Clinical Study Report Synopsis	
Drug Substance	Durvalumab
Study Code	D933AC00001
Edition Number	1.0
Date	21 February 2022
EudraCT Number	2018-004688-30
NCT Number	NCT03875235

A Phase III Randomized, Double-Blind, Placebo-Controlled, Multi-Regional, International Study of Durvalumab in Combination with Gemcitabine plus Cisplatin versus Placebo in Combination with Gemcitabine plus Cisplatin for Patients with First-Line Advanced Biliary Tract Cancers (TOPAZ-1)

Study dates:
First patient enrolled: 16 April 2019
Last patient enrolled: 11 December 2020
The analyses presented in this report are based on a clinical data lock date of 13 September 2021 (and a DCO of 11 August 2021)

Phase of development:
Therapeutic confirmatory (III)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

Patients were randomized from 17 countries: Asia (374 patients: South Korea [120], Thailand [83], Japan [78], Taiwan [60], India [24], China [5; global cohort only], and Hong Kong [4]), Europe (215 patients: France [47], UK [47], Poland [34], Italy [31], Russian Federation [25], Turkey [18], and Bulgaria [13]), North America (65 patients: all sites within the US), and South America (31 patients: Argentina [22] and Chile [9]).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Objective	Endpoint/variable	IA-2
Primary objective		
To assess the efficacy of Arm A compared to Arm B in terms of OS in patients with first-line advanced BTC [a]	OS	✓
Secondary objective		
To further assess the efficacy of Arm A compared to Arm B in terms of PFS, ORR, and DoR in patients with first-line advanced BTC	Endpoints based on Investigator assessment according to RECIST 1.1: PFS: Time from date of randomization until tumor progression or death due to any cause ORR: The percentage of evaluable patients with Investigator-assessed visit response of CR or PR DoR: Time from first documented response (CR or PR) until date of documented progression or death in the absence of disease progression	✓
For IA-1: To summarize the efficacy of Arm A compared to Arm B in terms of ORR and DoR in patients with first-line advanced BTC	ORR and DoR according to RECIST 1.1 using BICR assessments Note: As per the SAP, analyses of these outcomes were also performed according to Investigator assessment	IA-1
To assess disease-related symptoms, impacts, and HRQoL in patients treated with Arm A compared to Arm B	EORTC QLQ-C30: Global health status/QoL and impacts (eg, physical function); multi-term symptoms (eg, fatigue); and single items (eg, appetite loss, insomnia) EORTC QLQ-BIL21: Single-Item symptoms (eg, abdominal pain [item 42], pruritus [item 36], jaundice [item 35])	✓
To assess the efficacy of Arm A compared to Arm B by PD-L1 expression	Association of PD-L1 expression level with OS, PFS, ORR, DoR, and DCR according to RECIST 1.1 using Investigator assessments	✓
To assess the PK of durvalumab when used in combination with Gem/Cis	Serum concentration of durvalumab (peak and trough concentrations)	✓

Objective	Endpoint/variable	IA-2
To investigate the immunogenicity of durvalumab	Reporting tiered results of ADAs for durvalumab	✓
Safety objective		
To assess the safety and tolerability profile of Arm A compared to Arm B in patients with first-line advanced BTC	AEs, physical examinations, laboratory findings, WHO/ECOG PS, ECG and vital signs	✓
CCI		

[a] Specifically, this was achieved via analysis of superiority of D + Gem/Cis compared to placebo + Gem/Cis therapy. Patients in Arm A were assigned to D + Gem/Cis combination therapy; patients in Arm B were assigned to placebo + Gem/Cis therapy.

ADA, anti-drug antibody; AE, adverse event; BICR, blinded independent central review; BTC, biliary tract cancer; Cis, cisplatin 25 mg/m^2; CR, complete response; CSR, clinical study report; CCI DCR, disease control rate; DoR, duration of response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; CCI EORTC, European Organisation for Research and Treatment of Cancer; Gem, gemcitabine 1000 mg/m^2; CCI HRQoL, health-related quality of life; IA-1, Interim analysis-1; IA-2, Interim analysis-2; CCI ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; CCI PK, pharmacokinetic(s); PR, partial response; CCI PS, performance status; QLQ-BIL21, 21-Item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire; QLQ-C30, 30-Item Cancer Quality-of-Life Questionnaire; QoL, quality-of-life Questionnaire; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAP, statistical analysis plan; CCI WHO, World Health Organization.

Study design

This is a Phase III randomized, double-blind, placebo-controlled, multi-regional, study to assess the efficacy and safety of first-line treatment with durvalumab in combination with gemcitabine/cisplatin (D + Gem/Cis) versus placebo in combination with gemcitabine/cisplatin (placebo + Gem/Cis) in patients previously untreated for unresectable locally advanced or metastatic BTC. Randomization was stratified by disease status (initially unresectable versus recurrent) and primary tumor site (IHCC versus EHCC versus GBC).

Patients who fulfilled all of the inclusion criteria and none of the exclusion criteria were to be randomized in a 1:1 ratio to cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 (each administered on Days 1 and 8; Q3W) in combination with durvalumab 1500 mg (D + Gem/Cis) or placebo (placebo + Gem/Cis) via IV infusion (on Day 1; Q3W); starting on Cycle 1, for up to 8 cycles. After completing the chemotherapy treatment period, patients received 1500 mg durvalumab or placebo as monotherapy via IV infusion Q4W until clinical progression (or RECIST 1.1-defined radiological PD), unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met. An unblinded pharmacist prepared the IV solution for administration.

Tumor assessments were performed every 6 weeks (± 1 week) for the first 24 weeks (relative to the date of randomization) and then every 8 weeks (± 1 week) thereafter until RECIST 1.1-defined radiological disease progression (relative to the date of randomization) plus at least 1 additional follow-up scan. Up to IA-1, scans underwent BICR assessment. BICR results were not communicated to Investigators and the management of patients was based solely upon the Investigators' findings.

Target population and sample size

Eligibility criteria were selected to ensure enrolment of a wide range of patients with BTC including patients with cholangiocarcinoma (intrahepatic, extrahepatic) and GBC.

In this first-line setting, enrolment included adult patients with histologically confirmed locally advanced or metastatic BTC, who developed recurrent disease > 6 months after surgery (curative intent) or who had completed adjuvant therapy (chemotherapy and/or radiation) more than 6 months before the start of study treatment, with at least one target lesion by RECIST 1.1, and adequate organ and bone marrow function, and a WHO/ECOG PS of 0 or 1. Patients diagnosed with unresectable disease or metastatic at initial diagnosis were also included if previously untreated. The use of Gem/Cis as SoC in the study population was consistent with NCCN, ESMO, and Japanese treatment guidelines for BTC.

The study was powered to demonstrate superiority in the OS benefit of D + Gem/Cis versus placebo + Gem/Cis in patients previously untreated for unresectable locally advanced or metastatic BTC.

A hypothesis of improved OS could be tested using the global cohort when:

- Approximately [redacted] across D + Gem/Cis and placebo + Gem/Cis treatment groups [redacted] (IA-2).
  - Actual at DCO: 424 of the 496 expected OS events had occurred (85.5% of total expected events at FA; representing an 61.9% overall maturity for OS).
- Approximately [redacted] across D + Gem/Cis and placebo + Gem/Cis treatment groups [redacted] (FA).

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Details of the investigational products are presented in Table S1.

Table S1 Details of Study Treatments

	Treatment 1	Treatment 2	Treatment 3
Study treatment name	Durvalumab (MEDI4736)	Placebo (sterile saline or dextrose solution)	Standard of care (chemotherapy) [a]
Dosage formulation	500 mg vial solution for infusion after dilution, 50 mg/mL	Sterile solution of 0.9% (w/v) sodium chloride or 5% (w/v) dextrose for injection	As sourced locally
Route of administration	IV	IV	IV
Dosing instructions [b]	1500 mg IV Q3W or Q4W	0.9% (w/v) saline or 5% (w/v) dextrose volume matching durvalumab volume	Cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 on Day 1 and Day 8 Q3W for up to 8 cycles
Packaging and labelling	Study treatments were provided in 500 mg vials. Each vial was labelled in accordance with GMP Annex 13 and per country regulatory requirement [c]	Sourced locally by site	Sourced locally by site
Provider	AstraZeneca	Sourced locally by site	Sourced locally by site[d]
Batch numbers	[redacted]		NA

[a] The Gem/Cis regimen recommended for first-line BTC treatment according to NCCN, ESMO, and Japanese guidelines was adopted in this study.

[b] Detailed instructions on IP administration were provided in Sections 6.1.1.1, 6.1.1.2, and 6.1.1.3 of the CSP. Refer to Section 6.1.2 of the CSP for details on the duration of treatment.

