# The Evolving Standard of Care in Advanced Biliary Tract Cancers:
## Three-Year Survival Data Supports Durvalumab + gem-cis in First-Line Treatment

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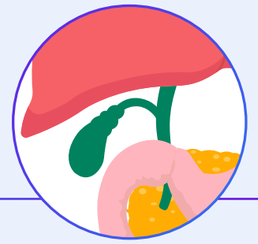
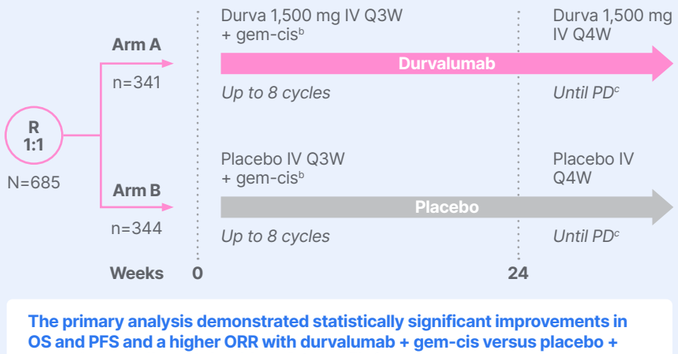
## Introduction



TOPAZ-1 is a Phase III, randomized, double-blind, placebo-controlled, multi-center, global study for 1L treatment with durvalumab + gem-cis[a] in adult patients with advanced biliary tract cancers (BTC).[1]

### Study population

- Previously untreated, unresectable, locally advanced or metastatic BTCs at initial diagnosis, including intrahepatic or extrahepatic cholangiocarcinoma and gallbladder carcinoma
- Recurrent disease >6 months after curative surgery or completion of adjuvant therapy[a]
- ECOG PS of 0 or 1



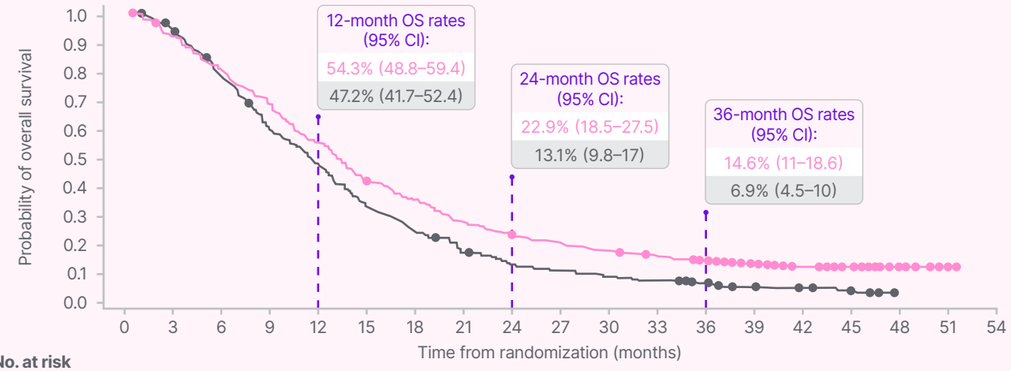

**The primary analysis demonstrated statistically significant improvements in OS and PFS and a higher ORR with durvalumab + gem-cis versus placebo + gem-cis, as well as a tolerable safety profile.[1]**

**This demonstration of the addition of durvalumab to gem-cis was the first advancement in the 1L setting for advanced BTCs in over 10 years.[1]**

| | | Durvalumab + gem-cis (n=341) | Placebo + gem-cis (n=344) |
|---|---|---|---|
| **Primary endpoint** | Median OS, months (95% CI) | 12.8 (11.1–14.0) | 11.5 (10.1–12.5) |
| | HR (95% CI) | 0.80 (0.66–0.97); p=0.021 | |
| **Key secondary endpoints[d]** | Median PFS, months (95% CI) | 7.2 (6.7–7.4) | 5.7 (5.6–6.7) |
| | HR (95% CI) | 0.75 (0.63–0.89); p=0.001 | |
| | ORR, % | (n=341) 26.7 | (n=343) 18.7 |
| | Safety, % | (n=338) | (n=342) |
| | TRAEs | 92.9 | 90.1 |
| | Serious TRAEs | 15.7 | 17.3 |
| | TRAEs leading to discontinuation | 8.9 | 11.4 |
| | Any immune-mediated AE | 12.7 | 4.7 |

## In the post-hoc 3-year analysis of TOPAZ-1:

**2x more patients** were estimated to be alive in the **durvalumab arm compared to placebo arm** (14.6% and 6.9%, respectively); a greater OS rate ratio compared with previous data cut-off points.[2*]




| No. at risk | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Durvalumab + gem-cis | 341 | 309 | 268 | 227 | 184 | 140 | 118 | 92 | 75 | 67 | 58 | 50 | 43 | 31 | 21 | 15 | 7 | 1 | 0 |
| Placebo + gem-cis | 344 | 316 | 260 | 199 | 159 | 110 | 82 | 59 | 43 | 37 | 30 | 25 | 18 | 11 | 8 | 4 | 0 | 0 | 0 |

