Poster 57P

Immune-mediated adverse event incidence, timing and association with efficacy in the Phase 3 TOPAZ-1 study of durvalumab or placebo plus gemcitabine and cisplatin in advanced biliary tract cancer

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Objective

- This analysis investigated the incidence, timing and association with efficacy of immune-mediated adverse events (imAEs) in the Phase 3 TOPAZ-1 study of durvalumab or placebo plus gemcitabine and cisplatin (GemCis) as first-line treatment for advanced biliary tract cancer (BTC)

Conclusions

- Most imAEs were grade 1 or 2 and manageable, and imAEs did not lead to an increase in the number of participants discontinuing study treatment
- imAEs occurred most frequently within 3 months but could occur at any time during the study, with median time to onset that varied according to imAE type
- Durvalumb plus GemCis was associated with an overall survival (OS) benefit versus placebo plus GemCis, irrespective of imAE occurrence
- Consistent with other studies, imAEs may be associated with greater OS benefit[1]; however, participant numbers were low for this analysis, and further investigation is warranted into this association
- imAEs could be managed based on the treatment guidelines; thus, people with BTC who experience imAEs can be considered for continued treatment with durvalumab plus GemCis

Plain language summary

Why did we perform this research?
The analysis described here was performed to assess side effects associated with the immune system in the TOPAZ-1 study: how often they occurred, their timing in relation to treatment and if they were associated with the length of time participants with BTC remained alive after being treated with durvalumab plus GemCis anti-cancer therapy

How did we perform this research?
Participants were treated with either durvalumab plus GemCis or placebo plus GemCis. Side effects were categorised as being associated with the immune system by an algorithm. They were counted and the time they began was recorded. The length of time participants remained alive was measured and linked to side effects associated with the immune system

What were the findings of this research?
Side effects associated with the immune system were mild and did not lead to more participants stopping treatment. The timing of side effects associated with the immune system varied. Participants benefited from treatment with durvalumab plus GemCis, regardless of whether or not they experienced side effects associated with the immune system

What are the implications of this research?
This research, alongside other research from the TOPAZ-1 study, supports durvalumab plus GemCis as a first treatment for 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

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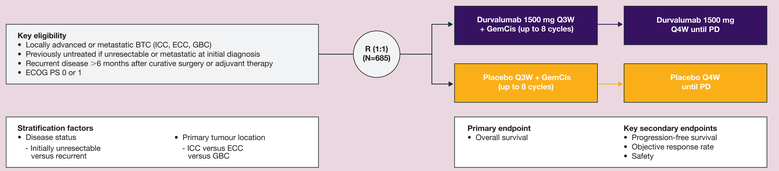
Introduction

- GemCis chemotherapy has been the first-line standard of care for advanced BTC worldwide for over a decade[2-5]
- At a planned interim analysis of TOPAZ-1 (NCT03875235), a statistically significant increase in OS was observed in participants treated with durvalumab plus GemCis versus placebo plus GemCis[6]
  - Based on the results of the TOPAZ-1 study, durvalumab plus GemCis is recommended for the first-line treatment of advanced BTC[7]
- Durvalumab is an immune checkpoint inhibitor targeting programmed cell death ligand-1 (PD-L1), and thus may cause imAEs
  - imAEs have been reportedly associated with improved OS for anti-PD-L1 immunotherapies[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 participants with advanced BTC (Figure 1)
- imAEs are AEs of special / possible interest linked to drug exposure with a likely immune-mediated mechanism and no clear alternate aetiology
  - Incidences of imAEs were calculated by programmatic adjudication
- OS hazard ratio (HR) was calculated using a Cox model with treatment as the only covariate, and median OS was calculated using the Kaplan-Meier method

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; PS, performance status; Q3 / 4W, every 3 / 4 weeks; R, randomised

