Atezolizumab Plus Chemotherapy With or Without Bevacizumab in Advanced Biliary Tract Cancer: Clinical and Biomarker Data From the Randomized Phase II IMbrave151 Trial

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ABSTRACT

PURPOSE Biliary tract cancers (BTCs) harbor an immunosuppressed tumor microenvironment and respond poorly to PD-1/PD-L1 inhibitors. Bevacizumab (anti–vascular endothelial growth factor) plus chemotherapy can promote anticancer immunity, augmenting response to PD-L1 inhibition.

PATIENTS AND METHODS This randomized, double-blind, proof-of-concept phase II study enrolled patients (n = 162) with previously untreated advanced BTC (IMbrave151; ClinicalTrials.gov identifier: NCT04677504). Patients were randomly assigned 1:1 to receive cycles of atezolizumab (1,200 mg) plus bevacizumab (15 mg/kg) or atezolizumab plus placebo once every 3 weeks until disease progression or unacceptable toxicity. All patients received cisplatin (25 mg/m²) plus gemcitabine (1,000 mg/m²; cisplatin plus gemcitabine [CisGem]) on days 1 and 8 once every 3 weeks for up to eight cycles. Stratification of patients was by disease status, geographic region, and primary tumor location. The primary end point was progression-free survival (PFS). No formal hypothesis testing was performed. Exploratory correlative biomarker analysis was undertaken using transcriptome analysis (n = 95) and mutation profiling (n = 102) on baseline tumor samples.

RESULTS Between February and September 2021, 162 patients were enrolled. Median PFS was 8.3 months in the bevacizumab arm and 7.9 months in the placebo arm (stratified hazard ratio [HR], 0.67 [95% CI, 0.46 to 0.95]). Median overall survival (OS) was 14.9 and 14.6 months in the bevacizumab and placebo arms, respectively (stratified HR, 0.97 [95% CI, 0.64 to 1.47]). The incidence of grade 3 or 4 adverse events was 74% in both arms. High *VEGFA* gene expression was associated with improved PFS (HR, 0.44 [95% CI, 0.23 to 0.83]) in the bevacizumab arm versus placebo.

CONCLUSION In unselected patients with advanced BTC, adding bevacizumab to atezolizumab plus CisGem modestly improves PFS but not OS. High *VEGFA* gene expression may represent a predictive biomarker of benefit from atezolizumab/bevacizumab, warranting further investigation.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

Biliary tract cancer (BTC) encompasses a group of invasive adenocarcinomas characterized by significant heterogeneity that is not only related to the anatomic site of origin (gallbladder *v* intrahepatic or extrahepatic cholangiocarcinoma [iCCA or eCCA]) but also driven by different molecular alterations that vary by site.[1] CCA is the second most common primary liver cancer after hepatocellular carcinoma (HCC), accounting for approximately 15% of all primary liver cancers and 3% of gastrointestinal malignancies.[2] The overall incidence and mortality associated with CCA are rising, primarily because of an increase in iCCA.[3]

BTC is frequently diagnosed at an advanced inoperable stage, which limits therapeutic options and results in a dismal

CONTEXT

Key Objective

Does the addition of bevacizumab (anti–vascular endothelial growth factor [VEGF]) to atezolizumab (anti–PD-L1) and chemotherapy improve clinical outcomes as first-line treatment for advanced biliary tract cancer (BTC)?

Knowledge Generated

In the intention-to-treat population, the triplet regimen of atezolizumab, bevacizumab, and chemotherapy demonstrated a modest improvement in progression-free survival, but not in objective response rate and overall survival relative to atezolizumab plus chemotherapy. A similar incidence of grade 3 and 4 adverse events was observed in both arms. Post hoc correlative biomarker analysis indicates a possible association between *VEGFA* gene expression and clinical benefit in the bevacizumab arm.

Relevance *(A.H. Ko)*

While the addition of anti-VEGF therapy to chemoimmunotherapy should not be routinely used in clinical practice for patients with advanced BTC, this therapeutic strategy warrants further evaluation, especially in specific biomarker-enriched subsets.*

*Relevance section written by *JCO* Associate Editor Andrew H. Ko, MD, FASCO.

prognosis. For over a decade, cisplatin plus gemcitabine (CisGem) has been the first-line standard of care for advanced BTC on the basis of the ABC-02 study, which reported improved overall survival (OS) compared with gemcitabine monotherapy.[4] Subsequent studies of triplet chemotherapy regimens or combinations of targeted therapies and chemotherapy, including antiangiogenic agents, have failed to improve efficacy compared with CisGem.[5-7] Molecularly targeted therapies are indicated for selected patients harboring genomic aberrations in the second line and beyond (eg, *IDH1* mutation, *FGFR2* fusion, *NTRK* fusion, *BRAFV600*^{E} mutation, *HER2* amplification, and *RET* fusion).[8-10] The modest benefit of chemotherapy coupled with the limited scope of targeted agents highlights the need for more effective treatment options.

