Poster 56P

Updated overall survival from the Phase 3 TOPAZ-1 study of durvalumab or placebo plus gemcitabine and cisplatin in patients with advanced 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; here, we assessed OS, the association of OS with best objective response (BoR) and safety data from TOPAZ-1 following an additional 6.5 months of follow-up after the primary analysis

Conclusions

- Durvalumab plus GemCis continues to demonstrate consistent, clinically meaningful and durable benefit versus placebo plus GemCis with longer-term follow-up
  - The two-year survival rate with durvalumab plus GemCis was approximately twice that of placebo plus GemCis
  - The survival benefit with durvalumab plus GemCis extends to participants with stable disease (SD) as well as responders
- The safety profile of durvalumab plus GemCis remains manageable, with no new safety signals observed with longer follow-up
- These updated OS and safety data further support durvalumab plus GemCis as a new first-line standard of care regimen for people with advanced BTC

Plain language summary

Why did we perform this research?
- GemCis is a standard first treatment for people with advanced BTC
- Participants who received durvalumab, a type of immunotherapy, plus GemCis lived longer than participants who received placebo plus GemCis in the original analysis of the TOPAZ-1 study
- Here, we conducted an updated analysis of TOPAZ-1 after participants had been observed for an additional 6.5 months to assess the benefit over more time

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, whether their tumours grew, got smaller or disappeared and the side effects they experienced during the study were measured

What were the findings of this research?
After additional observation, participants who received durvalumab plus GemCis continued to live longer than participants who received placebo plus GemCis, and this benefit was observed whether participants' tumours stayed the same size, got smaller or disappeared. The percentage of participants experiencing side effects, and the severity of those side effects, was similar between treatment groups

What are the implications of this research?
These results further support durvalumab plus GemCis as a new standard first 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/ct2/show/NCT03875235
Previous results from this study can be found here:
https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200015

This study was sponsored by AstraZeneca
Poster presented at the European Society for Medical Oncology (ESMO) Congress 2022 by Do-Youn Oh

Poster presented at the European Society for Medical Oncology (ESMO) Congress, Paris, France, 9–13 September 2022

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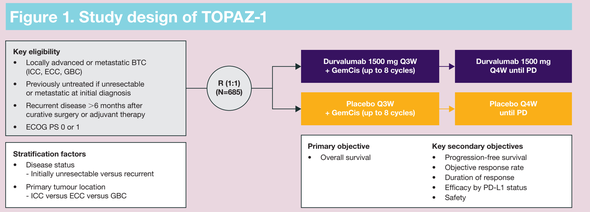
Introduction

- At the pre-planned interim analysis (IA, data cut-off: 11 August 2021) of TOPAZ-1 (NCT03875235), 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, threshold for significance=0.03)[1]
  - Durvalumab did not increase toxicity
- Based on these results from the TOPAZ-1 study, the National Comprehensive Cancer Network® considers durvalumab plus GemCis a preferred regimen for the first-line treatment of advanced BTC[2]
- A previous meta-analysis found that response rate and disease control rate with first-line chemotherapy are not strongly correlated with OS in advanced BTC[3]
- Here, we report an updated OS and safety analysis for TOPAZ-1 and a post hoc analysis to determine OS by BoR in TOPAZ-1

Methods

- TOPAZ-1 is a randomised, double-blind, global, Phase 3 study (Figure 1)
- This OS and safety analysis was conducted after 6.5 months of additional follow-up (data cut-off: 25 February 2022) after the primary analysis, with 76.9% overall OS event maturity
- Duration of follow-up was calculated in all participants using the inverse Kaplan-Meier method with the censoring indicator reversed
- OS HRs and 95% CIs for all randomised participants were calculated using a stratified Cox proportional hazards model, adjusting for disease status (initially unresectable or recurrent) and primary tumour location (intrahepatic cholangiocarcinoma [ICC], extrahepatic cholangiocarcinoma [ECC] or gallbladder cancer [GBC])
  - Subgroup analysis of OS used unstratified Cox proportional hazards models with treatment as covariate
- BoR was assessed by the investigator per Response Evaluation Criteria In Solid Tumours v1.1 in all randomised participants with measurable disease at baseline and defined as response (complete response or partial response), SD or progressive disease (PD); BoR was determined based on the IA data cut-off (11 August 2021); this represents the final BoR analysis
- OS by BoR was assessed only in those participants surviving ⩾3 months to avoid immortal time bias; HRs were calculated using a Cox proportional hazards model