Results and interpretation

Immune-mediated adverse events

- imAEs occurred in more participants in the durvalumab arm than in the placebo arm[6] (Table 1)
- The incidence of grade 3 or 4 imAEs[6] or serious imAEs was low in both arms (Table 1)
- Overall, 20 out of 43 (46.5%) participants with an imAE in the durvalumab arm and 8 out of 16 (50%) participants with an imAE in the placebo arm had an imAE that resolved (Table 1)
- The most common imAEs by category (>1% of participants in either arm) were hypothyroid events, dermatitis / rash, hepatic events and adrenal insufficiency (Figure 2)

Table 1. Incidence of immune-mediated adverse events*

	Durvalumab + GemCis (n=338)	Placebo + GemCis (n=342)
Participants with any imAE, n (%)[a]	**43 (12.7)**	**16 (4.7)**
Possibly related to study medication, n (%)	38 (11.2)	14 (4.1)
Grade 3 or 4, n (%)[b]	8 (2.4)[‡]	5 (1.5)[§]
Serious, n (%)	6 (1.8)	5 (1.5)
With outcome of death, n (%)	0	1 (0.3)[‖]
Leading to treatment discontinuation, n (%)	3 (0.9)[¶]	4 (1.2)**
Median time to onset (range), days†	108.0 (1–511)	86.5 (4–533)
Participants with resolved imAEs, n (%)	20 (5.9)	8 (2.3)
Median time to resolution (range), days†	54.0 (1–225)	50.0 (8–224)

*One participant may have more than one imAE; †In participants with any imAE (time to onset) or resolved imAEs (time to resolution); [a]Pneumonitis (n=1), alanine aminotransferase increased (n=1), immune-mediated hepatitis (n=1), diarrhoea (n=1), diabetic ketoacidosis (n=1), rash maculo-papular (n=2), immune-mediated arthritis (n=1); [b]Pneumonitis (n=1), autoimmune hepatitis (n=1), diarrhoea (n=1), hyperamylasaemia (n=1), arthritis (n=1); [‡]Polymyositis (n=1); [§]Interstitial lung disease (n=1), alanine aminotransferase increased (n=1), rash maculo-papular (n=1); **Pneumonitis (n=1), autoimmune hepatitis (n=1), blood creatine increased (n=1), polymyositis (n=1)

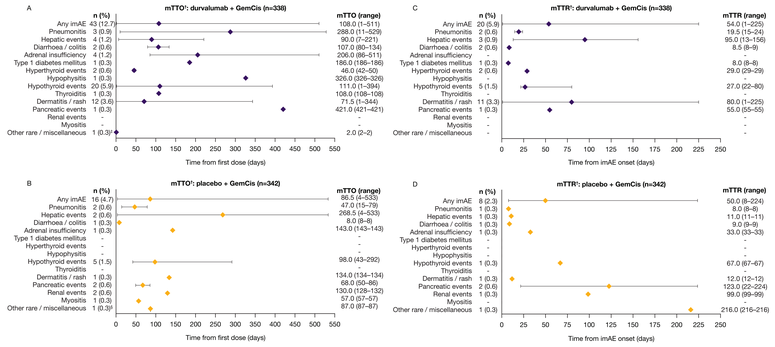
GemCis, gemcitabine and cisplatin; imAE, immune-mediated adverse event

- Overall, imAEs occurred most frequently within 3 months but could occur anytime during the clinical course (Figure 3)
- Median time to onset of imAEs by category ranged from 2 to >400 days in the durvalumab arm, with earlier presentation of dermatologic events and later presentation of pneumonitis and some endocrine events, although numbers were small (Figure 2)
- For the most common types of imAEs in the durvalumab arm that resolved, median time to resolution was less than 100 days (Figure 2)
- imAEs in the durvalumab arm required treatment more frequently than in the placebo arm (Table 2)
- imAEs were generally manageable and consistent with the known safety profile of durvalumab

