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ORIGINAL ARTICLE

Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer

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Abstract

BACKGROUND Patients with advanced biliary tract cancer have a poor prognosis, and first-line standard of care (gemcitabine plus cisplatin) has remained unchanged for more than 10 years. The TOPAZ-1 trial evaluated durvalumab plus chemotherapy for patients with advanced biliary tract cancer.

METHODS In this double-blind, placebo-controlled, phase 3 study, we randomly assigned patients with previously untreated unresectable or metastatic biliary tract cancer or with recurrent disease 1:1 to receive durvalumab or placebo in combination with gemcitabine plus cisplatin for up to eight cycles, followed by durvalumab or placebo monotherapy until disease progression or unacceptable toxicity. The primary objective was to assess overall survival. Secondary end points included progression-free survival, objective response rate, and safety.

RESULTS Overall, 685 patients were randomly assigned to durvalumab (n=341) or placebo (n=344) with chemotherapy. As of data cutoff, 198 patients (58.1%) in the durvalumab group and 226 patients (65.7%) in the placebo group had died. The hazard ratio for overall survival was 0.80 (95% confidence interval [CI], 0.66 to 0.97; P=0.021). The estimated 24-month overall survival rate was 24.9% (95% CI, 17.9 to 32.5) for durvalumab and 10.4% (95% CI, 4.7 to 18.8) for placebo. The hazard ratio for progression-free survival was 0.75 (95% CI, 0.63 to 0.89; P=0.001). Objective response rates were 26.7% with durvalumab and 18.7% with placebo. The incidences of grade 3 or 4 adverse events were 75.7% and 77.8% with durvalumab and placebo, respectively.

CONCLUSIONS Durvalumab plus chemotherapy significantly improved overall survival versus placebo plus chemotherapy and showed improvements versus placebo plus chemotherapy in prespecified secondary end points including progression-free survival and

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objective response rate. The safety profiles of the two treatment groups were similar. (Funded by AstraZeneca; ClinicalTrials.gov number, NCT03875235.)

Introduction

Biliary tract cancer, a heterogeneous group of malignancies that includes intrahepatic and extrahepatic cholangiocarcinoma, gallbladder cancer, and ampulla of Vater cancer,[1] is typically diagnosed at advanced stages for which curative surgery is not feasible and prognosis is poor.[1] Despite trials evaluating several targeted therapies, including cediranib, erlotinib, cetuximab, panitumumab, ramucirumab, and merestinib,[2-6] first-line standard of care for advanced disease (gemcitabine and cisplatin chemotherapy) has remained unchanged for the past decade and is associated with a median overall survival of 11.7 months and an estimated 24-month survival rate of approximately 15%,[7] highlighting the need for new therapies.[8,9]

Biliary tract cancer exhibits immunogenic features including expression of the immune checkpoint molecules, programmed cell death ligand 1 (PD-L1) and cytokine T-lymphocyte–associated protein 4 (CTLA-4), in the tumor microenvironment.[10-12] Early-phase studies have demonstrated clinical activity of immune checkpoint inhibitors in biliary tract cancer, including durvalumab, a PD-L1 inhibitor.[13-16] Furthermore, chemotherapy has been shown to have immunomodulatory effects in multiple cancer types,[17,18] and the addition of immunotherapy to chemotherapy has demonstrated improved outcomes versus chemotherapy alone in multiple solid tumor types.[19,20] Therefore, it was hypothesized that the addition of immune checkpoint inhibition to chemotherapy may improve clinical outcomes versus chemotherapy alone in biliary tract cancer. A phase 2 trial of durvalumab in combination with gemcitabine and cisplatin demonstrated promising efficacy, with an objective response rate of 72% and a median overall survival of 20.2 months and without dose-limiting toxicity, in a nonrandomized, single-center study, establishing proof of concept for this approach in advanced biliary tract cancer.[15] We performed a randomized, double-blind, global, phase 3 trial (TOPAZ-1; ClinicialTrials.gov number, NCT03875235), to evaluate the efficacy and safety of durvalumab plus gemcitabine and cisplatin versus placebo plus gemcitabine and cisplatin as a first-line treatment for patients with advanced biliary tract cancer.