Most BTCs are immunologically cold, with a desmoplastic tumor microenvironment (TME) that is characterized by poor infiltration of effector T cells and an abundance of suppressive immune cells that collectively enable tumor immune escape.[11-13] Consequently, response to PD-1 or PD-L1 inhibitors given as monotherapy is low.[14,15]

Chemotherapy, including cisplatin and gemcitabine, can promote an immune-permissive TME that augments response to PD-1/PD-L1 inhibition.[16] Studies have demonstrated the superiority of PD-1 or PD-L1 inhibitors combined with chemotherapy in a variety of solid tumors.[16] In advanced BTC, the TOPAZ-1 and KEYNOTE-966 phase III studies reported improved OS with either durvalumab (anti–PD-L1) or pembrolizumab (anti–PD-1), respectively, combined with CisGem compared with CisGem plus placebo.[17,18] Although the results of TOPAZ-1 and KEYNOTE-966 are encouraging, the survival benefit afforded by chemoimmunotherapy is modest, highlighting the need for more effective immunotherapy regimens.

Vascular endothelial growth factor (VEGF) is a growth factor regulating tumor angiogenesis that is overexpressed in 40%-75% of BTCs.[19,20] Despite this, randomized studies have failed to demonstrate the superiority of VEGF inhibitors combined with CisGem.[6,7] In addition to angiogenesis, VEGF is a potent driver of TME immunosuppression, resulting in resistance to PD-1/PD-L1 blockade.[21] VEGF promotes an immunosuppressive TME through multiple mechanisms, including perturbed antigen presentation, impaired immune effector infiltration, and expansion of immunosuppressive cell types.[21] PD-1/PD-L1 inhibitors combined with anti-VEGF agents are now standard treatment options for a renal cell carcinoma, non–small cell lung cancer, and HCC.[21] Atezolizumab in combination with bevacizumab is the first-line standard of care for unresectable HCC on the basis of the IMbrave150 trial, which demonstrated superior OS, progression-free survival (PFS), and objective response rate (ORR) compared with sorafenib.[22,23] Chemotherapy augments antitumor immunity through similar mechanisms to those modulated by VEGF inhibition, suggesting that they may act synergistically when combined with atezolizumab.[24] Triplet therapy with atezolizumab, bevacizumab, and platinum-based chemotherapy is approved for the first-line treatment of non–small cell lung cancer.[25]

IMbrave151 was designed to evaluate the efficacy and safety of atezolizumab in combination with cisplatin and gemcitabine with or without bevacizumab as first-line treatment for patients with advanced BTC. We report the final clinical data from IMbrave151 as well as key results from exploratory correlative biomarker analysis.

PATIENTS AND METHODS

Study Design

IMbrave151 is a global randomized, double-blind, placebo-controlled two-arm phase II trial (ClinicalTrials.gov identifier: NCT04677504) conducted in the United States, Europe, and Asia according to the guidelines of Good Clinical Practice and the principles of the Declaration of Helsinki. IMbrave151 was a noncomparative, proof-of-concept phase II study designed to assess the relative clinical benefit of both treatment regimens to inform a decision to proceed with a pivotal study (Appendix Fig A1, online only). The Protocol (online only) was approved by institutional review boards (IRBs) or ethics committees at each site.

Patients

Eligible patients had histologically or cytologically confirmed advanced (unresectable, recurrent, or metastatic) BTC, including iCCA, eCCA, or gallbladder cancer (GBC). No previous systemic treatment for advanced BTC was allowed (adjuvant or neoadjuvant treatment was permitted if completed at least 6 months before study treatment on day 1 of cycle 1). Patients were required to be 18 years or older, have an Eastern Cooperative Oncology Group performance status of 0 or 1, have adequate biliary drainage with no evidence of ongoing infection, have measurable disease as defined by RECIST 1.1, and have adequate end organ and hematologic function. Patients with esophagogastric varices or those deemed to be at high risk of variceal bleeding (see online study protocol) were required to undergo an esophagogastroduodenoscopy during screening or within 6 months before day 1 of cycle 1, with any varices assessed and treated per institutional standard of care. Patients with ampulla of Vater cancer or mixed CCA/HCC histology were excluded.

Procedures

Eligible patients were randomly assigned 1:1 to receive either atezolizumab and bevacizumab plus CisGem or atezolizumab and bevacizumab placebo plus CisGem. Random assignment was stratified according to location of the primary tumor (iCCA *v* eCCA *v* GBC), the presence or absence of metastatic disease, and geographic region (Asia *v* rest of the world).

Patients received either intravenous atezolizumab (1,200 mg) and intravenous bevacizumab (15 mg/kg) or atezolizumab (1,200 mg) and intravenous bevacizumab placebo every 3 weeks on day 1 of each 21-day cycle. Patients in both arms received intravenous cisplatin 25 mg/m^2 and gemcitabine 1,000 mg/m^2 every 3 weeks (on days 1 and 8 of each 21-day cycle), for a maximum of eight cycles. After completion of CisGem, patients continued to receive atezolizumab/bevacizumab or atezolizumab/placebo until unmanageable toxicity, disease progression per RECIST 1.1 (assessed by investigators), or loss of clinical benefit (including elective treatment beyond progression for patients who met protocol-defined criteria; see online protocol).

Tumor assessments (computed tomography or magnetic resonance imaging scans of the chest, abdomen, and pelvis) were conducted at screening and then every 9 (±1) weeks after initiation of study treatment regardless of dose delays, until radiographic disease progression per RECIST 1.1 or loss of clinical benefit. All patients provided written informed consent before any trial-specific procedures or treatment. Adverse events were recorded at every cycle and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. The study was performed with IRB approval at participating study centers.