[c] Label text prepared for durvalumab (MEDI4736) showed the product name as "MEDI4736" or "durvalumab (MEDI4736)," depending upon the agreed product name used in the approved study master label document. All naming conventions were correct during this transitional period.

[d] Under certain circumstances, when local sourcing was not feasible, an SoC (chemotherapy) treatment could be supplied centrally through AstraZeneca.

Under certain circumstances, rescue medication could be supplied by the Sponsor.

Abbreviations: BTC, biliary tract cancer; Cis, cisplatin 25 mg/m^2; CSP, clinical study protocol; ESMO, European Society for Medical Oncology; Gem, gemcitabine 1000 mg/m^2; GMP, Good Manufacturing Practice; IP, investigational product; IV, intravenous; NCCN, National Comprehensive Cancer Network; Q3W, every 3 weeks; Q4W, every 4 weeks; SoC, standard of care; w/v, weight/volume.

Duration of treatment

Patients received cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 (each administered on Days 1 and 8 Q3W) plus durvalumab 1500 mg (D + Gem/Cis) or placebo (placebo + Gem/Cis) via IV infusion Q3W, starting on Cycle 1, for up to 8 cycles. During Day 1 visits of each cycle, treatment administration of durvalumab or placebo occurred first, followed by chemotherapy. After completing the Gem/Cis treatment period, patients received 1500 mg durvalumab or placebo as monotherapy via IV infusion Q4W until clinical progression (or RECIST 1.1-defined radiological PD), unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

For patients who discontinued Gem/Cis due to causally related toxicity before completion of Cycle 8, treatment could continue with durvalumab or placebo monotherapy (Q4W) at the Investigator's discretion. During the first 8 cycles of durvalumab or placebo in combination with Gem/Cis, if durvalumab or placebo was discontinued due to durvalumab- or placebo-related toxicity, the patient was discontinued from study treatment.

During the treatment period, patients who were clinically stable at an initial RECIST 1.1-defined radiological PD could continue to receive study treatment at the discretion of the Investigator and patient as long as they were deemed to be receiving clinical benefit. Patients with rapid tumor progression or with symptomatic progression that required urgent medical intervention were not eligible for continuing durvalumab (or placebo).

Statistical methods

Analyses were pre-defined. Missing safety data were generally not imputed.

The key analysis sets comprised: FAS (all randomized patients [as randomized, regardless of actual treatment]); safety analysis set (all patients who received at least 1 dose of study treatment [as treated; a patient received any amount of durvalumab was reported in the D + Gem/Cis group]), PK analysis set (all patients who received at least 1 dose of durvalumab

per the protocol for whom any post-dose data are available and who did not violate or deviate from the protocol in ways that would significantly affect the PK analyses [as treated]); and ADA analysis set (all patients with non-missing baseline ADA and at least 1 post-baseline ADA result).

IA-1 (conducted in March 2021) included 685 randomized patients and was performed after randomization to the global cohort was complete and included 369 randomized patients who had had an opportunity to be followed up for at least 32 weeks (ie, randomized ≥ 32 weeks prior to the IA-1 DCO of 18 December 2020 [FAS 32w]). A small alpha expenditure of 0.001 was allocated to IA-1. The objective of IA-1 was to evaluate the efficacy of D + Gem/Cis in terms of clinical activity (as measured by ORR and DoR, per BICR assessment).

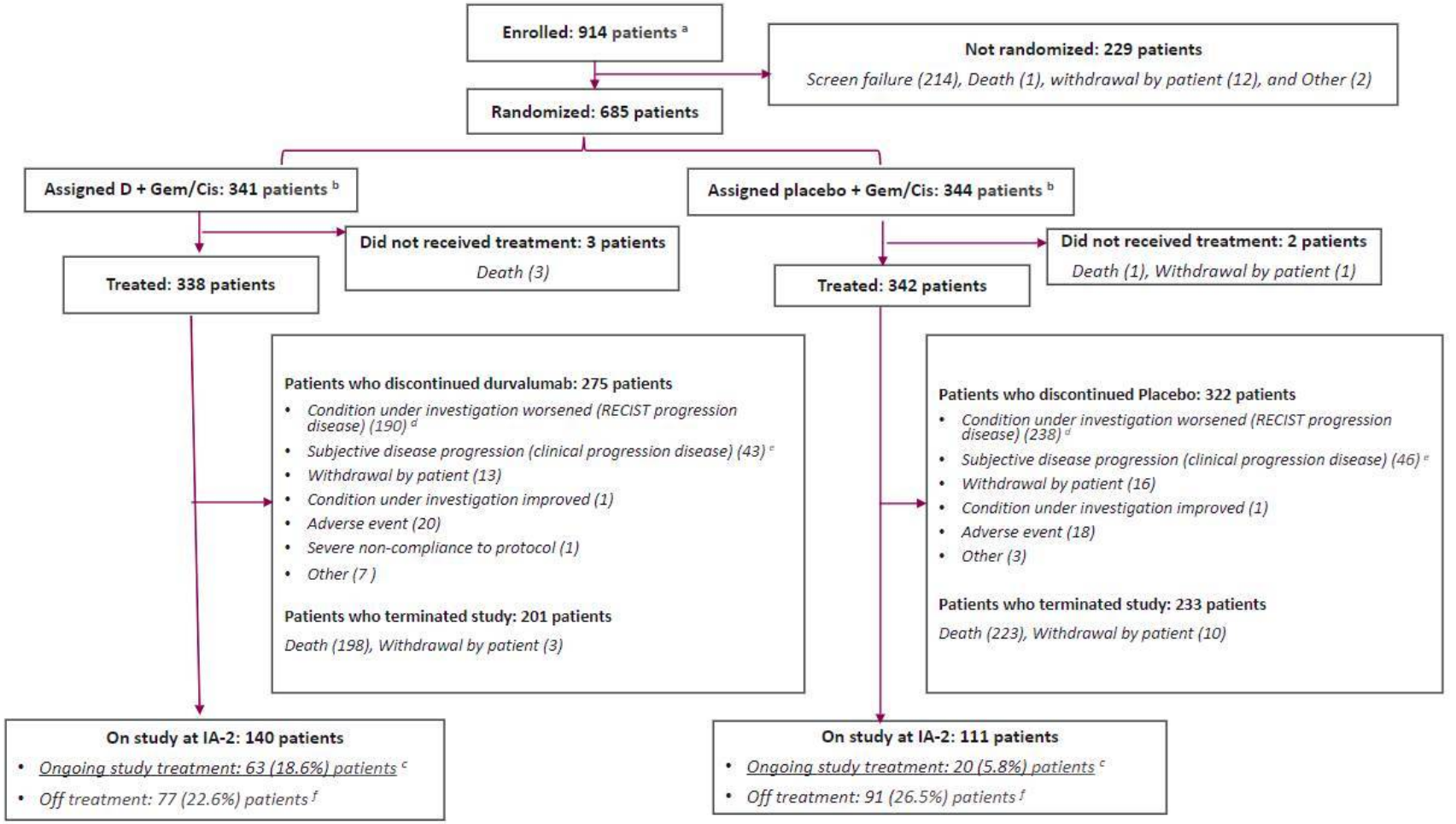
Strong control of the FWER at the remaining 4.9% level (2-sided) across the testing of OS and PFS endpoints was achieved through a combined approach of alpha allocation to the OS analyses (IA-2; whilst making provision for the potential for a subsequent, planned FA) via alpha-spending function and a hierarchical testing procedure. Progression-free survival was tested only after OS had met statistical significance at IA-2. The OS IA-2 occurred when 85.5% of the final number of expected OS events at FA was reached (424 of 496 OS events). Using the Lan DeMets spending function approximating O'Brien-Fleming boundaries, a 2-sided significance level of 0.0300 was applied to OS IA-2 for the log-rank test for OS. CCI [redacted]

The primary objective at IA-2 (DCO: 11 August 2021) was to evaluate the superiority of D + Gem/Cis compared with placebo + Gem/Cis in terms of OS, as analyzed using a stratified log-rank test (stratified by disease status and primary tumor location) to assess statistical inference. The treatment effect was estimated by HR and its 95% CI based on a Cox proportional hazards model (stratified by disease status and primary tumor location). Kaplan-Meier plots of OS were presented by treatment, and median OS and estimated OS rates at 12, 18, and 24 months were presented. As a lack of proportionality was evident, the variation in treatment effect was also described by piecewise HR (using Cox modelling). Progression-free survival, the key secondary endpoint, was analyzed using the same methodology as for OS. The ORR was analyzed using a stratified CMH test adjusting for the same factors as the primary endpoint OS. The treatment effect was estimated by odds ratio, 95% CI, and p-value. The remaining secondary endpoints (BOR, DCR, DoR, and change in target lesion size) were summarized descriptively. Prespecified subgroup analyses for OS, PFS, and ORR included disease status, primary tumor location, sex, age, race (Asian, Non-Asian ethnicity), region (Asia, ROW), WHO/ECOG PS (0, 1), extent of disease (locally advanced, metastatic), and PD-L1 status (TIP ≥ 1% versus < 1%). The MSI subgroup analyses were not performed because there were too few MSI High patients.