Methods

PATIENTS

Adults 18 years of age or older with histologically confirmed unresectable, locally advanced, or metastatic adenocarcinoma of the biliary tract, including intrahepatic or extrahepatic cholangiocarcinoma and gallbladder carcinoma, were eligible for inclusion. Eligible patients included those with previously untreated disease that was unresectable or metastatic at initial diagnosis as well as those who developed recurrent disease more than 6 months after surgery with curative intent and more than 6 months after the completion of adjuvant therapy. Other inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (on a 6-point scale, in which 0 is fully active and 5 is dead), one or more measurable lesions per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), and no prior exposure to immune-mediated therapy. Patients were excluded if they had ampullary carcinoma, active or prior documented autoimmune or inflammatory disorders, or known allergy or hypersensitivity to any study treatment. Full inclusion and exclusion criteria can be found in Sections 5.1 and 5.2 of the complete protocol, available with the full text of this article at evidence.nejm.org.

TRIAL DESIGN AND INTERVENTIONS

TOPAZ-1 was a phase 3, randomized, double-blind, placebo-controlled, global study. Patients were randomly assigned in a 1:1 ratio to receive durvalumab in combination with gemcitabine and cisplatin or placebo in combination with gemcitabine and cisplatin. Randomization was stratified by disease status (initially unresectable vs. recurrent) and primary tumor location (intrahepatic cholangiocarcinoma vs. extrahepatic cholangiocarcinoma vs. gallbladder cancer).

Durvalumab or placebo combined with gemcitabine and cisplatin was administered intravenously on a 21-day cycle for up to eight cycles. Durvalumab (1500 mg) or placebo was administered on day 1 of each cycle, in combination with gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2), which were administered on days 1 and 8 of each cycle. After completion of gemcitabine and cisplatin, 1500 mg of durvalumab or placebo monotherapy was administered once every 4 weeks until clinical or imaging (per RECIST v1.1) disease progression or until unacceptable toxicity,

withdrawal of consent, or any other discontinuation criteria were met. Patients who were clinically stable at initial disease progression could continue to receive study treatment at the discretion of the investigator and patient.

ASSESSMENTS

Tumor assessments were performed according to RECIST v1.1 using images obtained by computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis, and evaluated per investigator assessment. Assessments are described in detail in the Supplementary Methods of the Supplementary Appendix. Adverse events were reported from the time of informed consent through 90 days after the last dose of study treatment; the causal relationship between reported adverse events and study treatment was investigator-assessed. Other safety assessments included physical examinations, laboratory findings, ECOG performance status, electrocardiograms, and vital signs. Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire (EORTC QLQ-C30) with outcomes scored from 0 to 100 for each of the symptom scales, functional scales, and global measure of health. Higher scores on the functional scales and global measure of health indicate better function and health status, respectively, while higher scores on the symptom scales represent greater symptom severity. Health-related quality of life was also assessed using the EORTC 21-Item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire (EORTC QLQ-BIL21), which includes five multi-item domain scales and three single-item scales. For all items and scales, outcomes were scored from 0 to 100, with higher scores indicating greater symptom severity. A clinically meaningful change was defined as an absolute change of 10 or more for these scales (EORTC QLQ-C30 and EORTC QLQ-BIL21). Patient-reported treatment side effects were assessed using the Patient-Reported Outcomes–Common Terminology Criteria for Adverse Events, which consists of nominal categories (e.g., "none" to "very severe" or "not at all" to "very much").

OBJECTIVES AND END POINTS

The primary objective was to assess overall survival, defined as the time between randomization and death due to any cause, in the durvalumab versus the placebo group. Secondary end points included progression-free survival, objective response rate, duration of response, and disease control rate and efficacy by PD-L1 expression, according to RECIST v1.1 using investigator assessments, in the durvalumab versus placebo groups. Progression-free survival was defined as the time from date of randomization until the date of RECIST v1.1–defined imaging disease progression or death. Safety and side effects were assessed for the durvalumab and placebo groups. Adverse events were graded according to National Cancer Institute common terminology criteria for adverse events, version 5.0. All objectives are outlined in Section 3 of the protocol available at evidence.nejm.org.

TRIAL OVERSIGHT

AstraZeneca sponsored the trial and collaborated with the steering committee on the trial design and collection, analysis, and interpretation of the data. Data analyses were completed by PHASTAR, London, United Kingdom, and AstraZeneca. Durvalumab was provided by AstraZeneca. Good Clinical Practice guidelines of the International Conference on Harmonization and ethical considerations of the Declaration of Helsinki were followed. The study protocol was approved by local institutional review boards. Written informed consent was obtained from patients or their legal representatives before participation. An independent data monitoring committee reviewed unblinded safety data approximately every 6 months. The manuscript was prepared by the authors, with medical writing support funded by the sponsor. The authors and sponsor vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