Outcomes

The primary end point was investigator-assessed PFS (time from random assignment to disease progression per RECIST 1.1 or death from any cause, whichever occurs first). Secondary outcomes were OS, confirmed ORR per RECIST 1.1, duration of response (DOR), disease control rate, safety as assessed by the incidence and severity of adverse events, and patient-reported outcomes. Biomarker studies were conducted as exploratory analyses.

Biomarker Methods

Formalin-fixed, paraffin-embedded tumor tissue samples (either archival or from a new tumor biopsy) were collected for exploratory biomarker analyses when available. Transcriptome analysis was performed by RNA sequencing (TruSeq RNA Access technology; Illumina, San Diego, CA). Genetic profiling was performed using FoundationOne (F1CDx, Cambridge, MA) sequencing.

RNA-seq reads were first aligned to ribosomal RNA sequences to remove ribosomal reads. The remaining reads were then aligned to the human reference genome (NCBI Build 38) using GSNAP v.2013-11-01.[26] To quantify gene expression levels, the number of reads mapped to the exons of each RefSeq gene was calculated using the functionality provided by the R/Bioconductor package GenomicAlignments.[27] Raw counts were filtered by keeping genes that have CPM values (counts per million mapped reads) of >0.25 in more than 10% of samples, and were subsequently transformed with the voom function in the limma R package,[28] resulting in normalized log2(CPM) data. Gene signature scores were calculated for each sample as the arithmetic mean of log2(CPM) expression of all genes in a given signature (Appendix Table A1). The angiogenesis signature comprising *VEGFA*, *KDR*, *ESM1*, *PECAM1*, *FLT1*, *ANGPTL4*, and *CD34* was used. Additionally, xCell deconvolution analysis was performed using the log2(TPM + 1) (transcripts per million) as input.[29]

Statistical Analysis

IMbrave151 was initially designed to enroll approximately 150 patients to evaluate the PFS benefit of atezolizumab in

combination with CisGem with versus without bevacizumab as a first-line treatment for patients with advanced BTC. This study was not adequately powered for hypothesis testing. Therefore, with the prespecified 90 PFS events and two-sided significance level of 0.05, there was only 68% power to detect a statistically significant hazard ratio (HR) of 0.6. Median PFS was estimated to be 9 months for the atezolizumab plus placebo arm. The study was later amended to have a longer follow-up so that an evaluation of OS benefit could be completed when at least 90 deaths had occurred. Along with the final OS analyses, the primary PFS analyses were updated with the longer follow-up and are reported here.

Toxicity was assessed using Common Terminology Criteria for Adverse Events version 5.0[30] by comparing frequency, severity, and causality of adverse events and other clinically relevant physical examinations and laboratory tests between the two treatment arms.

All efficacy analyses were conducted in the intention-to-treat (ITT) population, which consisted of all randomly assigned patients. Safety analysis was done in the safety-evaluable population (all patients who received at least one dose of their assigned treatment).

HRs and associated 95% CIs for PFS and OS were estimated using a stratified Cox proportional hazards regression model. The Kaplan-Meier method was used to calculate medians for time-to-event end points including PFS, OS, and DOR, with the Brookmeyer-Crowley method being used to calculate the 95% CI. ORR and disease control rate were calculated along with respective 95% CIs estimated by the Clopper-Pearson method. Correlative biomarker analyses were not adjusted for multiple testing.

According to the study protocol, three analyses were prespecified (Appendix Table A2). The results of the final analysis are reported here.

RESULTS

Between February and September 2021, 162 patients were enrolled from 48 sites in 13 countries/regions (Fig 1). The overaccrual by 12 patients is within 10% of target and was due to rapid accrual. Three patients did not receive any study treatment (one in the bevacizumab arm and two in the placebo arm). The data cutoff for the final analysis was January 16, 2023. The minimum duration of follow-up from the date of enrolling the last patient was 16 months. Patient demographics and disease characteristics were generally balanced between the treatment groups (Table 1). Of the 162 patients randomly assigned, 54% were male, 44% were enrolled in Asia, 55% were younger than 65 years, 83% had metastatic disease, and 55% had iCCA. One third of the patients had undergone previous BTC surgery (28% and 39% in the bevacizumab and placebo arms, respectively). A modest imbalance in age <65 years and sex was noted. In the patient population evaluable for PD-L1 status, 43% of patients had a PD-L1 tumor area positivity score of ≥1 (39% and 48% in the bevacizumab and placebo arms, respectively).

The primary objective was to estimate the efficacy, as measured by PFS, in each treatment arm. No formal