Study population

The causes of study treatment discontinuation were consistent with the disease under study and the study treatments. At IA-2 DCO, 63 (18.6%) patients were still receiving treatment with durvalumab and 20 (5.8%) patients were still receiving treatment with placebo (Figure S1).

Figure S1 Patient Disposition (All Patients)



[a] Informed consent received.

[a] Full analysis set - all patients randomized regardless of study treatment administration.

[b] Percentages were calculated from number of patients who received any treatment.

[c] RECIST 1.1-defined radiological progression of disease.

[d] Clinical progression without RECIST 1.1-defined radiological progression of disease.

[e] May include patients who never received study treatment.

Cis, cisplatin 25 mg/m^2; D, durvalumab 1500 mg; Gem, gemcitabine 1000 mg/m^2; IA-2, interim analysis 2; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Source: Table 14.1.1.

The observed protocol deviations do not raise any concerns regarding the overall conduct or quality of the study or the interpretation of the results, or with respect to the safety profile observed within the patient population described at IA-2 (reported for 4.7% patients in the D + Gem/Cis group vs 1.7% patients in the placebo + Gem/Cis group). The principal difference between the two treatment groups is that 8 patients randomized to the D + Gem/Cis group received a single (first administration) of placebo and were subsequently treated with D + Gem/Cis as per their randomized allocation. Overall, both treatment groups were similar in terms of minimal impact from the COVID-19 pandemic, which is not judged to have meaningfully impacted the overall quality of the study, including the conduct, data, and interpretation of results.

Both treatment groups were similar in terms of the number of patients in the various analysis sets (Table S2).

Table S2 Analysis Sets

	Number of patients		
	D + Gem/Cis (N = 341)	**Placebo + Gem/Cis (N = 344)**	**Total (N = 685)**
Patients randomized [a]	341	344	685
Patients included in full analysis set [a]	341	344	685
Patients included in safety analysis set [b]	338	342	680
Patients included in PK analysis set [c]	314	0	314
Patients included in ADA analysis set [d]	240	231	471

[a] The FAS was defined as all randomized patients and was analyzed on an ITT basis.

[b] The safety analysis set was defined as all patients who received any amount of study treatment.

[c] The PK analysis set was defined as all patients who received at least one dose of D for whom any post-dose PK data are available.

[d] The ADA analysis set - all patients who received at least one dose of D or placebo for whom baseline and any post-dose ADA data are available.

ADA, antidrug antibody; Cis, cisplatin 25 mg/m^2; D, durvalumab 1500 mg; FAS, full analysis set; Gem, gemcitabine 1000 mg/m^2; ITT, intent-to-treat; PK, pharmacokinetic(s).

Source: Table 14.1.4.

The median age was 64 years (range: PPD with 46.7% of patients aged 65 years or older. Approximately half of patients were male (50.4%), and 56.4% of patients were of Asian ethnicity. Demographic characteristics were balanced across both treatment groups.

Overall, disease characteristics at screening were balanced across both treatment groups (Table S3).

Table S3 Key Disease Characteristics (FAS)

	Number (%) of patients		
	D + Gem/Cis (N = 341)	**Placebo + Gem/Cis (N = 344)**	**Total (N = 685)**
Stratification factors, per IVRS			
Initially unresectable	274 (80.4)	276 (80.2)	550 (80.3)
Recurrent	67 (19.6)	68 (19.8)	135 (19.7)
Primary tumor location			
IHCC	194 (56.9)	197 (57.3)	391 (57.1)
EHCC	62 (18.2)	63 (18.3)	125 (18.2)
GBC	85 (24.9)	84 (24.4)	169 (24.7)
Histology type			
Adenocarcinoma	311 (91.2)	313 (91.0)	624 (91.1)
Overall disease classification			
Any Locally advanced	209 (61.3)	213 (61.9)	422 (61.6)
Locally advanced only	38 (11.1)	57 (16.6)	95 (13.9)
Any Metastatic	303 (88.9)	286 (83.1)	589 (86.0)
WHO/**ECOG PS**			
(0) Normal activity	173 (50.7)	163 (47.4)	336 (49.1)
(1) Restricted activity	168 (49.3)	181 (52.6)	349 (50.9)
PD-LI expression			
High (TIP ≥ 1%)	197 (57.8)	205 (59.6)	402 (58.7)
Low/negative (TIP < 1%)	103 (30.2)	103 (29.9)	206 (30.1)
Missing	41 (12.0)	36 (10.5)	77 (11.2)
MSI status			
High	3 (0.9)	2 (0.6)	5 (0.7)
Stable	160 (46.9)	168 (48.8)	328 (47.9)
Missing [a]	178 (52.2)	174 (50.6)	352 (51.4)
Virology status			
No Viral Hepatitis	187 (54.8)	174 (50.6)	361 (52.7)
Any Viral Hepatitis B	69 (20.2)	81 (23.5)	150 (21.9)
Prior Hepatitis C	8 (2.3)	10 (2.9)	18 (2.6)
Missing	82 (24.0)	83 (24.1)	165 (24.1)

[a] Overall, 5 of 333 (1.5%) patients with an MSI result were MSI high (Table 14.1.6) MSI status missing includes MSI-unknown and not tested.

Cis, cisplatin 25 mg/m^2; D, durvalumab 1500 mg; ECOG, Eastern Cooperative Oncology Group; EHCC, extrahepatic cholangiocarcinoma; FAS, full analysis set; GBC, gallbladder cancer; Gem, gemcitabine 1000 mg/m^2; IHCC, intrahepatic cholangiocarcinoma; IVRS, interactive voice response system; MSI, microsatellite instability; N, number of patients in treatment group; n = Number of patients in category or analysis; PD-L1, programmed cell death-ligand-1; PS, performance status; TIP, tumor and/or immune cell positivity; WHO, World Health Organization.

The extent of disease at baseline was generally balanced across both treatment groups, including the presence of lymph node, liver, and/or bone and locomotor metastases (overall, reported for 51.7%, 42.8%, and 7.3% patients, respectively).

The past and current medical history reported was generally typical of the co-morbidities seen in this patient population, and similar between both treatment groups. Previous BTC treatment included adjuvant cytotoxic chemotherapy (7.6% patients) and radiotherapy (2.8% patients) and balanced between both treatment groups. Among patients who had received prior systemic adjuvant chemotherapy, 94.2% of had received a single prior regimen.

Overall, 104 (15.2%) patients had a prior history of biliary stenting or drainage procedures at baseline and 186 (27.2%) patients had undergone other prior surgical procedures for BTC (curative for 19.1% patients and non-curative for 8.0% patients). Concomitant (on-study) surgery related to disease under study was reported for 4 (1.2%) patients in the D + Gem/Cis group and 5 (1.5%) patients in the placebo + Gem/Cis group.

Overall, subsequent anti-cancer therapy was reported for 145 (42.5%) patients in the D + Gem/Cis group and 170 (49.4%) patients in the placebo + Gem/Cis group (mostly, cytotoxic chemotherapy: 137 [40.2%] patients and 156 [45.3%] patients, by respective treatment group).

A total of 178 patients in the D + Gem/Cis group vs 196 patients in the placebo + Gem/Cis group were randomized from sites in Asia and 163 patients vs 148 patients (by respective treatment group) were randomized from sites outside of Asia (RoW). Overall and by treatment group, the demographic characteristics of patients were balanced between regions. Overall, the observed baseline characteristics reflected the multi-regional design of TOPAZ-1. The distribution of baseline characteristics by region (Asia vs RoW) displayed some differences, including the observation that the cohort from Asian countries had higher rates of recurrent disease at baseline, WHO/ECOG PS of 1, metastatic disease, hepatitis B infection (any), and PD-L1 expression high status (TIP $\geq$ 1%).

