standard of care for patients with advanced or metastatic BTC[4,5]
- Here, we report an updated 3-year OS and safety analysis for TOPAZ-1

Methods

- TOPAZ-1 is a randomised, double-blind, global, Phase 3 study evaluating the efficacy and safety of durvalumab plus GemCis as first-line treatment for patients with advanced BTC (**Figure 1**, **Figure 2**)
- Participants previously untreated for unresectable, locally advanced, recurrent or metastatic BTC were randomised 1:1 to durvalumab (1500 mg) or placebo plus gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2), every 3 weeks for up to 8 cycles, followed by durvalumab or placebo monotherapy every 4 weeks until disease progression, unacceptable toxicity or other discontinuation criteria were met
- In this long-term follow-up analysis, OS and serious adverse events (SAEs) were assessed after approximately 26 months (DCO: 23 October 2023) from the primary analysis and approximately 36 months from the date of the last participant being randomised, with 89% overall OS maturity. Only SAEs were reported in this analysis as this was the only type of AE reported by physicians after the 25 February 2022 DCO

Figure 1. Countries and regions enrolling patients into the TOPAZ-1 study

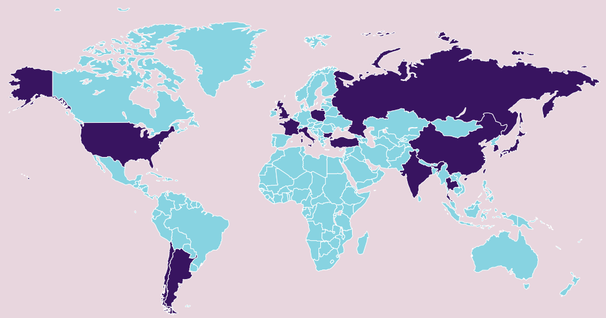
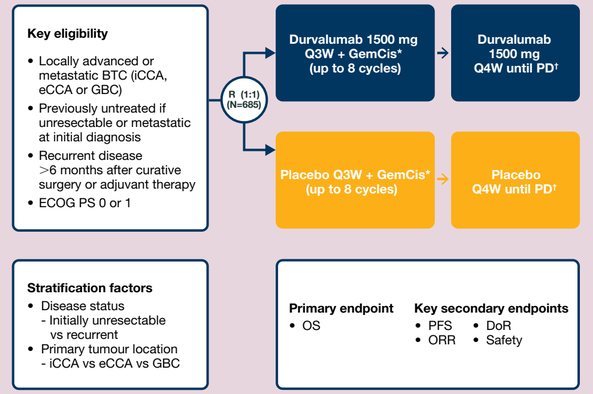


Figure 2. Study design of TOPAZ-1



*On Days 1 and 8 Q3W up to 8 cycles. †Unless there is unacceptable toxicity, withdrawal of consent or another discontinuation criterion is met.

BTC, biliary tract cancer; DoR, duration of response; eCCA, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2); iCCA, intrahepatic cholangiocarcinoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PS, performance status; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomised.

Results

Duration of follow-up

- At DCO for this analysis, median (95% CI) follow-up time using reverse Kaplan-Meier method was 41.3 (39.3–44.1) months in all patients, 42.9 (39.8–44.3) months with durvalumab plus GemCis, and 41.8 (36.7–46.2) months with placebo plus GemCis (**Figure 3**)

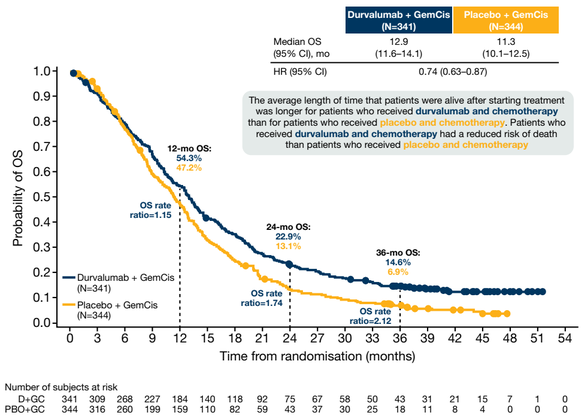
Figure 3. Duration of follow-up

Patients who received **durvalumab and chemotherapy** were observed for a greater length of time because they tended to live longer than patients who received placebo and chemotherapy

Efficacy

- At the 3-year DCO, the OS benefit with the addition of durvalumab to GemCis improved versus previous DCOs (HR, 0.74; 95% CI, 0.63–0.87 vs HR, 0.76; 95% CI, 0.64–0.91 and HR, 0.80; 95% CI, 0.66–0.97; **Table 1**)
- Median OS (95% CI) using Kaplan-Meier estimate was 12.9 (11.6–14.1) months in the durvalumab plus GemCis arm and 11.3 (10.1–12.5) months in the placebo plus GemCis arm (**Table 1**, **Figure 4**)