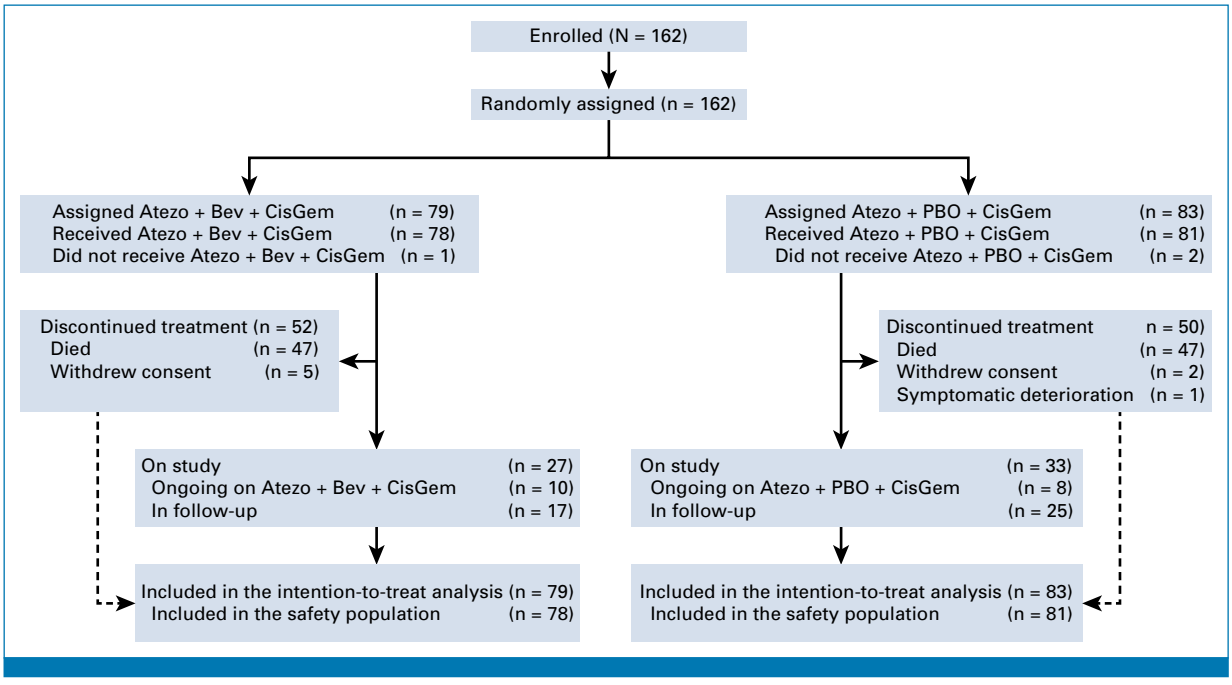

FIG 1. CONSORT diagram. Atezo, atezolizumab; Bev, bevacizumab; CisGem, cisplatin plus gemcitabine; PBO, placebo.

TABLE 1. Baseline Demographics and Patient Characteristics

Characteristic	Atezo + Bev + CisGem (n = 79)	Atezo + PBO + CisGem (n = 83)	All Patients (N = 162)
Median age, years (range)	61 (36-79)	65 (37-79)	63 (36-79)
Age <65 years, No. (%)	51 (64.6)	38 (45.8)	89 (54.9)
Male, No. (%)	49 (62)	38 (45.8)	87 (53.7)
Race, No. (%)			
White	41 (51.9)	46 (55.4)	87 (53.7)
Asian	37 (46.8)	35 (42.2)	72 (44.4)
Black/African American	1 (1.3)	1 (1.2)	2 (1.2)
Unknown	0	1 (1.2)	1 (0.6)
Region, No. (%)[a]			
Asia	34 (43)	35 (42.2)	69 (42.6)
Rest of the world	45 (57)	48 (57.8)	93 (57.4)
ECOG PS, No. (%)			
0	42 (53.2)	43 (51.8)	85 (52.5)
1	37 (46.8)	40 (48.2)	77 (47.5)
PD-L1 (TAP) status, No. (%)[b]	n = 57	n = 63	n = 120
<1%	35 (61.4)	33 (52.4)	68 (56.7)
≥1%	22 (38.6)	30 (47.6)	52 (43.3)
Metastatic disease, No. (%)[a]	n = 75	n = 80	n = 155
Yes	64 (85.3)	64 (80)	128 (82.6)
No	11 (14.7)	16 (20)	27 (17.4)
Anatomic location of primary tumor, No. (%)[a]			
iCCA	46 (58.2)	43 (51.8)	89 (54.9)
eCCA	13 (16.5)	17 (20.5)	30 (18.5)
GBC	20 (25.3)	23 (27.7)	43 (26.5)
Median CA-19.9 at baseline, kU/L (range)	46.3 (0-199,970)	66.9 (0-335,091)	57.2 (0-335,091)
Previous BTC surgery, No. (%)	22 (27.8)	32 (38.6)	54 (33.3)

Abbreviations: Atezo, atezolizumab; Bev, bevacizumab; BTC, biliary tract cancer; CA, cancer antigen; CisGem, cisplatin plus gemcitabine; eCCA, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder cancer; iCCA, intrahepatic cholangiocarcinoma; PBO, placebo; TAP, tumor area positivity score.
[a]Per electronic case report form.
[b]Per VENTANA SP263 PD-L1 assay.

hypothesis testing was undertaken to establish statistical significance for the primary end point. At the data cutoff, 63 patients (80%) in the bevacizumab arm and 73 patients (88%) in the placebo arm had a PFS event. Median PFS was 8.3 months (95% CI, 6.8 to 10.6) in the bevacizumab arm and 7.9 months (95% CI, 6.2 to 8.5) in the placebo arm (HR, 0.67 [95% CI, 0.46 to 0.95]; Fig 2). The 6-month PFS rate was 78% in the bevacizumab arm and 63% in the placebo arm. The 12-month PFS rate was 33% in the bevacizumab arm and 20% in the placebo arm. Descriptive subgroup analysis showed a PFS benefit (HR < 1) for the bevacizumab arm in almost all subgroups. There was a trend toward improved PFS in patients with iCCA or GBC in the bevacizumab arm.