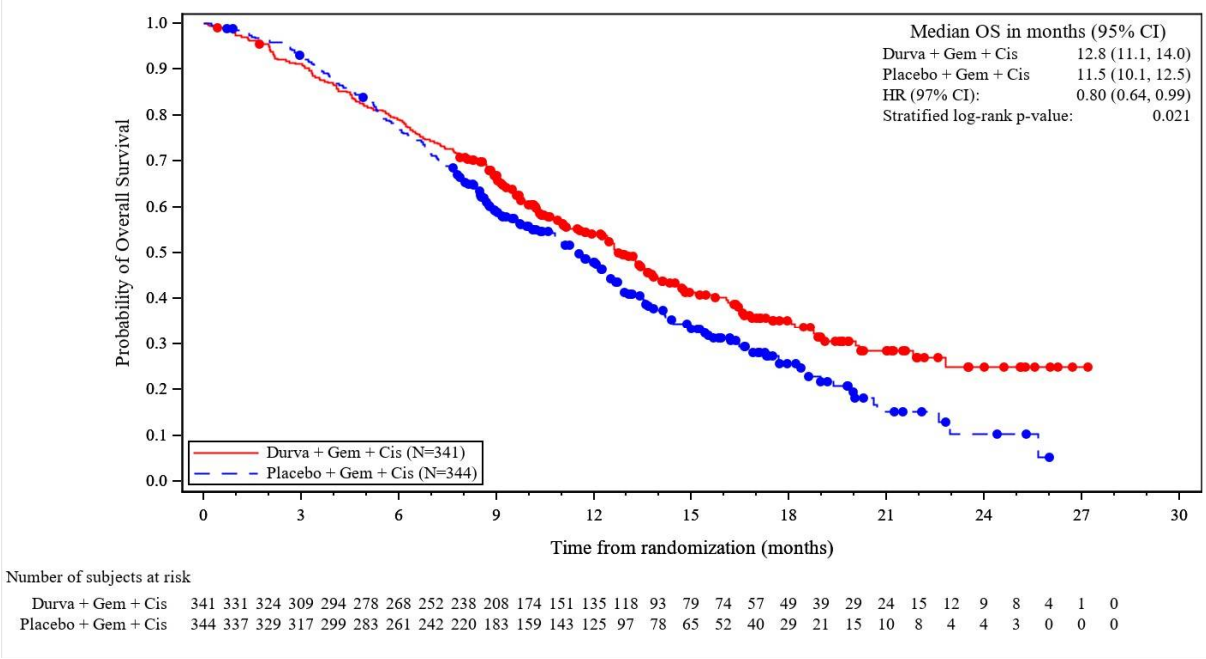
Summary of efficacy results

Primary endpoint

TOPAZ-1 was conducted in all-comer first-line BTC patients and represents the largest of currently ongoing international, Phase III studies in BTC to report data. The study, which employed a rigorous, double-blind, placebo-controlled study design, met its primary objective at IA-2 (61.9% overall maturity for OS) by demonstrating the superiority of OS for D + Gem/Cis versus placebo + Gem/Cis in patients previously untreated for unresectable locally advanced or metastatic BTC. Note: At IA-2, more patients were still receiving treatment with durvalumab than placebo (63 [18.6%]) vs 20 [5.8%] patients, by respective treatment).

At the time of the IA-2, 424 death events had occurred (85.5% of total expected events at FA; representing 61.9% overall maturity for OS). Treatment with D + Gem/Cis resulted in a statistically significant, clinically meaningful, and sustained improvement in OS compared with placebo + Gem/Cis: HR of 0.80 (97% CI: 0.64, 0.99, p = 0.021); corresponding to an 20% reduction in the overall risk of death. The OS curves were similar until 6 months, after which there was a clear and sustained separation of OS curves that favored D + Gem/Cis, with the difference in OS between treatment groups becoming increasingly apparent over time (Figure S2).

Figure S2 Kaplan-Meier Plot of OS (FAS)



Patients not known to have died at the time of analysis were censored at the last recorded date on which the patient was last known to be alive.

Dots indicate a censored observation.

CI, confidence interval. Cis, cisplatin 25 mg/m^2; Durva, durvalumab 1500 mg; FAS, full analysis set; Gem, gemcitabine 1000 mg/m^2; HR, hazard ratio; OS, overall survival.

The median OS was longer with D + Gem/Cis (12.8 months [95% CI: 11.1, 14]) compared with placebo + Gem/Cis (11.5 months [95% CI: 10.1, 12.5]). The difference in OS between treatment groups was increasingly apparent over time, as seen with the estimated OS rates at 12 months (54.1% for D + Gem/Cis vs 48.0% for placebo + Gem/Cis), 18 months (35.1% vs 25.6%), and 24 months (24.9% vs 10.4%).

The kernel-smoothed hazard estimates (post hoc analysis) and the log-log (event times) versus log (time) curves both confirmed a departure from the assumption of proportional hazards, with a turning point around 6 months. The piecewise HR was 0.91 (95% CI: 0.66, 1.26) from 0 to 6 months and 0.74 (95% CI: 0.58, 0.94) after 6 months (ie, before and after separation of the OS curves). At DCO, 78.6% patients were alive in the D + Gem/Cis group at 6 months and had the opportunity for treatment benefit from the addition of D to Gem/Cis, with OS events or drop-out reported for reported for 21.4% of patients prior to 6 months.

The results of the sensitivity analyses of OS were consistent with those of the primary OS analysis (ie, there was no impact on findings due to potential attrition bias and covariates did not impact the treatment effect).

A prespecified analysis to assess interaction with the treatment effect from stratification factors (disease status [initially unresectable, recurrent] and primary tumor location [intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer]) demonstrated consistency of treatment effect. Improvements in OS, in favor of patients receiving D + Gem/Cis, were consistently observed across the prespecified subgroups, including PD-L1 negative/low (category TIP < 1%). However, the study was not sized for any of the individual subgroup evaluations and no adjustments were made for multiplicity. The lower number of patients and events across the individual subgroups may lead to greater uncertainty in their point estimates and wider CIs. It is also noted that imbalance in other baseline covariates may have contributed to differences in HR across subgroups. In alignment with the prespecified analysis at the TIP 1% cut-off, post hoc analyses using additional TIP cut-offs (5% and 10%) indicated a consistency of treatment effect across PD-L1 subgroups, which suggests that PD-L1 expression may not be a useful predictive biomarker to guide durvalumab use in BTC.

At the prespecified IA-2 analysis (with 61.9% overall maturity for OS), the D + Gem/Cis group performed similarly to other studies of immune checkpoint inhibitors + chemotherapy vs chemotherapy alone (conducted in multiple solid tumor types), including delayed

separation of the OS curves and a subset of patients with enduring OS, as reflected in the relatively flat tail of the OS curve from around 18 months. At IA-2, Gem/Cis had performed as expected, with a median OS that was consistent the historical median OS of approximately 1 year. In contrast to the D + Gem/Cis group, the placebo + Gem/Cis OS curve showed the expected continuing decline that is typical with chemotherapies (ie, approaching zero more rapidly and without evidence of a subgroup of individuals with long-term OS, ie, the absence of a tail or plateau in the OS curve for the placebo + Gem/Cis group).

Planned follow-up of long-term survivorship

Given that the difference between treatment groups for OS in favor of D + Gem/Cis was increasingly apparent over time (including a larger number of censored patients still at risk in the later time points for D + Gem/Cis compared to placebo + Gem/Cis), additional follow-up may allow for further characterization of long-term survivorship from D + Gem/Cis. In contrast, substantial change in the OS Kaplan-Meier curve for the placebo + Gem/Cis group is not expected, as the median OS was consistent with published studies, including ABC-02 that also showed remarkably similar OS rates at 18 and 24 months in the Gem/Cis arm. In TOPAZ-1, at 65.7% maturity for the placebo + Gem/Cis group, only 4 patients were observed as alive at 24 months; falling to zero by 26 weeks. The similarity between current data from TOPAZ-1 and published data suggest that (with additional follow-up) long-term survivorship in this treatment group will be similar to ABC-02, in which only 2 patients were observed as alive at 30 months.

This remarkable similarity to published studies (including ABC-02), the representative nature of patients recruited to TOPAZ-1, together with the OS data maturity at IA-2 indicate that the OS curve for the placebo will remain similar with longer follow-up and fully recapitulate that of ABC-02. Additionally, within TOPAZ-1, a substantial number of long-term objective responders was absent from the placebo + Gem/Cis group, 86.3% patients had progressed or died, the estimated PFS rate at 12 months was 6.6%, and only 5.8% patients remained on study treatment. There have been no major advancements to improve OS in second-line therapy for BTC since ABC-02. Most patients go on to receive standard chemotherapy, as was the case for TOPAZ-1, in which 293 of 315 patients who received subsequent anti-cancer therapy went on to receive chemotherapy). Consequently, substantial prolongation of OS resulting from second-line therapies are not anticipated.