STATISTICAL ANALYSIS

Efficacy objectives were evaluated in the full analysis set, which included all patients randomly assigned to treatment. The primary analysis of overall survival tested for the superiority of the durvalumab regimen relative to placebo and was analyzed using a log-rank test stratified by disease status (initially unresectable vs. recurrent) and primary tumor location (intrahepatic cholangiocarcinoma vs. extrahepatic cholangiocarcinoma vs. gallbladder cancer). This interim analysis was planned for when approximately 397 of the expected 496 deaths at final analysis had occurred, providing an approximate 75% power to detect a significant difference in overall survival, with a two-sided significance level of 0.0238 according to the Lan–DeMets approximation of O'Brien–Fleming alpha spending function boundaries. By the data cutoff of August 11, 2021, 424 deaths had occurred, and the actual two-sided significance level was 0.03. Because a statistically significant improvement in overall survival in the durvalumab arm compared

with the placebo arm was observed at the planned interim analysis, the key secondary end point of progression-free survival was formally evaluated at this interim analysis. For overall survival and progression-free survival, the effect of durvalumab versus placebo was estimated by the hazard ratio with a 95% confidence interval (CI) and two-sided P value. Progression-free survival in the durvalumab versus placebo treatment groups was tested using a log-rank test, with a two-sided significance level of 0.0481 that was derived based on the alpha spending function approximating Pocock boundaries. No multiplicity adjustments for the other secondary and exploratory end points were defined. Therefore, only point estimates and 95% CIs are provided. The CIs for end points other than overall survival and progression-free survival have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects. Further details on the statistical analysis are described in the Supplementary Methods.

The results of this planned interim analysis were reviewed by an independent data monitoring committee, which concluded that the data met the prespecified criteria for a statistically significant difference in the primary objective (overall survival) per the statistical analysis plan with acceptable safety. Since the trial reached statistical significance for the primary objective on the basis of this prespecified interim analysis, the sponsor was unblinded, and the results presented herein are to be considered the final, formal statistical analysis for overall survival. The TOPAZ-1 study is ongoing, allowing for further, exploratory follow-up analyses of overall survival.

Results

PATIENTS AND TREATMENT

From April 2019 to December 2020, 914 patients were enrolled at 105 sites in 17 countries. In total, 685 patients were randomly assigned to treatment: 341 to the durvalumab group and 344 to the placebo group. Of these patients, 338 and 342 received treatment, respectively (Fig. S1). Patient demographics and disease characteristics were generally balanced between the treatment groups (Tables 1, S1, and S2). The representativeness of the trial participants in TOPAZ-1 is described in Table S3. At data cutoff (August 11, 2021), the median duration of follow-up was 16.8 months (95% CI, 14.8 to 17.7) in the durvalumab group and 15.9 months (95% CI, 14.9 to 16.9) in the placebo group. In addition, 275 patients (81.4%) in the durvalumab group discontinued durvalumab and 322 patients (94.2%) in the placebo group discontinued placebo. Of the full analysis set, the number of patients who received one or more regimens of subsequent anticancer therapy post-discontinuation was 145 (42.5%) in the durvalumab group and 170 (49.4%) in the placebo group (Table S4).

PRIMARY OBJECTIVE

As of data cutoff, 198 patients (58.1%) in the durvalumab group and 226 patients (65.7%) in the placebo group had died. Overall survival was significantly longer with durvalumab versus placebo (hazard ratio, 0.80; 95% CI, 0.66 to 0.97; P=0.021). Median overall survival was 12.8 months (95% CI, 11.1 to 14.0) in the durvalumab group and 11.5 months (95% CI, 10.1 to 12.5) in the placebo treatment group (Fig. 1A).

The estimated overall survival rates for durvalumab and placebo were 54.1% (95% CI, 48.4 to 59.4) and 48.0% (95% CI, 42.4 to 53.4) at 12 months, 35.1% (95% CI, 29.1 to 41.2) and 25.6% (95% CI, 19.9 to 31.7) at 18 months, and 24.9% (95% CI, 17.9 to 32.5) and 10.4% (95% CI, 4.7 to 18.8) at 24 months, respectively.

The overall survival Kaplan–Meier curve separated at approximately 6 months of treatment, after which there was a clear and sustained separation of the survival curves in favor of the durvalumab group. The overall survival hazard ratio was 0.91 (95% CI, 0.66 to 1.26) up to 6 months and 0.74 (95% CI, 0.58 to 0.94) after 6 months. Furthermore, a kernel-smoothed estimate of the hazard function and the associated log-log (event times) versus log (time) plot confirmed a departure from the assumption of the proportional hazards (Fig. S2).