Investigator-assessed confirmed ORR was 26.6% in the bevacizumab arm and 26.5% in the placebo arm (Table 2). A single complete response was observed in each treatment arm. The median duration of confirmed response was 10.3 months (95% CI, 6.7 to 16.7) in the bevacizumab arm and 6.2 months (95% CI, 4.3 to 6.7) in the placebo arm (stratified HR, 0.28 [95% CI, 0.12 to 0.68]; Appendix Fig A2). The percentage of patients with an ongoing response for 1 year was 47.8% in the bevacizumab arm and 9.6% in the placebo arm. Because of the lack of difference in ORR, but marked prolongation of response in the bevacizumab arm, an exploratory post hoc analysis was conducted to evaluate the association between ORR and PFS. In 43 patients with a confirmed best response of complete or partial response, PFS was improved in the bevacizumab arm compared with the placebo arm (HR, 0.32 [95% CI, 0.13 to 0.75]; Appendix Fig A3A). In the 91 patients with a confirmed best response of stable disease, there was no difference in PFS between the two treatment arms (HR, 0.95 [95% CI, 0.59 to 1.53]; Appendix Fig A3A). Similar associations were observed for OS (Appendix Fig A3B).

At the data cutoff, 47 (59.5%) patients in the bevacizumab arm and 48 (57.8%) patients in the placebo arm had died.

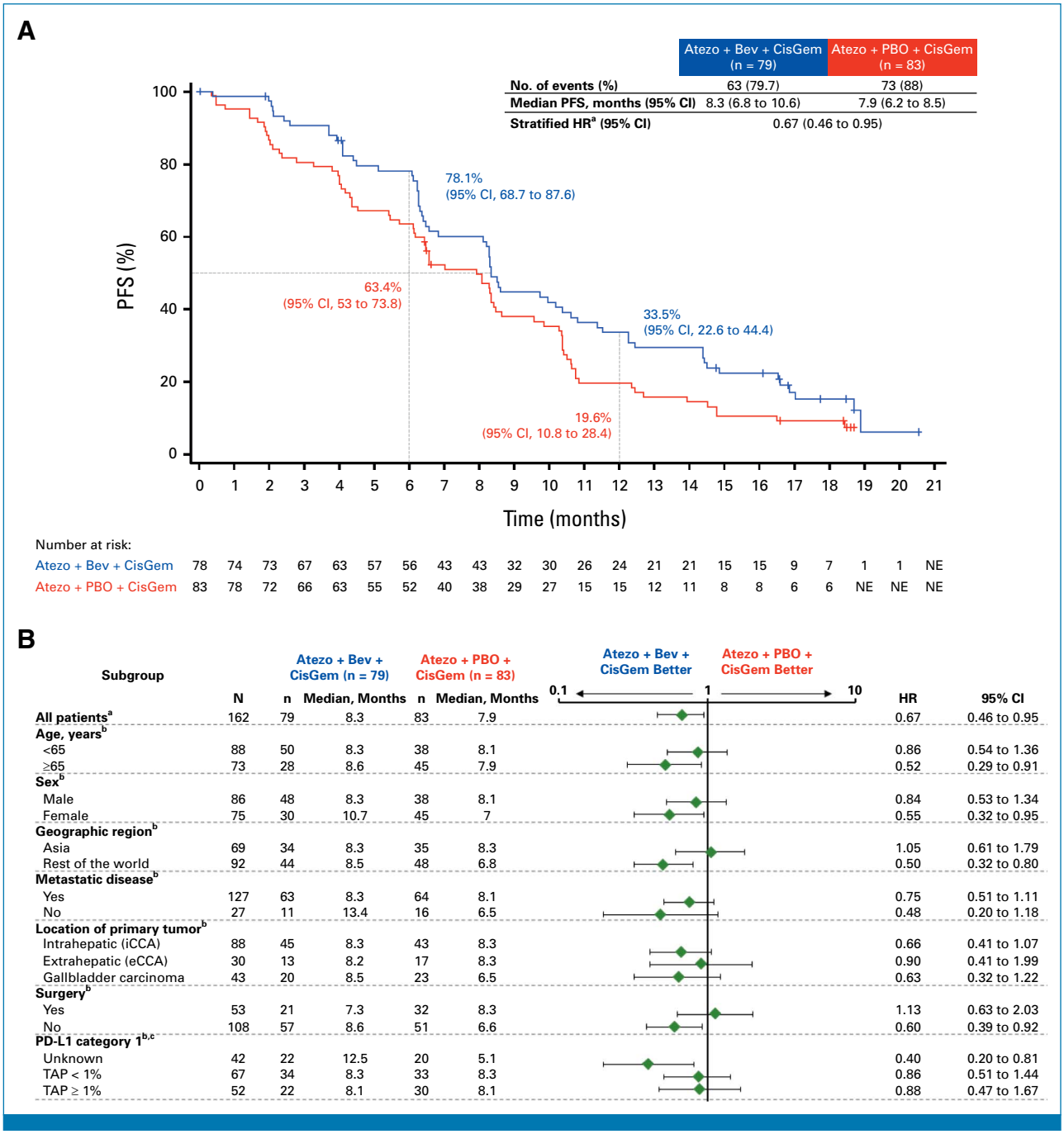

FIG 2. (A) PFS curve and (B) PFS forest plot. A patient in the Bev arm had a missing death date and was excluded from the Kaplan-Meier curve. [a]Stratified analysis. [b]Unstratified Cox regression analysis. [c]Per VENTANA SP-263 PD-L1 assay. Atezo, atezolizumab; Bev, bevacizumab; CisGem, cisplatin plus gemcitabine; eCCA, extrahepatic cholangiocarcinoma; GBC, gall bladder carcinoma; HR, hazard ratio; iCCA, intrahepatic cholangiocarcinoma; PBO, placebo; PFS, progression-free survival; TAP, tumor area positivity score.