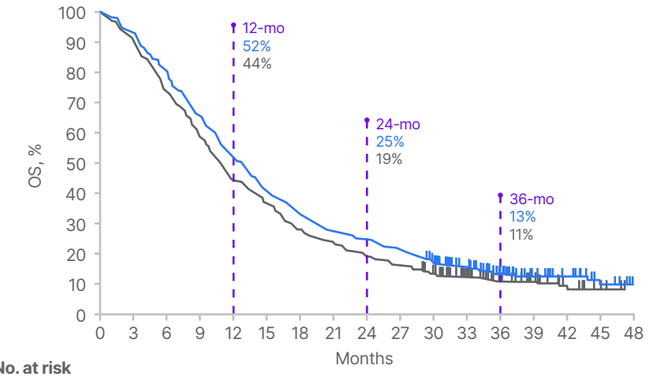
*The 3-year OS analysis was conducted post hoc and not powered for statistical significance.

Data cut off was October 23, 2023. At the 3-year analysis, OS maturity was 89%. Median duration of follow-up was 42.9 months in the durvalumab arm and 41.8 months in the placebo arm.

- The safety profile of durvalumab + gem-cis remained consistent with previous analyses, with no new signals detected.[1,2]
- Among extended long-term survivors (patients alive ≥30 months after baseline; n=88), patients treated with durvalumab + gem-cis were more likely to be extended long-term survivors (n=58/88). No individual subgroup drove long-term survival.[2]

## Three-year follow-up data from KEYNOTE-966

**KEYNOTE-966** was a similar study comparing **gem-cis with or without pembrolizumab**; however, unlike TOPAZ-1,[†] it continued gemcitabine beyond 8 cycles.[3*]




| No. at risk | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembro + gem-cis | 553 | 496 | 430 | 350 | 275 | 217 | 176 | 147 | 131 | 113 | 86 | 64 | 39 | 21 | 15 | 6 | 0 | | |
| Placebo + gem-cis | 536 | 483 | 394 | 313 | 236 | 195 | 149 | 125 | 102 | 86 | 63 | 43 | 27 | 20 | 10 | 4 | 0 | | |

*The 3-year OS analysis was not powered for statistical significance.

Data cut off was November 14, 2023. Median duration of follow-up was 36.6 months.

[†]We cannot draw any definitive conclusions from indirect comparisons, as the study design, demographics and other criteria may differ between trials.

## Additional analyses conducted for TOPAZ-1:*

*These analyses were not powered for statistical significance.

### Patient subgroups
Consistent OS results across various patient subgroups, including regional subgroups,[4] primary tumor location,[5] and disease status.[6]

### Additional safety analysis
Durvalumab + gem-cis was associated with an OS benefit versus placebo, irrespective of imAE occurrence.[1,7]

### QoL
No detriment in QoL as assessed by TTD in the durvalumab group compared with placebo.[8]

### Mutation status
Benefit consistently observed with durvalumab, including in patients with clinically actionable alterations.[9]

### Antibiotics
No meaningful difference in OS for patients who received antibiotics during the study period compared with those who did not.[10]

### Prognostic factors
Analysis supports this regimen in patients with previously untreated advanced BTCs, irrespective of baseline demographics, disease characteristics, clinical or laboratory factors.[11]

### SAT use
Median duration of first SAT was similar for both arms, suggesting that durvalumab does not impact the efficacy of SAT.[3] Longer time to first subsequent anti-cancer therapy in the durvalumab arm compared to the placebo arm (median: 18.7 months [95% CI: 13.2–42.2] and 12.3 months [95% CI: 11.3–24.1]).[2]

## Conclusion

**TOPAZ-1 is the first global Phase III study to evaluate an immuno-oncology-based regimen in the 1L advanced BTC setting, with numerous secondary analyses that support its use in a broad population[1]**


**Data from the 3-year follow-up analysis of TOPAZ-1 supports the use of durvalumab + gem-cis as SoC in patients with locally advanced or metastatic BTCs[2,13]**

### Footnotes:

[a]Chemotherapy and/or radiation; [b]Cisplatin (25 mg/m$^2$) followed by gemcitabine (1,000 mg/m$^2$), each administered on Days 1 and 8, Q3W for up to 8 cycles (SoC chemotherapy); [c]Until confirmed PD, withdrawal of consent, or another discontinuation criteria is met. [d]PFS and ORR were measured according to RECIST v1.1 using investigator assessments.

### Abbreviations:

1L: first line; AE: adverse event; BTC: biliary tract cancer; Durva: durvalumab; ECOG PS: Eastern Cooperative Oncology Group performance status; gem-cis: gemcitabine + cisplatin; imAE: immune-mediated adverse event; IV: intravenous; ORR: objective response rate; OS: overall survival; PD: progressive disease; pembro: pembrolizumab; PFS: progression-free survival; QnW: every n weeks; R: randomization; SAT: subsequent anti-cancer therapy; SoC: standard of care; TRAE: treatment-related adverse event; TTD: time to deterioration.

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