Figure 1. Study design of TOPAZ-1



BTC, biliary tract cancer; ECC, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; ICC, intrahepatic cholangiocarcinoma; PD, progressive disease; PD-L1, programmed cell death ligand-1; PS, performance status; Q3 / 4W, every 3 / 4 weeks; R, randomised

Results and interpretation

Study population

- The details of the TOPAZ-1 participant population have been previously reported[1]
  - Participant demographics and disease characteristics were generally balanced between treatment groups

Duration of follow-up

- At data cut-off for this analysis, median (95% CI) follow-up time was 23.4 (20.6–25.2) months and 22.4 (21.4–23.8) months for durvalumab plus GemCis and placebo plus GemCis, respectively

Overall survival

- With 6.5 months of additional follow-up, the OS benefit with the addition of durvalumab to GemCis numerically improved versus the IA (HR [95% CI], 0.76 [0.64–0.91] from 0.80 [0.66–0.97] at IA[1]; Figure 2)
  - The piecewise HR (95% CI) after the 6-month landmark improved to 0.71 (0.58–0.88) from 0.74 (0.58–0.94) at IA[1]
  - Two-year survival (95% CI) was 23.6% (18.7–28.9) in the durvalumab arm and 11.5% (7.6–16.2) in the placebo arm
- OS benefit (HRs <1) was observed across all prespecified subgroups, including disease status at baseline (initially unresectable or recurrent disease), region (Asia or rest of world), primary tumour location (ICC or ECC or GBC) and diagnostic stage (locally advanced or metastatic disease; Figure 3)

Best objective response

- There was a higher proportion of responders in the durvalumab plus GemCis arm versus the placebo plus GemCis arm (Table 1)
  - Among non-responders, a majority of participants had a BoR of SD in both treatment groups (Table 1)

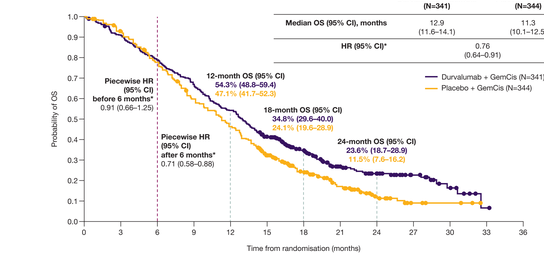
Overall survival by best objective response

- OS HRs (95% CIs) for participants with a BoR of response (0.69 [0.46–1.04]) or SD (0.77 [0.62–0.96]) favoured durvalumab plus GemCis (Figure 4)
- Among responders, there was a clear and sustained separation of the durvalumab plus GemCis and placebo plus GemCis curves beginning approximately 15 months after randomisation
  - Similarly, among participants with a BoR of SD, there was sustained separation between the curves at approximately 6 months
- Among participants with a BoR of PD, median OS (95% CI) was 5.7 (3.6–8.9) months in the durvalumab arm and 6.7 (4.5–8.5) months in the placebo arm

Safety

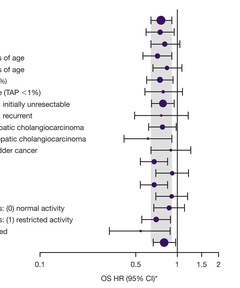
- The incidence of adverse events (AEs) and treatment-related AEs (any, grade 3 or 4 or leading to discontinuation of treatment or death) was similar between treatment arms (Table 2) and consistent with the safety profile observed at the primary analysis

Figure 2. Kaplan-Meier curve of overall survival



*Durvalumab + GemCis versus placebo + GemCis. An HR <1 favours durvalumab + GemCis
CI, confidence interval; GemCis, gemcitabine and cisplatin; HR, hazard ratio; OS, overall survival