Median OS was 14.9 months (95% CI, 11.6 to 18) in the bevacizumab arm and 14.6 months (95% CI, 11.2 to not estimable) in the placebo arm (stratified HR, 0.97 [95% CI, 0.64 to 1.47]; Fig 3). In the bevacizumab arm, 92% (95% CI, 85.8 to 98.1) and 59% (95% CI, 47.7 to 70.3) of patients were alive at 6 and 12 months, respectively. In the placebo arm, 80.5% (95% CI, 72 to 89.1) of patients were alive at 6 months and 54.6% (95% CI, 43.7 to 65.4) were alive at 12 months.

In the bevacizumab arm, the median number of atezolizumab and bevacizumab cycles administered was 11 (range, 1-32) and 10 (range, 1-32), respectively. In the placebo arm, the median number of atezolizumab and placebo cycles administered was 10 (range, 1-30) and 9 (range, 1-30), respectively. In both arms, the median number of cisplatin or gemcitabine cycles administered was 8 (range, 1-8; Appendix Table A3).

TABLE 2. Confirmed ORR and DOR

Confirmed Response	Atezo + Bev + CisGem (n = 79)	Atezo + PBO + CisGem (n = 83)
ORR,[a] No. (%)	21 (26.6)	22 (26.5)
95% CI	17.3 to 37.7	17.4 to 37.3
CR, No. (%)	1 (1.3)	1 (1.2)
PR, No. (%)	20 (25.3)	21 (25.3)
SD, No. (%)	48 (60.8)	44 (53)
PD, No. (%)	5 (6.3)	9 (10.8)
Missing/unevaluable,[b] No. (%)	5 (6.3)	8 (9.6)
DCR,[c] No. (%)	63 (79.7)	63 (75.9)
DOR	n = 21	n = 22
Median, months (95% CI)	10.3 (6.7 to 16.7)	6.2 (4.3 to 6.7)
6-month rate, % (95% CI)	90 (76.9 to 100)	52.5 (31.1 to 73.9)
12-month rate, % (95% CI)	47.8 (25.4 to 70.3)	9.6 (0 to 22.1)

NOTE. Minimum follow-up duration: 16 months.
Abbreviations: Atezo, atezolizumab; Bev, bevacizumab; CisGem, cisplatin plus gemcitabine; CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; PBO, placebo; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Confirmed objective response on the basis of investigator assessment per RECIST 1.1.
[b]Patients who withdrew from treatment before the first scan were considered missing. Patients for whom a RECIST response assessment was performed, but best response could not be evaluated because of obstruction of view or poor image quality, were considered unevaluable.
[c]DCR is defined as CR + PR + SD ≥ 9 weeks.

Treatment-related grade 3 or 4 adverse events were reported in 69% of patients in the bevacizumab arm and 64% in the placebo arm (Table 3). The majority of common adverse events occurred in the induction phase compared with the maintenance phase in both treatment arms. The most common adverse events (≥20% overall incidence in either treatment arm) were grade 1 or 2 (Appendix Fig A4). Anemia, decreased neutrophil count, nausea, constipation, and decreased platelet count were the most common adverse events in both treatment arms. All-grade hypertension was more frequently reported in the bevacizumab arm than in the placebo arm (38.5% *v* 18.5%). Discontinuation of any treatment component was observed in 14% and 11% of patients in the bevacizumab and placebo arms, respectively (Table 3). Deaths due to adverse events were observed in five patients (6.4%) in the bevacizumab arm and six (7.4%) in the placebo arm, of which one (1.3%) and two (2.5%), respectively, were related to treatment. A single fatal case of upper gastrointestinal bleeding was reported in the bevacizumab arm. Grade 3 or 4 protocol-defined adverse events of special interest for atezolizumab occurred in 15.4% and 14.8% of patients in the bevacizumab and placebo arms, respectively. Atezolizumab adverse events of special interest requiring systemic corticosteroids occurred in 16.7% of patients in the bevacizumab arm and 4.9% in the placebo arm.

Exploratory biomarker studies were conducted to identify molecular correlates that may be associated with clinical outcomes. Demographic and baseline characteristics in biomarker-evaluable population subgroups were generally consistent with those in the ITT population (Table 4). Biomarker associations with clinical outcomes are discussed when the 95% CI for PFS HR did not cross 1 for PFS.

Transcriptome analysis was performed on baseline tumor tissues from 95 patients (46 and 49 in the bevacizumab and placebo arms, respectively). High *VEGFA* gene expression, on the basis of median expression score, appeared to be associated with improved PFS in the bevacizumab arm compared with the placebo arm (HR, 0.44 [95% CI, 0.23 to 0.83]; Fig 4). In the *VEGFA*-low gene expression group, the PFS HR was 1.20 (95% CI, 0.64 to 2.25). There was a trend toward improved OS in the *VEGFA*-high subgroup in favor of the bevacizumab arm (HR, 0.65 [95% CI, 0.31 to 1.37]; Fig 4). High expression of the angiogenesis gene signature, on the basis of median split, did not appear to strongly differentiate PFS or OS benefit in the bevacizumab arm compared with the placebo arm (Appendix Fig A5). On the basis of xCell deconvolution analysis, tumors enriched with hepatocytes appeared to derive PFS benefit from the addition of bevacizumab (HR, 0.47 [95% CI, 0.24 to 0.92]; Fig 4). *VEGFA* gene expression was higher in iCCA and GBC than in eCCA (Appendix Fig A6).