Figure 4. Kaplan-Meier curve of overall survival



CI, confidence interval; GemCis, gemcitabine+cisplatin; HR, hazard ratio; mo, months; OS, overall survival; PBO, placebo

- At the 3-year DCO, the 12- and 24-month OS rates were higher for durvalumab plus GemCis compared with placebo plus GemCis, consistent with previous analyses (**Table 1**, **Figure 5**)
- The OS rate (95% CI) of patients alive at 36 months was 14.6% (11.0–18.6) in the durvalumab plus GemCis arm and 6.9% (4.5–10.0) in the placebo plus GemCis arm (**Table 1**, **Figure 5**)

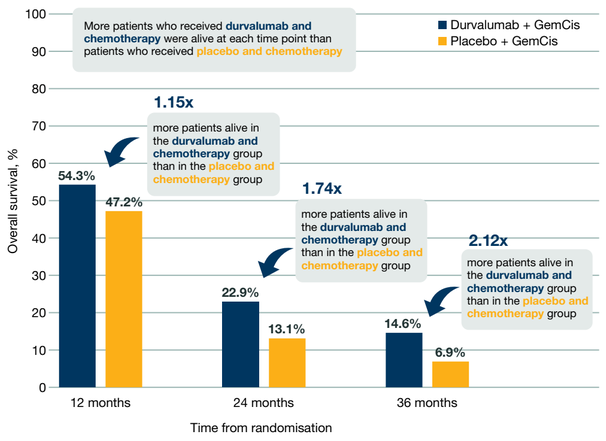
Table 1. Overall survival

	DCO: 23 October 2023*		DCO: 25 February 2022*		DCO: 11 August 2021	
	D+GC (N=341)	PBO+GC (N=344)	D+GC (N=341)	PBO+GC (N=344)	D+GC (N=341)	PBO+GC (N=344)
Median OS (95% CI), months	12.9 (11.6–14.1)	11.3 (10.1–12.5)	12.9 (11.6–14.1)	11.3 (10.1–12.5)	12.8 (11.1–14.0)	11.5 (10.1–12.5)
OS HR (95% CI)	0.74 (0.63–0.87)		0.76 (0.64–0.91)		0.80 (0.66–0.97)	
12-month OS rate (95% CI), %	54.3 (48.8–59.4)	47.2 (41.7–52.4)	54.3 (48.8–59.4)	47.1 (41.7–52.3)	54.1 (48.4–59.4)	48.0 (42.4–53.4)
24-month OS rate (95% CI), %	22.9 (18.5–27.5)	13.1 (9.8–17.0)	23.6 (18.7–28.9)	11.5 (7.6–16.2)	24.9 (17.9–32.5)	10.4 (4.7–18.8)
36-month OS rate (95% CI), %	14.6 (11.0–18.6)	6.9 (4.5–10.0)	–	–	–	–

*The 23 October 2023 and 25 February 2022 DCOs were exploratory analyses with no formal statistical testing.

CI, confidence interval; D, durvalumab; DCO, data cut-off; GC, gemcitabine+cisplatin; OS, overall survival; PBO, placebo.

Figure 5. Overall survival rates at 12, 24 and 36 months



GemCis, gemcitabine+cisplatin.

Safety

- Average (standard deviation) duration of exposure to durvalumab or placebo was 8.97 (8.942) months with durvalumab plus GemCis and 6.29 (4.228) months with placebo plus GemCis
- The incidence of SAEs and treatment-related SAEs was similar between treatment arms and consistent with the safety profile observed at previous analyses (**Table 2**, **Figure 6**)

Table 2. Serious adverse events

	DCO: 23 October 2023*		DCO: 25 February 2022*		DCO: 11 August 2021	
	D+GC (N=338)	PBO+GC (N=342)	D+GC (N=338)	PBO+GC (N=342)	D+GC (N=338)	PBO+GC (N=342)
Any SAE, n (%)	165 (48.8)	152 (44.4)	161 (47.6)	151 (44.2)	160 (47.3)	149 (43.6)
Treatment-related SAEs, n (%)†	52 (15.4)	59 (17.3)	52 (15.4)	59 (17.3)	53 (15.7)	59 (17.3)

Safety data percentages are calculated from the safety population (n=338 for D+GC and n=342 for PBO+GC); SAE data was the only type of AE data reported after the 25 February 2022 DCO. Two new AEs with the outcome of death were reported in D+GC since the primary analysis (DCO: 11 August 2021), both unrelated to study treatment. *The 23 October 2023 and 25 February 2022 DCOs were exploratory analyses with no formal statistical testing. †As assessed by the investigator.

AE, adverse event; D, durvalumab; DCO, data cut-off; GC, gemcitabine+cisplatin; PBO, placebo; SAE, serious adverse event.

Figure 6. Treatment-related serious adverse events

Serious adverse events that were considered to be related to treatment* occurred in:

*As assessed by the investigator; serious adverse events are defined as side effects that are life-threatening, require hospitalisation, cause lasting problems or death, or result in a birth defect.

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Disclosures

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