Overall survival by immune-mediated adverse event occurrence

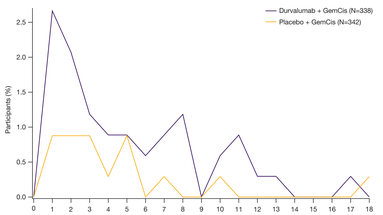
- Median duration of follow-up for censored participants was similar for those who experienced an imAE versus those who did not for both the durvalumab (13.2 months vs 13.8 months) and placebo (12.5 months vs 12.7 months) arms (Figure 4)
- Although the number of participants experiencing an imAE was low in both arms, there appears to be no detriment to survival in participants with imAEs (Figure 4)
- Adding durvalumab to GemCis was associated with improved OS versus placebo plus GemCis, regardless of whether participants experienced an imAE or not: OS HRs (95% confidence intervals) were 0.83 (0.68–1.01) in participants without imAE and 0.66 (0.30–1.56) in those with an imAE (Figure 4)
- In the durvalumab arm, median OS was longer in participants with an imAE than in those without an imAE, and OS HRs favoured participants who experienced an imAE versus those who did not (Figure 5)

Figure 2. Time to onset (A, B) and resolution (C, D) of immune-mediated adverse events by AESI category*



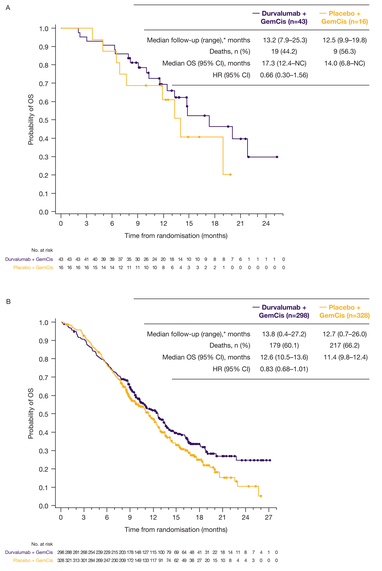
*One participant may have more than one imAE; †In participants with an imAE; ‡Immune-mediated arthritis; §Arthritis
AESI, adverse event of special interest; GemCis, gemcitabine and cisplatin; imAE, immune-mediated adverse event; mTTO, median time to onset; mTTR, median time to resolution

Figure 3. Percent of participants with immune-mediated adverse events over time



The percentage of participants with at least one imAE out of the total number of participants in each treatment arm over time is shown
GemCis, gemcitabine and cisplatin; imAE, immune-mediated adverse event

Figure 4. Overall survival for durvalumab versus placebo for participants (A) with or (B) without an immune-mediated adverse event



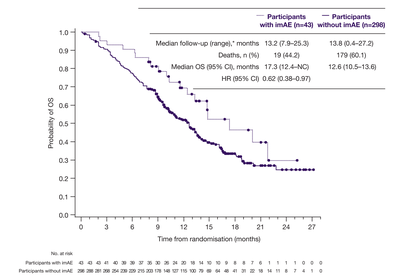
*For censored participants
CI, confidence interval; GemCis, gemcitabine and cisplatin; HR, hazard ratio; NC, not calculable; OS, overall survival

Table 2. Treatment for immune-mediated adverse events

	Durvalumab + GemCis (n=338)	Placebo + GemCis (n=342)
Participants with any imAE, n (%)[a]	**43 (12.7)**	**16 (4.7)**
Systemic corticosteroids	27 (8.0)	12 (3.5)
High-dose steroids	13 (3.8)	10 (2.9)
Endocrine therapy	22 (6.5)	5 (1.5)
Other immunosuppressant	1 (0.3)	1 (0.3)

GemCis, gemcitabine and cisplatin; imAE, immune-mediated adverse event

Figure 5. Overall survival by immune-mediated adverse event occurrence in the durvalumab arm



*For censored participants
CI, confidence interval; HR, hazard ratio; imAE, immune-mediated adverse event; NC, not calculable; OS, overall survival

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Disclosures

MH, JX*, HK, KH and NR are employees of and hold stock in AstraZeneca. LA and D-YO report membership on an advisory board for AstraZeneca. D-YO and HT report research grants from AstraZeneca. LA, AS, JC and MP report invited speaker roles for AstraZeneca. MP is a principal investigator for AstraZeneca (non-financial). RG, S-SY, JOP and GV report no conflicts of interest related to AstraZeneca. Full author disclosures are available with the published abstract.

*At the time the study was conducted

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