SECONDARY OBJECTIVES

Median progression-free survival was 7.2 months (95% CI, 6.7 to 7.4) with durvalumab and 5.7 months (95% CI, 5.6 to 6.7) with placebo (Fig. 1B). The hazard ratio for progression-free survival was 0.75 (95% CI, 0.63 to 0.89; P=0.001). The investigator-assessed confirmed objective response rate (sum of the rate of complete responses and partial responses in patients with measurable disease) was 26.7% (n=341) in the durvalumab group and 18.7% (n=343) in the placebo group (odds ratio, 1.60; 95% CI, 1.11 to 2.31). The number of patients achieving a confirmed complete response was 7 (2.1%) with durvalumab and

Table 1. Patient Demographics and Baseline Characteristics in the Full Analysis Set.*

Parameter	Durvalumab plus Gemcitabine and Cisplatin (n=341)	Placebo plus Gemcitabine and Cisplatin (n=344)	Total (N=685)
Median age (range) — yr	64 (20–84)	64 (31–85)	64 (20–85)
Female sex — no. (%)	172 (50.4)	168 (48.8)	340 (49.6)
Race — no. (%)			
Asian	185 (54.3)	201 (58.4)	386 (56.4)
Region — no. (%)			
Asia	178 (52.2)	196 (57.0)	374 (54.6)
Rest of the world	163 (47.8)	148 (43.0)	311 (45.4)
ECOG performance status of 0 — no. (%)	173 (50.7)	163 (47.4)	336 (49.1)
Primary tumor type — no. (%)			
Intrahepatic cholangiocarcinoma	190 (55.7)	193 (56.1)	383 (55.9)
Extrahepatic cholangiocarcinoma	66 (19.4)	65 (18.9)	131 (19.1)
Gallbladder	85 (24.9)	86 (25.0)	171 (25.0)
Disease status — no. (%)			
Initially unresectable	274 (80.4)	279 (81.1)	553 (80.7)
Recurrent	67 (19.6)	64 (18.6)	131 (19.1)
Disease classification — no. (%)			
Locally advanced†	38 (11.1)	57 (16.6)	95 (13.9)
Metastatic	303 (88.9)	286 (83.1)	589 (86.0)
MSI status — no. (%)			
High	3 (0.9)	2 (0.6)	5 (0.7)
Stable	160 (46.9)	168 (48.8)	328 (47.9)
Missing‡	178 (52.2)	174 (50.6)	352 (51.4)
Virology status — no. (%)			
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)
Active viral hepatitis B	8 (2.3)	14 (4.1)	22 (3.2)
Prior hepatitis C	8 (2.3)	10 (2.9)	18 (2.6)
Missing	82 (24.0)	83 (24.1)	165 (24.1)
PD-L1 expression — no. (%)			
TAP ≥1%	197 (57.8)	205 (59.6)	402 (58.7)
TAP <1%	103 (30.2)	103 (29.9)	206 (30.1)
Missing	41 (12.0)	36 (10.5)	77 (11.2)

* ECOG denotes Eastern Cooperative Oncology Group, MSI microsatellite instability, PD-L1 programmed cell death ligand 1, ROW rest of world, and TAP tumor area positivity (proportion of tumor and/or immune cells with PD-L1 staining at any intensity).

† Patient has only locally advanced sites of disease.

‡ MSI status missing includes MSI-unknown and not tested.

2 (0.6%) with placebo, and the number of patients achieving a confirmed partial response was 84 (24.6%) with durvalumab and 62 (18.1%) with placebo. The percentage of patients with continued response for 9 months or more was 32.6% with durvalumab and 25.3% with placebo. The percentage of patients with continued response for 12 months or more was 26.1% with durvalumab and 15.0% with placebo. Tumor responses are summarized in Table 2.