CCI [redacted]

Key secondary endpoint

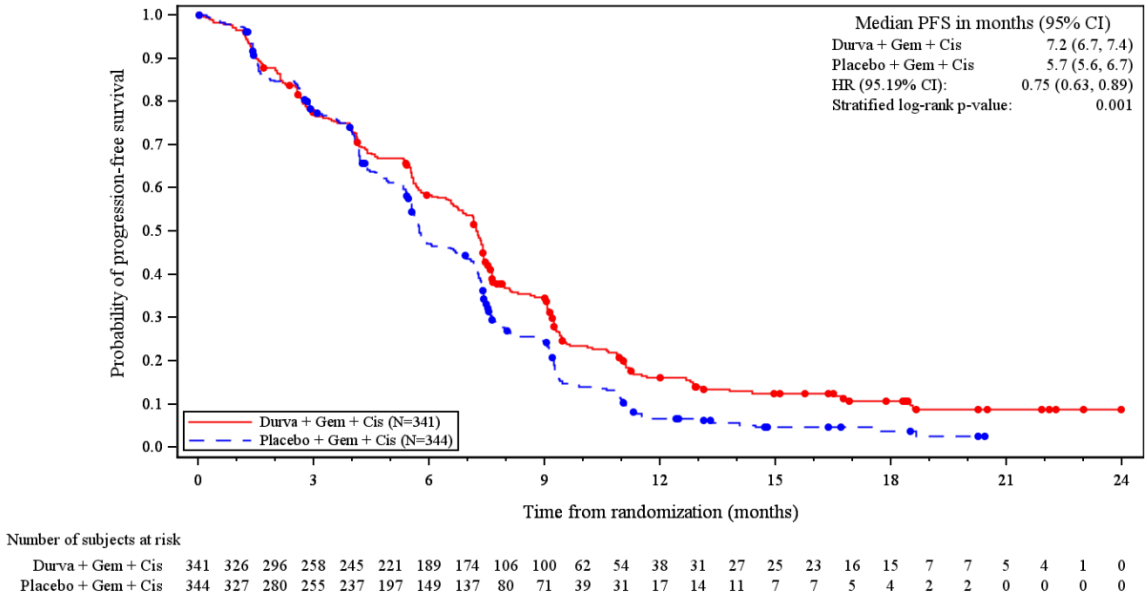
PFS was included in the multiple testing procedures and could be formally tested. At the time of the IA-2, 573 of the 590 expected PFS events at FA had occurred (97.1% of total expected events at FA; representing an 83.6% overall maturity for PFS). Treatment with D + Gem/Cis resulted in a statistically significant, clinically meaningful, and sustained improvement in PFS compared with placebo + Gem/Cis: the HR was 0.75 (95.19% CI: [0.63, 0.89], p = 0.001); corresponding to a 25% reduction in the overall risk of progression or death with the addition of D to Gem/Cis.

Overall, the PFS curves were similar until 4 months, after which there was a sustained separation of PFS curves that favored D + Gem/Cis (Figure S3).

The median PFS was longer with D + Gem/Cis (7.2 months [95% CI: 6.7, 7.4]) compared to placebo + Gem/Cis (5.7 months [95% CI: 5.6, 6.7]). The sustained difference in PFS between both treatment groups was reflected in the estimated PFS rates at 6 months (58.3% in the D + Gem/Cis group vs 47.2% for placebo + Gem/Cis), 9 months (34.8% vs 24.6%), and 12 months (16.0% vs 6.6%).

At the prespecified IA-2 analysis (with 83.6% overall maturity for PFS), more patients were progression-free in the D + Gem/Cis group (56 [16.4%] patients in the D + Gem/Cis group vs 28 [8.1%] patients in the placebo + Gem/Cis group). The D + Gem/Cis PFS curve suggests a subset of patients with enduring PFS, as reflected in the tail of the PFS curve after 12 months. In contrast to the D + Gem/Cis group, the placebo + Gem/Cis PFS curve showed the expected continuing decline that is typical with chemotherapies (ie, approaching zero more rapidly and without evidence of a subgroup of individuals with long-term PFS).

Figure S3 Kaplan-Meier Plot of PFS (FAS)



Dots indicate a censored observation.

PFS based on Investigator assessments according to RECIST 1.1.

Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment prior to the 2 missed visits and therefore excluded from the number of events.

CI, confidence interval. Cis, cisplatin 25 mg/m^2; Durva, durvalumab 1500 mg; FAS, full analysis set; Gem, gemcitabine 1000 mg/m^2; HR, hazard ratio; N, number of patients in treatment group; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

The results of the sensitivity analyses of PFS were consistent with those of the primary PFS analysis: no impact on findings from potential attrition bias, covariates did not impact the treatment effect, and a sensitivity analysis to assess any potential evaluation-time bias that could be introduced if scans were not performed at the protocol-scheduled time points.

A prespecified analysis to assess interaction with the treatment effect from stratification factors demonstrated consistency of treatment effect. Improvements in PFS in favor of patients receiving D + Gem/Cis (compared to those receiving placebo + Gem/Cis) were consistently observed across the prespecified subgroups. All the estimated HRs favored D + Gem/Cis. The lower number of patients and events across the individual subgroups may lead to greater uncertainty in their point estimates and wider CIs. It is also noted that imbalance in other baseline covariates may have contributed to differences in HR across subgroups.

Secondary endpoints

ORR, BOR, and tumor shrinkage

Treatment with D + Gem/Cis resulted in a clinically meaningful improvement in confirmed ORR (per Investigator using RECIST 1.1]) compared with placebo + Gem/Cis: 91 (26.7%) vs 64 (18.7%), by respective treatment group (odds ratio: 1.60 [95% CI: 1.11, 2.31], nominal p = 0.011). The ORR benefit with D + Gem/Cis was consistently observed across the prespecified subgroups and sensitivity analyses. Note: Up to IA-1, scans underwent BICR assessment. Results were not communicated to Investigators and the management of patients was based solely upon the Investigators' findings. There was general concordance between BICR and Investigator assessments of ORR (patients with measurable disease at baseline) at IA-1: 28.6% and 28.1% (respectively) for the D + Gem/Cis group vs 19.6% and 17.9% (respectively) for the placebo + Gem/Cis group. The Investigator assessed ORR (patients with measurable disease at baseline) at IA-1 (FAS-32w, N = 369) and at IA-2 (FAS, N = 684) were consistent.

For D + Gem/Cis, there were more complete responses (7 [2.1%] patients compared to 2 [0.6%] patients in the placebo + Gem/Cis group) and more partial responses (84 [24.6%] compared to 62 [18.1%] patients, by respective treatment group). As expected, irrespective of treatment, OS was longer for patients who achieved objective response compared to non-responders, but there were substantially more responders in the D + Gem/Cis group compared to the placebo + Gem/Cis group.

Overall, responses occurred earlier for D + Gem/Cis compared to placebo + Gem/Cis (median of 1.6 months compared to 2.7 months, respectively).

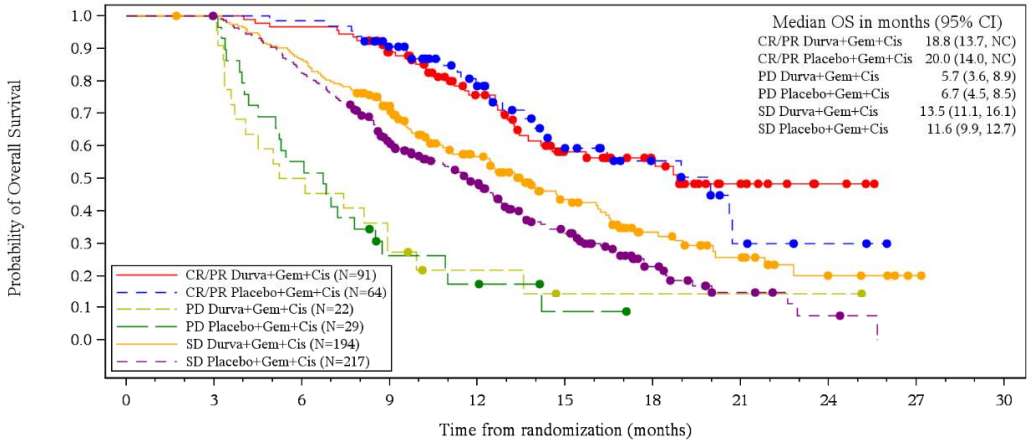
The first post-baseline tumor assessment was scheduled for 6 ± 1 weeks after randomization, and a BOR of SD of at least 5 weeks' duration was reported for 200 (58.7%) patients in the D + Gem/Cis group vs 220 (64.1%) patients the placebo + Gem/Cis group. A BOR of PD was reported at a similar frequency in both treatment groups (13.8% and 14.9% patients, by respective treatment group).

OS by response status (post hoc analysis)

The OS benefit for D + Gem/Cis was driven not only by responders but also by patients with a BOR of SD (Figure S4). As expected, irrespective of treatment, OS was longer for patients who achieved objective response compared to non-responders, but there were substantially more responders in the D + Gem/Cis group (n = 91) compared to the placebo + Gem/Cis group (n = 64), with the D + Gem/Cis group, also showing better DoR. Among patients with a BOR of SD, there was a clear and sustained separation of the OS curves from approximately 5 months, with a median OS of 13.5 months for D + Gem/Cis compared to 11.6 months for

placebo + Gem/Cis. The difference between treatment groups for OS among patients with a BOR of SD was increasingly apparent over time, as seen with the estimated OS rates at 12 months (56.8% for D + Gem/Cis vs 48.5% for placebo + Gem/Cis), 18 months (33.5% vs 22.9%), and 24 months (20.1% vs 7.4%).