Figure 3. Forest plot of subgroup analysis of overall survival



	Durvalumab + GemCis n/N (%)	Placebo + GemCis n/N (%)	OS HR (95% CI)*
All patients	248 / 341 (72.7)	279 / 344 (81.1)	0.76 (0.64–0.91)
Sex: male	126 / 169 (74.6)	148 / 176 (84.1)	0.75 (0.59–0.95)
Sex: female	122 / 172 (70.9)	131 / 168 (78.0)	0.81 (0.64–1.04)
Age at randomisation: <65 years of age	123 / 181 (68.0)	150 / 184 (81.5)	0.72 (0.56–0.91)
Age at randomisation: ⩾65 years of age	125 / 160 (78.1)	129 / 160 (80.6)	0.84 (0.66–1.08)
PD-L1 expression: high (TAP ⩾1%)	149 / 199 (74.9)	172 / 207 (83.1)	0.75 (0.60–0.93)
PD-L1 expression: low / negative (TAP <1%)	71 / 103 (68.9)	81 / 103 (78.6)	0.79 (0.58–1.09)
Disease status at randomisation: initially unresectable	209 / 274 (76.3)	240 / 279 (86.0)	0.79 (0.65–0.95)
Disease status at randomisation: recurrent	39 / 67 (58.2)	39 / 64 (60.9)	0.76 (0.49–1.20)
Primary tumour location: intrahepatic cholangiocarcinoma	136 / 190 (71.6)	153 / 193 (79.3)	0.78 (0.62–0.99)
Primary tumour location: extrahepatic cholangiocarcinoma	45 / 66 (68.2)	55 / 65 (84.6)	0.61 (0.41–0.91)
Primary tumour location: gallbladder cancer	67 / 85 (78.8)	71 / 86 (82.6)	0.90 (0.64–1.25)
Race: Asian	134 / 185 (72.4)	174 / 201 (86.6)	0.68 (0.54–0.85)
Race: non-Asian	114 / 156 (73.1)	105 / 143 (73.4)	0.92 (0.70–1.20)
Region: Asia	130 / 178 (73.0)	170 / 196 (86.7)	0.68 (0.54–0.85)
Region: rest of the world	118 / 163 (72.4)	109 / 148 (73.6)	0.91 (0.70–1.18)
WHO / ECOG performance staus: (0) normal activity	126 / 173 (72.8)	125 / 163 (76.7)	0.87 (0.68–1.12)
WHO / ECOG performance staus: (1) restricted activity	122 / 168 (72.6)	154 / 181 (85.1)	0.70 (0.55–0.89)
Diagnostic stage: locally advanced	22 / 38 (57.9)	45 / 57 (78.9)	0.54 (0.32–0.88)
Diagnostic stage: metastatic	226 / 303 (74.6)	234 / 286 (81.8)	0.80 (0.67–0.97)

*Durvalumab + GemCis versus placebo + GemCis. An HR <1 favours durvalumab + GemCis
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GemCis, gemcitabine and cisplatin; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death ligand-1; TAP, tumour area positivity; WHO, World Health Organization

Table 1. Best objective response

	Durvalumab + GemCis (N=341)	Placebo + GemCis (N=343)
Responders,†* n (%)	91 (26.7)	64 (18.7)
Complete response,† n (%)	7 (2.1)	2 (0.6)
Partial response,† n (%)	84 (24.6)	62 (18.1)
Non-responders, n (%)	250 (73.3)	279 (81.3)
Stable disease, n (%)	200 (58.7)	220 (64.1)
Progressive disease,† n (%)	47 (13.8)	51 (14.9)
Not evaluable	3 (0.9)	8 (2.3)

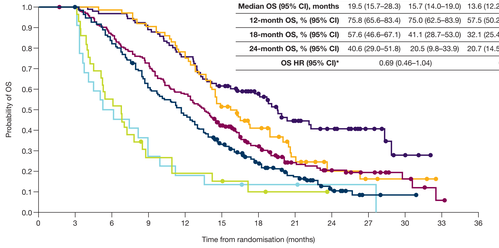
*Confirmed response; †Death recorded within 13 weeks after randomisation is considered progression
GemCis, gemcitabine and cisplatin