The overall and progression-free survival benefits observed with durvalumab in combination with gemcitabine and cisplatin were generally consistent across the clinically relevant subgroups analyzed (Fig. 2A and 2B). In patients with a PD-L1 tumor area positivity (TAP) score of 1% or greater (≥1% of tumor area occupied by tumor and/or immune cells with PD-L1 staining at any intensity), the hazard ratio for overall survival with durvalumab versus placebo was 0.79 (95% CI, 0.61 to 1.00). In patients with a TAP score

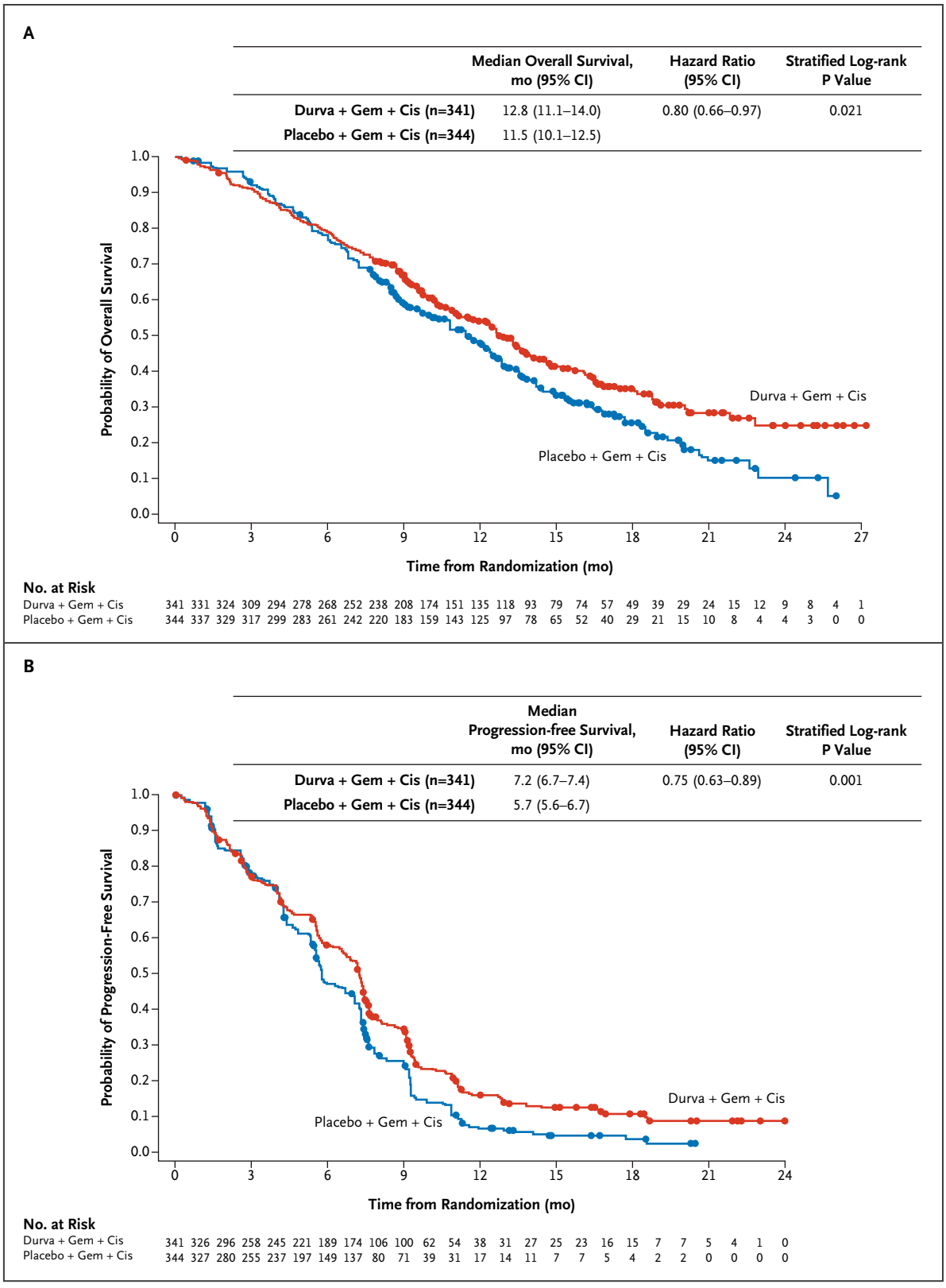

Figure 1. Kaplan–Meier Curves of Overall and Progression-Free Survival in the Full Analysis Set.

Kaplan–Meier curves are presented for overall survival (Panel A) and progression-free survival (Panel B). CI denotes confidence interval, Cis cisplatin, Durva durvalumab, and Gem gemcitabine.