Genetic profiling of baseline tumor samples (n = 102) showed a mutational landscape consistent with previous studies of BTC (Appendix Fig A7A). The most frequently mutated genes (with known functional impact) included *TP53* (51%), *CDKN2A* (31%), *ARID1A* (26%), *CDKN2B* (22%), *KRAS* (17.5%; mostly G12D), and *SMAD4* (12%). Other clinically relevant aberrations occurred in *IDH-1* (6.7%), *FGFR2* (4.9%), *ERBB2* (16%), and *BRAF* (4.9%). Patients with mutations in the PI3K/AKT pathway (*PIK3CA*, *AKT1*, *PTEN*, or *PIK3R1*), occurring in approximately 22.5% (23 of 102) of biomarker-evaluable patients, appeared to have worse OS in the bevacizumab arm than in the placebo arm (HR, 3.95 [95% CI, 1.30 to 12]; Appendix Fig A7B). No difference was observed in patients without mutations. In the bevacizumab arm, patients with mutations in the PI3K/AKT pathway appeared to have shorter OS than patients without mutations (HR, 3.26 [95% CI, 1.40 to 7.59]), while no association was observed between PI3K/AKT pathway mutation status and clinical outcomes in the placebo arm (Appendix Fig A7C).

DISCUSSION

To the best of our knowledge, IMbrave151 is the first randomized study to evaluate concurrent PD-L1/VEGF blockade in combination with chemotherapy in advanced BTC. In the ITT population, the addition of bevacizumab to atezolizumab