Table 2. Adverse events

	Durvalumab + GemCis (N=338)	Placebo + GemCis (N=342)
Any AE, n (%)	336 (99.4)	338 (98.8)
Grade 3 or 4 AE	250 (74.0)	257 (75.1)
AE leading to death	13 (3.8)	14 (4.1)
AE leading to discontinuation	43 (12.7)	52 (15.2)
Any TRAE, n (%)	314 (92.9)	308 (90.1)
Grade 3 or 4 TRAE	206 (60.9)	217 (63.5)
TRAE leading to death	2 (0.6)	1 (0.3)
TRAE leading to discontinuation	30 (8.9)	39 (11.4)

AE, adverse event; GemCis, gemcitabine and cisplatin; TRAE, treatment-related adverse event

Figure 4. Kaplan-Meier curve of overall survival by best objective response



	Responders (CR / PR)		Stable disease		Progressive disease	
	Durvalumab + GemCis (N=91)	Placebo + GemCis (N=64)	Durvalumab + GemCis (N=194)	Placebo + GemCis (N=217)	Durvalumab + GemCis (N=22)	Placebo + GemCis (N=29)
Median OS (95% CI), months	19.5 (15.7–28.3)	15.7 (14.0–19.0)	13.6 (12.2–14.7)	11.5 (9.9–12.8)	5.7 (3.6–8.9)	6.7 (4.5–8.5)
12-month OS, % (95% CI)	75.8 (65.6–83.4)	75.0 (62.5–83.9)	57.5 (50.2–64.1)	48.0 (41.2–54.5)	18.2 (5.7–36.3)	19.2 (7.2–35.5)
18-month OS, % (95% CI)	57.6 (46.6–67.1)	41.1 (28.7–53.0)	32.1 (25.4–39.1)	23.8 (18.2–29.9)	13.6 (3.4–30.9)	10.2 (2.1–25.9)
24-month OS, % (95% CI)	40.6 (29.0–51.8)	20.5 (9.8–33.9)	20.7 (14.5–27.6)	10.6 (6.1–16.5)	13.6 (3.4–30.9)	NC
OS HR (95% CI)*	0.69 (0.46–1.04)		0.77 (0.62–0.96)		NC	

No. at risk

CR / PR durvalumab + GemCis	91	91	91	91	91	88	88	88	84	81	78	73	69	63	58	54	50	43	39	33	27	24	22	20	18	16	13	9	8	4	3	2	1	0	0
CR / PR placebo + GemCis	64	64	64	64	64	63	63	62	60	58	56	53	48	44	40	32	30	25	22	17	15	11	8	7	5	5	5	3	2	2	2	2	1	0	0
SD durvalumab + GemCis	194	194	193	193	186	175	167	154	147	140	125	116	111	102	91	77	65	51	47	39	32	26	24	23	17	16	13	11	9	6	5	3	2	1	0
SD placebo + GemCis	217	217	217	216	206	195	178	164	150	131	122	115	103	88	79	67	58	48	41	35	31	25	20	13	9	6	4	2	1	1	1	0	0	0	0
PD durvalumab + GemCis	22	22	22	22	15	13	11	10	9	6	5	5	4	4	3	3	3	2	2	2	2	2	1	1	1	1	1	0	0	0	0	0	0	0	0
PD placebo + GemCis	29	29	29	29	23	20	16	12	10	7	7	5	5	5	5	4	3	3	2	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0

To avoid immortal time bias, only participants surviving >3 months were included in this OS by best objective response analysis
*Durvalumab + GemCis versus placebo + GemCis. An HR <1 favours durvalumab + GemCis
CI, confidence interval; CR, complete response; GemCis, gemcitabine and cisplatin; HR, hazard ratio; NC, not calculable; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease

Acknowledgements

This study was sponsored by AstraZeneca. The authors would like to thank the participants, their families and caregivers and all investigators involved in this study. Editorial assistance was provided by Brian Woolums, PhD, of CMC Connect, a division of IPG Health Medical Communications, and was funded by AstraZeneca in accordance with Good Publication Practice (GPP3) guidelines (*Ann Intern Med* 2015).

Disclosures

NR and GC are employees of and hold stock in AstraZeneca. MW is an employee of AstraZeneca. D-YO reports consulting or advisory fees from AstraZeneca. AV reports honoraria for advisory boards and presentations from AstraZeneca. Full author disclosures are available with the published abstract.

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