Table 2. Tumor Response in the Full Analysis Set.*		
Parameter	Durvalumab plus Gemcitabine and Cisplatin (n=341)	Placebo plus Gemcitabine and Cisplatin (n=343)
Objective response rate — no. (%)†	91 (26.7)	64 (18.7)
Complete response	7 (2.1)	2 (0.6)
Partial response	84 (24.6)	62 (18.1)
Disease control rate — no. (%)‡	291 (85.3)	284 (82.6)
Median duration of response (IQR) — mo§	6.4 (4.6–17.2)	6.2 (3.8–9.0)
Patients with continued response — %		
≥3 mo	88.9	89.0
≥6 mo	59.3	54.2
≥9 mo	32.6	25.3
≥12 mo	26.1	15.0
Median time to response (IQR) — mo¶	1.6 (1.3–3.0)	2.7 (1.4–4.1)

* IQR denotes interquartile range and RECIST v1.1 Response Evaluation Criteria in Solid Tumors, version 1.1.

† By investigator assessment using RECIST v1.1. Analysis of objective response rate was based on patients in the final analysis set who had measurable disease at baseline. There was one patient who did not have measurable disease at baseline in the placebo group.

‡ The rate of best objective response of complete response, partial response, and stable disease. Analysis of disease control rate was based on all patients in the full analysis set (n=341 for durvalumab and n=344 for placebo).

§ Time from the first documentation of a response until the date of progression, death, or the last evaluable RECIST assessment. Analysis of duration of response was based on patients in the full analysis set who had an objective response and measurable disease at baseline (n=91 for durvalumab and n=64 for placebo).

¶ Time from the date of randomization until the date of first documented response. Analysis of time to response was based on patients in the full analysis set who had an objective response and measurable disease at baseline (n=91 for durvalumab and n=64 for placebo).

of less than 1%, the hazard ratio for overall survival with durvalumab versus placebo was 0.86 (95% CI, 0.60 to 1.23).

SAFETY

The safety analysis set included 680 patients who received one or more doses of durvalumab (n=338) or placebo (n=342). The median (range) duration of study treatment was 7.3 months (0.1 to 24.5) for durvalumab and 5.8 months (0.2 to 21.5) for placebo (Table S5).

In the durvalumab group, the median (interquartile range) relative dose intensity of durvalumab, gemcitabine, and cisplatin was 100 (93.8 to 100), 93.8 (82.5 to 100), and 93.8 (83.3 to 100), respectively. In the placebo group, the median (interquartile range) relative dose intensity of placebo, gemcitabine, and cisplatin was 100 (95.0 to 100), 93.8 (82.2 to 100), and 93.8 (81.3 to 100), respectively.

Any grade adverse events occurred in 336 patients (99.4%) in the durvalumab group and 338 patients (98.8%) in the placebo group (Table 3). Grade 3 or 4 adverse events occurred in 256 patients (75.7%) in the durvalumab group and 266 patients (77.8%) in the placebo group (Table 3). The rate of discontinuation of any treatment component due to adverse events was 13.0% in the durvalumab group and 15.2% in the placebo group (Table 3). The number of deaths due to adverse events was 12 (3.6%) in the durvalumab group and 14 (4.1%) in the placebo group (Table 3). The most common adverse events were anemia (48.2%), nausea (40.2%), constipation (32.0%), and neutropenia (31.7%) in the durvalumab group and anemia (44.7%), nausea (34.2%), and decreased neutrophil count (31.0%) in the placebo group (Table S6). Grade 3 or 4 treatment-related adverse events that occurred in 2% or more of patients in the durvalumab and placebo groups are listed in Table S7. The rate of immune-mediated adverse events was 12.7% with durvalumab and 4.7% with placebo. Grade 3 or 4 immune-mediated adverse events occurred in 2.4% of patients in the durvalumab group and 1.5% in the placebo group (Table S8).

Discussion

TOPAZ-1 was a phase 3 study that evaluated immunotherapy plus chemotherapy as first-line treatment for advanced biliary tract cancer. In previously untreated advanced biliary tract cancer, durvalumab plus gemcitabine and cisplatin demonstrated statistically significant prolonged overall survival versus placebo plus gemcitabine and cisplatin. The overall survival rates at 18 and 24 months, and