Figure S4 **Kaplan-Meier Plot of OS by Confirmed Objective Response (RECIST 1.1, per Investigator) (Post Hoc Analysis) (FAS Patients With Objective Response and Measurable Disease at Baseline)**



Number of subjects at risk

CR/PR Durva+Gem+Cis	91	91	91	91	91	88	88	88	84	75	68	58	51	45	38	31	29	25	22	16	12	9	6	5	3	2	0	0	0
CR/PR Placebo+Gem+Cis	64	64	64	64	64	63	63	62	60	52	46	41	35	28	23	18	17	12	11	9	7	4	3	2	2	2	0	0	0
PD Durva+Gem+Cis	22	22	22	22	15	13	11	10	9	6	4	3	3	3	2	1	1	1	1	1	1	1	1	1	1	1	0	0	0
PD Placebo+Gem+Cis	29	29	29	29	23	20	16	12	10	6	6	4	4	3	3	1	1	1	0	0	0	0	0	0	0	0	0	0	0
SD Durva+Gem+Cis	194	194	193	193	186	175	167	154	145	127	102	90	81	70	53	47	44	31	26	22	16	14	8	6	5	5	4	1	0
SD Placebo+Gem+Cis	217	217	217	216	206	195	178	164	147	122	105	96	84	65	52	46	34	27	18	12	8	6	5	2	2	1	0	0	0

Patients not known to have died at the time of analysis were censored at the last recorded date on which the patient was last known to be alive. Dots represented censored observations.

Note: A 3-month landmark analysis is in use.

Cis, cisplatin 25 mg/m^2; CI, confidence interval; CR, complete response; D, durvalumab 1500 mg; FAS, full analysis set; Gem, gemcitabine 1000 mg/m^2; OS, overall survival; NC, not calculable; PR, partial response; PD, progressive disease; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Patients with a BOR of SD that had any tumor shrinkage: minor responders (post hoc analysis)

Overall, tumor shrinkage was larger for D + Gem/Cis compared to placebo + Gem/Cis. In both treatment groups, around two-thirds of patients with a BOR of SD had any tumor shrinkage (ie, up to < 30% reduction in target lesions) but the magnitude of the tumor shrinkage was larger for these patients in the D + Gem/Cis group. Among these minor responders, there was a clear, early, and sustained separation of the OS curves that favored D + Gem/Cis, with a median OS of 14.0 months for D + Gem/Cis compared to 12.5 months for placebo + Gem/Cis. The difference between treatment groups for minor responders was increasingly apparent over time, as seen with the estimated OS rates at 12 months (59.9% for

D + Gem/Cis vs 51.1% for placebo + Gem/Cis), 18 months (36.5% vs 25.2%), and 24 months (24.2% vs 6.0%).

DoR

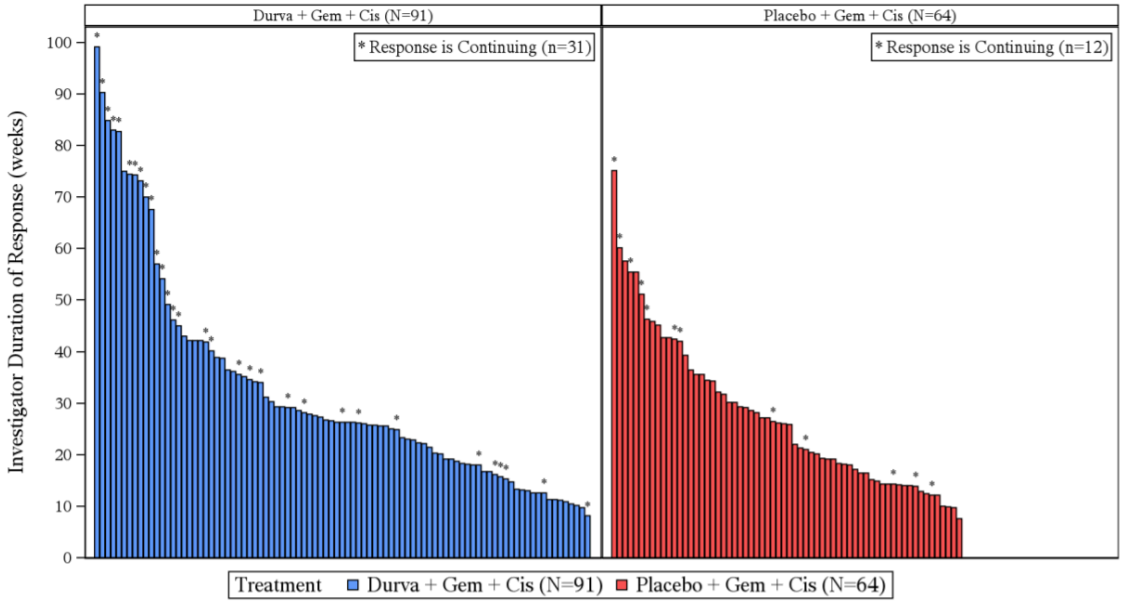
In addition to there being more confirmed responses in the D + Gem/Cis group (91 patients) than in the placebo + Gem/Cis group (64 patients), the responses in the D + Gem/Cis group were more durable.

The DoR Kaplan-Meier curves favored D + Gem/Cis from 4 months with a subset of patients with enduring DoR reflected in the tail of the curve from 9 months, as reflected in the higher estimates for rates for patients remaining in response at 9 months (32.6% patients in the D + Gem/Cis group vs 25.3% patients in the placebo + Gem/Cis group) and at 12 months (26.1% vs 15.0% patients). In contrast, the placebo + Gem/Cis DoR curve showed continuing decline over time.

At DCO, the interquartile range for DoR ranged from 4.6 months to 17.2 months in the D + Gem/Cis group with ongoing responses for 31 of 91 (34.1%) responders (of whom, the vast majority [71.0%] were still receiving durvalumab). Whilst in the placebo + Gem/Cis group, the interquartile range for DoR ranged from 3.8 months to 9.0 months with ongoing responses for 12 of 64 (18.8%) responders (58.3% of whom were still receiving placebo). A by-treatment group waterfall plot (post hoc analysis) was provided to illustrate the observed DoR for each treatment group, including censoring. Responses of at least 15.5 months duration (each ongoing at DCO) were reported for 10 patients for D + Gem/Cis vs 1 patient for placebo + Gem/Cis (Figure S5).

Given these disparities between the treatment groups in terms of the overall shape of the DoR curves, the greater frequency of ongoing responses in the D + Gem/Cis group (that was not restricted to later time points), the greater proportion of ongoing responders remaining on study treatment for D + Gem/Cis, and the emergence of a subset of patients with enduring DOR reflected in the tail of the curve from 9 months for D + Gem/Cis (compared to continuing decline over time for placebo + Gem/Cis), longer follow-up would be required to assess the eventual DoR for the D + Gem/Cis group both overall (including a potential eventual separation of the medians: 6.4 months for D + Gem/Cis compared to 6.2 months for placebo + Gem/Cis) and for those patients with the most enduring tumor responses that are characteristic of immunotherapies

Figure S5 Duration of Confirmed Objective Response per Investigator According to RECIST 1.1: Waterfall Plots (FAS; Patients With Objective Response and Measurable Disease at Baseline) (Post Hoc Analysis)



Each bar represented one patient.

* denotes ongoing responses. Note: Response was continuing if Investigator duration of response was censored and the patient does not have a censored progressive disease/death.

Cis, cisplatin 25 mg/m^2; Durva, durvalumab 1500 mg; FAS, full analysis set; Gem, gemcitabine 1000 mg/m^2; N, number of patients in treatment group; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

The DoR benefit (including the benefit at 12 months) observed with D + Gem/Cis compared to placebo + Gem/Cis was consistently seen across subgroups (geographical region, primary tumor location, and disease status.

DCR

Disease control rate favored D + Gem/Cis from 24 weeks: 57.5% in the D + Gem/Cis group vs 48.3% in the placebo + Gem/Cis group (for DCR-24w), 41.9% vs 36.3% (for DCR-32w, by respective treatment group), and 35.2% vs 27.0% (for DCR-48w).