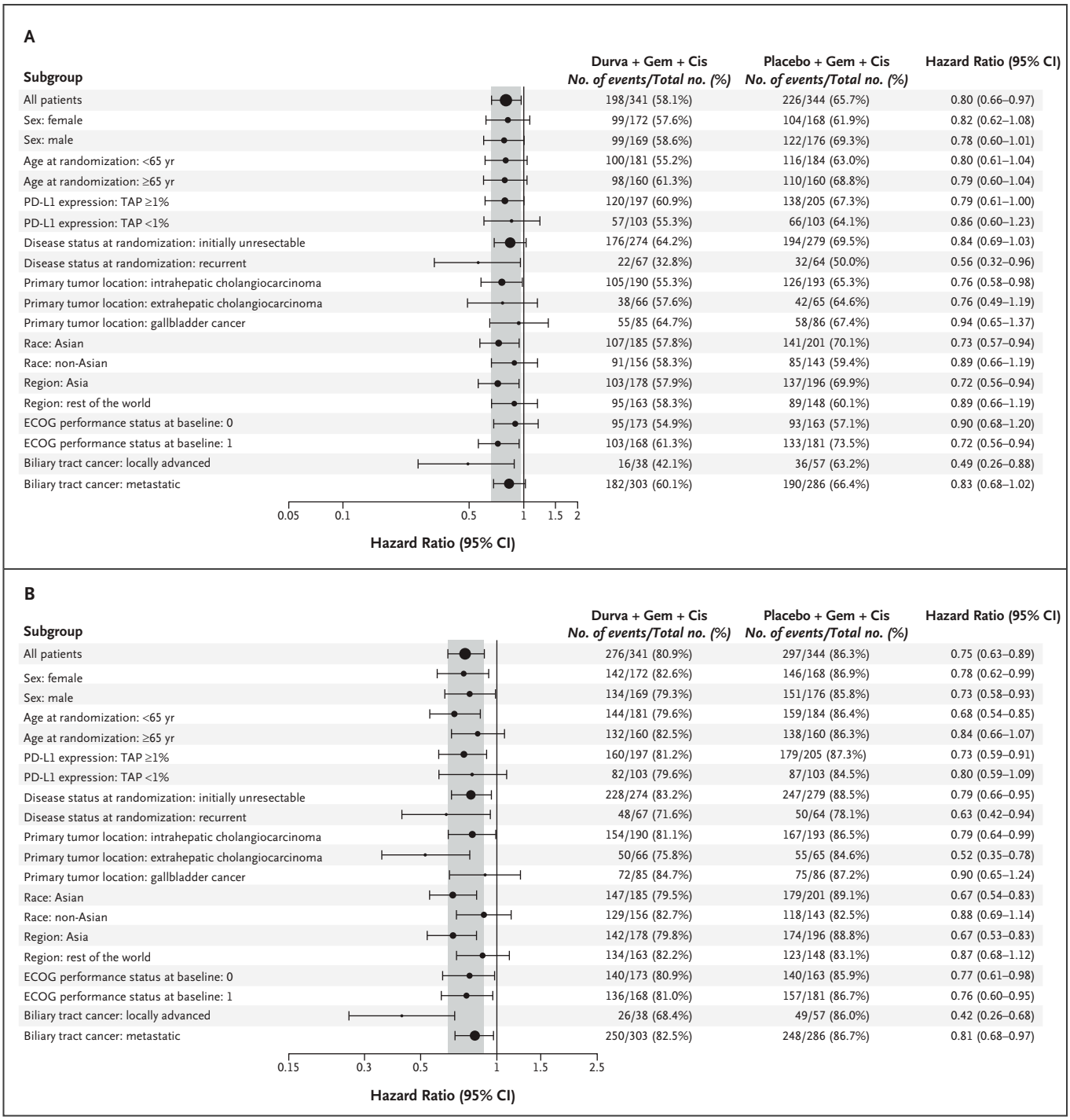

Figure 2. Forest Plots of Overall and Progression-Free Survival by Subgroup for Durvalumab versus Placebo in the Full Analysis Set.

Forest plots are presented for overall survival (Panel A) and progression-free survival (Panel B). The circle size is proportional to the number of events observed. Race is defined as patients who identify as Asian or non-Asian regardless of geography. Rest of the world includes patients enrolled in Europe, North America, and South America. CI denotes confidence interval, Cis cisplatin, Durva durvalumab, ECOG Eastern Cooperative Oncology Group, Gem gemcitabine, PD-L1 programmed cell death ligand 1, and TAP tumor area positivity (proportion of tumor and/or immune cells with PD-L1 staining at any intensity).

Table 3. Summary of Safety Data in the Safety Analysis Set.

Parameter	Durvalumab plus Gemcitabine and Cisplatin (n=338)	Placebo plus Gemcitabine and Cisplatin (n=342)
Adverse events — no. (%)		
Any grade	336 (99.4)	338 (98.8)
Serious	160 (47.3)	149 (43.6)
Grade 3 or 4	256 (75.7)	266 (77.8)
Leading to discontinuation of any study treatment	44 (13.0)	52 (15.2)
Leading to death	12 (3.6)	14 (4.1)
Treatment-related adverse events — no. (%)		
Any grade	314 (92.9)	308 (90.1)
Serious	53 (15.7)	59 (17.3)
Grade 3 or 4	212 (62.7)	222 (64.9)
Leading to discontinuation of any study treatment	30 (8.9)	39 (11.4)
Leading to death*	2 (0.6)	1 (0.3)

* Treatment-related adverse events leading to death were ischemic stroke and hepatic failure in the durvalumab treatment group and polymyositis in the placebo treatment group.

the increasingly divergent overall survival Kaplan–Meier curves, characterized by the extended tail of the durvalumab arm in the TOPAZ-1 trial, are consistent with the delayed separation of the overall survival Kaplan–Meier curve that is expected with immunotherapy and chemotherapy combinations in solid tumors.[19-21]

The large, international patient population in the TOPAZ-1 trial was representative of the general population of patients with advanced biliary tract cancer, and characteristics were generally well balanced between treatment groups. A trend toward overall and progression-free survival benefit with durvalumab and chemotherapy was observed across all subgroups analyzed. Although the Asia subgroup appeared to have a relatively larger improvement in survival compared with the rest-of-the-world subgroup, the study was not sized for any individual subgroup evaluations, and no adjustments were made for multiplicity. In addition, the median duration of follow-up in censored patients was approximately 2 months longer in the Asia subgroup compared with the rest-of-the-world subgroup. Because the difference in overall survival rates between treatments continued to increase over time, additional follow-up time may show an improved survival benefit for the rest-of-the-world subgroup. In addition, imbalance in baseline characteristics between the region subgroups, such as the higher proportion of patients with recurrent disease and an ECOG performance score of 1 in Asia compared with the rest of the world, may have contributed to differences in point estimates of the hazard ratios in the subgroups. The addition of durvalumab to chemotherapy benefited patients with tumors characterized by a PD-L1 TAP of 1% or greater and a TAP of less than 1%, indicating that PD-L1 status may have limited value in predicting clinical benefit with durvalumab plus chemotherapy in this patient population. Compared with placebo plus chemotherapy, durvalumab plus chemotherapy was associated with a similar rate of discontinuations due to adverse events; in addition, observed toxicities with durvalumab plus chemotherapy were similar to those commonly seen with either chemotherapy or immunotherapy alone. Importantly, durvalumab did not add additional toxicity to that observed with chemotherapy in this double-blinded trial, and the rates of grade 3 or 4 adverse events were very similar between treatment groups.

First-line standard of care for advanced biliary tract cancer was established more than 10 years ago from the ABC-02 trial, which demonstrated a median overall survival of 11.7 months with gemcitabine and cisplatin versus 8.1 months with gemcitabine monotherapy.[7] Outcomes in the gemcitabine and cisplatin group of TOPAZ-1 were comparable to historical controls of gemcitabine and cisplatin,[7,22] with a median overall survival of 11.5 months and estimated 18- and 24-month survival rates of 25.6% and 10.4%, respectively.[7,22] Our data show that the addition of durvalumab to chemotherapy as first-line treatment was associated with an overall survival hazard ratio of 0.80 (95% CI, 0.66 to 0.97; P=0.021). Although 24.9% and 10.4% of patients were alive at 24 months in the durvalumab and placebo groups, respectively, it is not known whether long-term survival rates exceeding 24 months can be achieved for

patients with advanced biliary tract cancer with the addition of durvalumab to chemotherapy.

Although patient characteristics were generally well balanced between treatment groups, it should be noted that microsatellite instability (MSI) status was missing for approximately 50% of patients in each treatment group due to either an insufficient tissue sample or a test result of MSI status unknown. Of the 333 patients with evaluable MSI status, 5 (1.5%) had MSI-high tumors, which is consistent with previous reports of MSI-high prevalence in patients with biliary tract cancer.[1,23] Therefore, the statistically significant improvement in overall survival observed in this study is unlikely to be solely attributed to efficacy with durvalumab in the small subset of patients with MSI-high tumors. Exploratory analyses using tumor tissue samples are needed to assess potential survival and response correlations to biomarkers, including driver mutations and tumor mutational burden.

In conclusion, the global, phase 3 TOPAZ-1 trial, at a preplanned interim analysis, met the primary objective of a statistically significant improvement in overall survival in patients with advanced biliary tract cancer of 7.6 percentage points; this occurred with similar percentages of Grade 3 and 4 adverse events in both groups. The trial is ongoing toward completion.

Disclosures

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