PROs

Patient-reported outcomes were included as secondary endpoints (EORTC QLQ-C30 and EORTC BIL-21). Compliance rates for PROs were high at baseline and remained relatively high for both treatment groups. Baseline scores were comparable for both treatment groups (slightly lowered health status and mild symptomatology for fatigue, pain, insomnia, appetite loss, abdominal pain, weight loss, anxiety, and tiredness). There was no detriment in QoL with a trend towards slight improvement in time to deterioration favoring D + Gem/Cis for global

health status, functioning (emotional, social), fatigue, nausea/vomiting, dyspnea, insomnia, diarrhea, abdominal pain, jaundice, pain, and anxiety. There was no detriment in QoL with a trend towards clinically meaningful improvement in improvement rate favoring D + Gem/Cis for global health status/QoL, functioning (physical, emotional, social), insomnia, jaundice, weight loss, eating, pain, anxiety, and tiredness. Overall, change from baseline analyses (including MMRM) were consistent with no detriment in QoL with a trend towards slight improvement favoring D + Gem/Cis for global health status/QoL, emotional functioning symptoms, dyspnea, pruritus, jaundice, weight loss, and pain.

Summary of pharmacokinetic results

No formal non-compartmental analysis was conducted due to the sparse PK sampling scheme in this study. Based on 314 patients in the PK analysis set, durvalumab PK concentrations were within the expected exposure range following 1500 mg Q3W in combination with chemotherapy.

Following durvalumab 1500 mg Q3W in combination with Gem/Cis, geometric mean (geometric %CV) of peak concentrations on Week 0 was 423.0 µg/mL (180.0%). At Cycle 5, the trough and peak concentrations were 205.6 µg/mL (53.04%) and 604.6 µg/mL (56.11%), respectively. At Cycle 7, the trough concentration was 222.8 µg/mL (96.14%), indicating steady-state had been reached by Week 12.

Summary of immunogenicity results

Within the ADA analysis set (patients in the safety analysis set who had non-missing baseline and at least 1 non-missing post-baseline ADA result), ADA prevalence (16 [6.7%] patients for the D + Gem/Cis group and 19 [8.2%] patients for the placebo + Gem/Cis group) and ADA incidence (2 [0.8%] and 7 [3.0%] patients, by respective treatment group) were low and numerically similar between both treatment groups. The low ADA-positive rate and low ADA titer observed in the placebo group is consistent with the targeted 1% false-positive rate of the ADA assay. Out of 16 ADA-positive patients in the D + Gem/Cis group, 2 patients were treatment-emergent ADA-positive and 14 patients were ADA-positive at baseline only. Both treatment-emergent ADA-positive patients were transiently positive with low ADA titer (maximum titers of 4 and 8) and negative for nAb. Only 2 patients in each treatment group were nAb-positive.

There were only 2 treatment-emergent ADA-positive patients, so it was not possible to formally assess the potential impact of ADA on PK; however, their serum durvalumab concentration time profiles were within the range of ADA-negative patients. With only 2 patients in the D + Gem/Cis group who were treatment-emergent ADA-positive, an assessment of the potential impact of ADA on efficacy could not be done. The low incidence of treatment-emergent ADA and nAb in the D + Gem/Cis group limits the potential for any impact of ADA on safety, and immunogenicity had no apparent impact on the safety in terms

of the categories of AEs reported (overall or in terms of SAEs or reporting any CTCAE Grade 3 or 4 TEAEs). There was no instance of an infusion-related reaction among patients who were ADA-positive. The types of AEs reported in patients positive for durvalumab ADA were similar to those reported in patients who were negative for durvalumab ADA. There were no new types of events or events clearly suggestive or indicative of infusion reactions or immune complex disease.

Summary of safety results

At the time of IA-2, the median (min, max) duration of exposure to the durvalumab component of the regimen was longer for the D + Gem/Cis group (7.33 [range: 0.1 to 24.5] months) compared to the placebo component of the placebo + Gem/Cis group (5.77 [range: 0.2 to 21.5] months); corresponding to a median (min, max) of 10 (range 1 to 29) and 8 (0.1 to 26) treatment cycles by respective treatment group. The frequency of dose delays for the durvalumab or placebo component was similar between the D + Gem/Cis and placebo + Gem/Cis groups, with > 3 delays to durvalumab or placebo therapy reported for 8.3% and 6.7% patients, by respective treatment group. The median duration of delay was similar between the treatment groups (approximately 14 days). The median number of chemotherapy treatment cycles received was similar in both treatment groups for gemcitabine (8 cycles in both treatment groups) and cisplatin (8 cycles in the D + Gem/Cis group and 7.5 cycles in the placebo + Gem/Cis group). Overall, patients were able to tolerate up to 8 cycles of Gem/Cis when given in combination with durvalumab. Comparing the D + Gem/Cis and the placebo + Gem/Cis treatment groups, 60.1% and 52.0% patients received all 8 cycles of gemcitabine (by respective treatment group) and 59.2% and 50.0% patients received all 8 cycles of cisplatin (by respective treatment group). The median relative dose intensity was 100% for durvalumab or placebo, and 93.8% each for gemcitabine and cisplatin in both treatment groups. The PRO data were supportive of the tolerability of D + Gem/Cis.

The majority of patients experienced at least 1 AE (approximately 99% patients in each group). A similar proportion of patients in each group experienced an AE assessed as causally related to any study treatment (92.9% patients in the D + Gem/Cis group and 90.1% patients in the placebo + Gem/Cis group). The most commonly reported AEs (≥ 20% in either treatment group) were anemia (48.2% patients in the D + Gem/Cis group and 44.7% patients in the placebo + Gem/Cis group), nausea (40.2% and 34.2% patients, by respective treatment group), constipation (32.0% and 28.9% patients), neutropenia (31.7% and 29.8% patients), fatigue (26.9% and 26.3% patients), neutrophil count decreased (26.9% vs 31% patients), decreased appetite (25.7% vs 23.1% patients), platelet count decreased (20.7% vs 23.1% patients), and pyrexia (20.1% vs 16.4% patients). The only AE PT reported with a ≥ 5% difference between the treatment groups was nausea. For the majority of patients, the maximum reported CTCAE grade was Grade 3 or 4 and similar between treatment groups: 73.7% patients (D + Gem/Cis group) vs 75.1% patients (placebo + Gem/Cis group).

Maximum CTCAE Grade 3 or 4 events were assessed as causally related for 62.4% vs 64.6% patients, by respective treatment group. The majority of the maximum Grade 3 or 4 AEs were either hematological (following chemotherapy) or were consistent with the underlying disease condition in this patient population (eg, cholangitis). The most common maximum CTCAE Grade 3 or 4 AEs by preferred term were generally similar between treatment groups, those with a ≥ 3% difference between the treatment groups were neutrophil count decreased (21.0% patients in the D + Gem/Cis group vs 25.7% patients in the placebo + Gem/Cis group) and cholangitis (6.5% vs 3.2% patients, by respective treatment group). The addition of durvalumab to Gem/Cis did not result in an earlier time to first onset of AEs (overall [6 days in both treatment groups] or any CTCAE Grade 3 or 4 [including patients with subsequent Grade 5 events: 39 days in the D + Gem/Cis group compared with 29 days in the placebo + Gem/Cis group]).

The majority of deaths were attributed by the Investigator to disease under investigation only (more than 90% for both treatment groups). Adverse events with an outcome of death were reported for 3.6% patients in the D + Gem/Cis group and 4.1% patients in the placebo + Gem/Cis group, with preferred terms dispersed across system organ classes, with no obvious trends. Fatal AEs were assessed as causally related for 2 (0.6%) patients in the D + Gem/Cis group (ischemic stroke, hepatic failure) vs 1 (0.3%) patient in the placebo + Gem/Cis group (polymyositis).

Overall, both treatment groups were similar with respect to the occurrence of SAEs. Serious AEs were reported for 160 (47.3%) patients in the D + Gem/Cis group and 149 (43.6%) patients in the placebo + Gem/Cis group, causally related for 53 (15.7%) vs 59 (17.3%) patients, by respective treatment group. Serious AEs with a ≥ 2% difference between the treatment groups comprised anemia (3.6% patients in the D + Gem/Cis group vs 1.2% patients in the placebo + Gem/Cis group), cholangitis (7.4% vs 5.0% patients, by respective treatment group) and abdominal pain (0.3% vs 2.3%). Causally related SAEs reported for ≥ 2 patients in any treatment group, included anemia (2.7% patients in the D + Gem/Cis group and 1.2% patients in the placebo + Gem/Cis group), acute kidney injury (1.5% and 0.6% patients, by respective treatment group), fatigue (1.5% and 0.6% patients), febrile neutropenia (1.2% and 1.2% patients), platelet count decreased (1.2% and 0.9% patients), pyrexia (1.2% and 0.9% patients), and thrombocytopenia (0.9% and 1.2% patients).

Adverse events that led to the discontinuation of any study treatment were reported for 44 (13.0%) patients in the D + Gem/Cis group (43/44 patients discontinued Gem/Cis and 21/44 patients discontinued durvalumab) and 52 (15.2%) patients in the placebo + Gem/Cis group (47/52 patients discontinued Gem/Cis and 18/52 patients discontinued placebo). There was no particular pattern in the type of AEs that led to treatment discontinuation, with preferred terms dispersed across diverse system organ classes. Overall, AEs that led to the

discontinuation of study treatment were assessed as causally related for 30 (8.9%) patients in the D + Gem/Cis group and 39 (11.4%) patients in the placebo + Gem/Cis group.

Adverse events leading to dose modification any of the study treatments were reported at a similar frequency across both treatment groups: 222 (65.7%) patients in the D + Gem/Cis group and 244 (71.3%) patients in the placebo + Gem/Cis group.

Given the disease of study, hepatic and biliary SMQs were evaluated. Overall, biliary events were reported for 23.4% patients in the D + Gem/Cis group and 22.5% patients in the placebo + Gem/Cis group. Biliary events were assessed as causally related for 1.8% and 4.4% patients, by respective treatment group. Any CTCAE Grade 3 or 4 biliary events (including patients with subsequent Grade 5 events) were reported for 14.8% and 14.6% patients, by respective treatment group. Any CTCAE Grade 3 or 4 biliary events were assessed as causally related for 0.3% and 1.5% patients, by respective treatment group. The addition of D to Gem/Cis did not lead to an increase in surgical procedures related to the biliary tract (such as biliary stenting or drainage: 17.3% and 18.6% patients, by respective treatment group). Overall, hepatic events were reported for 27.2% patients in the D + Gem/Cis group and 26.3% patients in the placebo + Gem/Cis group. Hepatic events were assessed as causally related for 10.7% and 11.4% patients, by respective treatment group. Any CTCAE Grade 3 or 4 hepatic events were reported for 9.5% and 12.6% patient, by respective treatment group. Any CTCAE Grade 3 or 4 hepatic events were assessed as causally related for 2.7% and 2.9% patients, by respective treatment group. Both treatment groups were also similar for each of these AE categories when the aforementioned grouped terms were considered at the level of constituent preferred terms.

Given the association of hematological events with treatment with Gem/Cis, hematopoietic cytopenias were evaluated using SMQs. Overall, hematopoietic cytopenias were reported for 79.9% patients in the D + Gem/Cis group and 77.8% patients in the placebo + Gem/Cis group. Hematopoietic cytopenias were assessed as causally related for 75.7% and 73.4% patients, by respective treatment group. Any CTCAE Grade 3 or 4 hematopoietic cytopenias (including patients with subsequent Grade 5 events) were reported for 57.7% and 59.1% patients, by respective treatment group. Any CTCAE Grade 3 or 4 hematopoietic cytopenias were assessed as causally related for 183 (54.1%) and 193 (56.4%) patients, by respective treatment group. Both treatment groups were also similar for each of these AE categories when the grouped term of hematopoietic cytopenias was considered at the level of constituent preferred terms.

Adverse events reported in the renal and urinary disorders system organ class were balanced across treatment groups, 9.8% patients in the D + Gem/Cis group vs 10.2% patients in the placebo + Gem/Cis group. Renal events (a known toxicity associated with Gem/Cis) were also evaluated. The frequency of acute kidney injury events was higher in the D + Gem/Cis group

compared to the placebo + Gem/Cis group. Thirteen (3.8%) patients experienced acute kidney injury events in the D + Gem/Cis group compared to 7 (2.0%) patients in the placebo + Gem/Cis group. Conversely, AEs of blood creatinine increased, most of which were CTCAE Grade 1 or 2, were reported at a lower frequency in the D + Gem/Cis group compared to the placebo + Gem/Cis group (3.0% patients compared to 9.9% patients, by respective treatment group). The characteristics of the acute kidney injury events were similar across both treatment groups with most events being CTCAE Grade 3 SAEs; although, the proportion of patients with maximum CTCAE Grade 3 or 4 events was higher in the D + Gem/Cis group (3.3% patients compared to 1.5% patients in the placebo + Gem/Cis group). Events were consistent in nature between both treatment groups in terms of clinical course and management: 9 patients recovered in the D + Gem/Cis group and 5 patients recovered or were recovering in the placebo + Gem/Cis group (at time of DCO), with most patients treated with rehydration. None of the events were assessed as causally related to durvalumab by the Investigator and no patient discontinued durvalumab in response to an acute kidney injury event. Six patients in the D + Gem/Cis group had an acute kidney injury event considered causally related to Gem/Cis by the Investigator, with one patient discontinuing cisplatin in response. Overall, the events were reversible and manageable with other standard interventions in both treatment groups.

A total of 204 (60.4%) patients in the D + Gem/Cis group and 187 (54.7%) patients in the placebo + Gem/Cis group experienced an AESI/AEPI. Of these, 43 (12.7%) and 16 (4.7%) patients had an event that was adjudicated as an imAE. For the majority of patients, imAEs were of CTCAE Grade 1 or 2, with any CTCAE Grade 3 or 4 imAEs (including patients with subsequent Grade 5 events) reported for 8 (2.4%) patients in the D + Gem/Cis group and 5 (1.5%) patients in the placebo + Gem/Cis group. In the D + Gem/Cis group, imAEs had resolved for 20 (5.9%) patients and imAEs were unresolved at DCO for 23 (6.8%) patients. In the placebo + Gem/Cis group, imAEs had resolved for 9 (2.6%) patients and imAEs were unresolved at DCO for 7 (2.0%) patients. The imAEs in the D + Gem/Cis group more frequently required concomitant treatments compared to the placebo + Gem/Cis group: systemic corticosteroids (8.0% patients in the D + Gem/Cis group compared to 3.5% patients in the placebo + Gem/Cis group), high dose steroids (3.8% patients compared to 2.9% patients, by respective treatment group) and endocrine therapy (6.5% patients compared to 1.5% patients). Overall, 1 patient in each treatment group received other immunosuppressants for the treatment of imAEs. No patient in the D + Gem/Cis group had a fatal imAE. An imAE with an outcome of death was reported for 1 (0.4%) patient in the placebo + Gem/Cis group (polymyositis). Serious imAEs were reported for 6 (1.8%) patients in the D + Gem/Cis group and 5 (1.5%) patients in the placebo + Gem/Cis group. Immune-mediated AEs leading to discontinuation of any study treatment were reported for 3 (0.9%) and 4 (1.2%) patients, by respective treatment group. The frequency of infusion reactions (captured as AESI at a grouped term level) was reported at a frequency of 3.8% compared to 1.8% patients, by respective treatment group.

Descriptive statistics of individual laboratory changes by visit showed that hematology values recovered after the chemotherapy period. Hematology and clinical chemistry parameters were a maximum of CTCAE Grade 0 (normal), 1, or 2 for the majority of patients in the D + Gem/Cis group and placebo Gem/Cis group. Overall, shifts to CTCAE Grade 3 or 4 hematology and clinical chemistry parameters were similar between both treatment groups. Overall, liver biochemistry test abnormalities observed on-treatment were similar between both treatment groups and were typically in the range of ≥ 3 × to ≤ 5 × ULN or > 5 × to ≤ 8 × ULN for ALT or AST. Potential Hy's law cases were identified for 36 (10.7%) patients in the in the D + Gem/Cis group vs 50 (14.7%) patients in the placebo + Gem/Cis group. All cases of potential Hy's law were subject to review by the AstraZeneca Hepatic Safety Knowledge Group, after which no cases were confirmed as true or likely Hy's law cases; all potential Hy's law were assessed as being due to disease progression or underlying disease, and no indication of a causal relationship to study treatment. The frequency potential viral hepatitis reactivation based on the changes in viral load of increased HBV DNA from the baseline was similar between both treatment groups, and consistent with published data for chemotherapy alone (< 5% patients).

Worsening CrCl was reversible and transient for 60.0% vs 58.7% patients, by respective treatment group, for whom subsequent values were available. Overall, findings of shifts in creatinine and creatinine clearance, AEs of blood creatinine increased, and AEs of acute kidney injury, suggest that such events were transient, reversible, and resolved with standard intervention and were mostly assessed by the Investigator as causally related to cisplatin and/or gemcitabine in both treatment groups.

Urinalysis, vital signs, ECG, and physical findings did not raise any safety concerns.

Conclusion(s)

The results of TOPAZ-1 indicate that the combination of durvalumab with SoC chemotherapy represents a new safe and effective therapy to address the significant unmet medical need of patients with advanced BTC:

- Treatment with D + Gem/Cis resulted in a statistically significant, clinically meaningful, and sustained improvement in OS compared with placebo + Gem/Cis. This benefit was consistent across key secondary endpoints (PFS, ORR, and DoR) and prespecified subgroups.
- Durvalumab PK concentrations were within the expected exposure range following 1500 mg Q3W in combination with chemotherapy.
- The combination had a manageable safety/tolerability profile (consistent with the established safety profiles of the individual components and similar drop-out rate between both treatment groups).