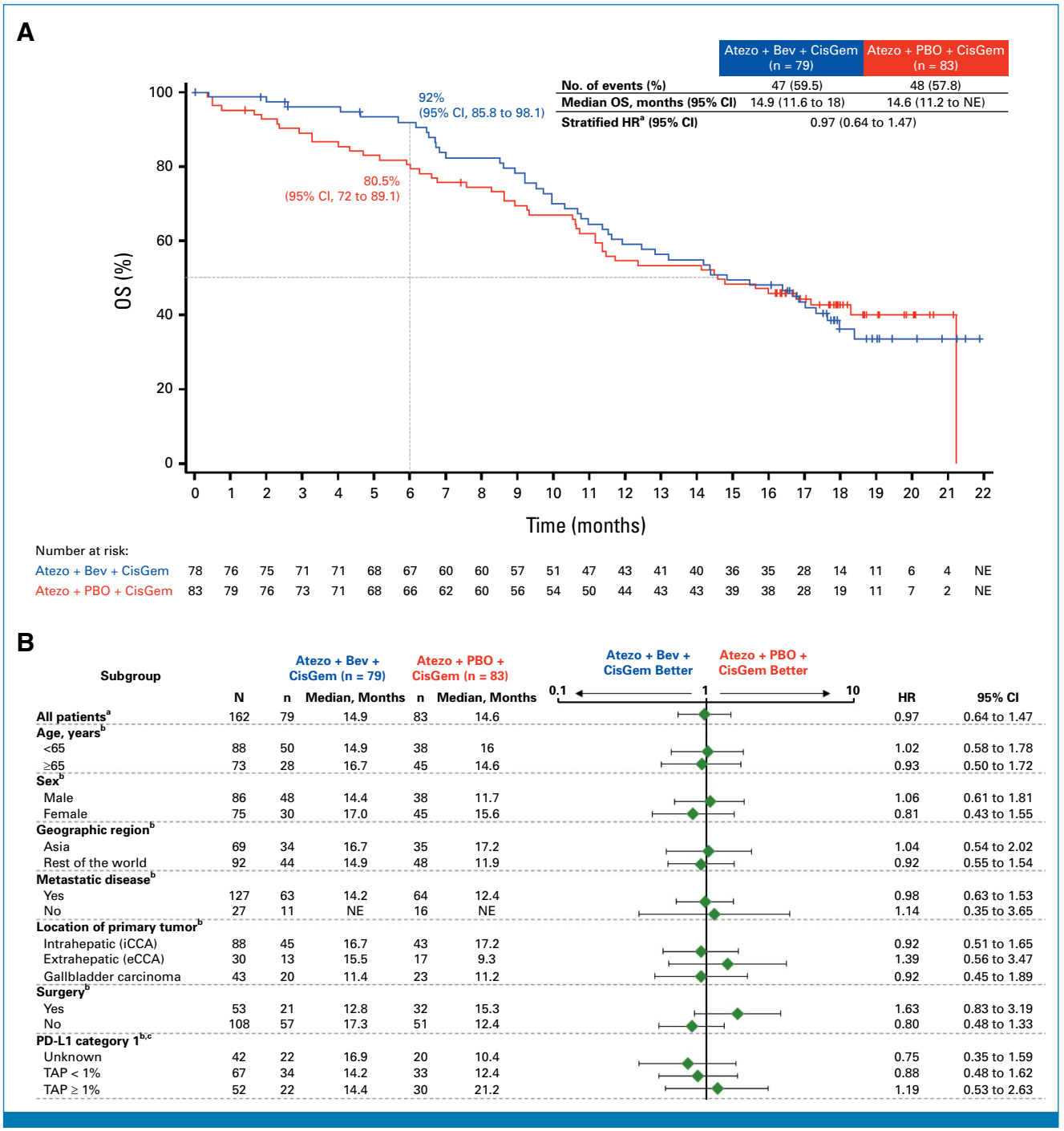

FIG 3. (A) OS curve and (B) forest plot. A patient in the Bev arm had a missing death date and was excluded from the Kaplan-Meier curve. [a]Stratified analysis. [b]Unstratified Cox regression analysis. [c]Per VENTANA SP-263 PD-L1 assay. Atezo, atezolizumab; Bev, bevacizumab; CisGem, cisplatin plus gemcitabine; eCCA, extrahepatic cholangiocarcinoma; GBC, gall bladder carcinoma; HR, hazard ratio; iCCA, intrahepatic cholangiocarcinoma; NE, not estimable; OS, overall survival; PBO, placebo; TAP, tumor area positivity score.

and CisGem was associated with a modest improvement in the primary end point of PFS. A PFS benefit of adding bevacizumab to chemoimmunotherapy was generally consistent across most of the prespecified subgroups and was sustained at 6 and 12 months. Although subgroup analyses should be interpreted with caution, patients with iCCA and GBC appeared to derive greater PFS benefit from bevacizumab than those with eCCA.

Although ORR was identical in both arms, DOR was markedly prolonged in the bevacizumab arm. The prolonged DOR in the bevacizumab arm likely accounts for the trend in improved PFS for patients with complete or partial response. Radiographic response can be difficult to assess in BTC, and it tends to correlate poorly with OS.[31,32] Interestingly, an exploratory study of tumor growth modeling using radiologic tumor measurements from IMbrave151 demonstrated

TABLE 3. Safety Summary

No. of Patients With ≥1	CIT+ Chemo Phase		CIT-Only Phase		Overall Period	
	Atezo + Bev + CisGem (n = 78)	Atezo + PBO + CisGem (n = 81)	Atezo + Bev (n = 54)	Atezo + PBO (n = 53)	Atezo + Bev + CisGem (n = 78)	Atezo + PBO + CisGem (n = 81)
AE, any cause	78 (100)	81 (100)	43 (79.6)	45 (84.9)	78 (100)	81 (100)
TRAE	76 (97.4)	77 (95.1)	30 (55.6)	28 (52.8)	76 (97.4)	78 (96.3)
Grade 3/4 AE, any cause	55 (70.5)	56 (69.1)	22 (40.7)	16 (30.2)	58 (74.4)	60 (74.1)
Grade 3/4 TRAE	52 (66.7)	48 (59.3)	11 (20.4)	10 (18.9)	54 (69.2)	52 (64.2)
AE leading to death	3 (3.8)	5 (6.2)	2 (3.7)	1 (1.9)	5 (6.4)	6 (7.4)
TRAE leading to death	1 (1.3)[a]	2 (2.5)	0	0	1 (1.3)	2 (2.5)
Serious AE	30 (38.5)	33 (40.7)	14 (25.9)	16 (30.2)	36 (46.2)	43 (53.1)
Serious TRAE	19 (24.4)	15 (18.5)	4 (7.4)	4 (7.5)	23 (29.5)	17 (21)
AE leading to withdrawal from any treatment	6 (7.7)	7 (8.6)	6 (11.1)	2 (3.8)	11 (14.1)	9 (11.1)
AE leading to withdrawal from Atezo	3 (3.8)	0	4 (7.4)	1 (1.9)	7 (9)	1 (1.2)
AE leading to dose modification/interruption from any treatment	67 (85.9)	71 (87.7)	21 (38.9)	20 (37.7)	68 (87.2)	74 (91.4)
AESI for Atezo	25 (32.1)	34 (42)	18 (33.3)	23 (43.4)	37 (47.4)	46 (56.8)
AESI for Bev	45 (57.7)	27 (33.3)	16 (29.6)	6 (11.3)	49 (62.8)	33 (40.7)

Abbreviations: AE, adverse event; AESI, adverse event of special interest; Atezo, atezolizumab; Bev, bevacizumab; CisGem, cisplatin plus gemcitabine; CIT, cancer immunotherapy; PBO, placebo; TRAE, treatment-related adverse event.

[a]Patient died as a result of upper gastrointestinal hemorrhage after receiving four cycles of study treatment. The investigator considered the event to be not related to Atezo but related to the other three drugs. Other possible etiologic factors for the event include disease under study (hepaticojejunostomy site near artery).

TABLE 4. BEP Versus ITT Baseline Demographics

Characteristic	BEP (n = 95)	ITT (n = 162)
Median age, years (range)	64 (39-79)	63 (36-79)
Age <65 years, No. (%)	49 (51.6)	89 (54.9)
Male, No. (%)	48 (50.5)	87 (53.7)
Race, No. (%)		
White	48 (50.5)	87 (53.7)
Asian	46 (48.4)	72 (44.4)
Black or African American	0	2 (1.2)
Unknown	1 (1.1)	1 (0.6)
Region, No. (%)[a]		
Asia	45 (47.4)	69 (42.6)
Rest of the world	50 (52.6)	93 (57.4)
Baseline ECOG PS, No. (%)		
0	51 (53.7)	85 (52.5)
1	44 (46.3)	77 (47.5)
PD-L1 (TAP) status at baseline, No. (%)[b]	n = 86	n = 120
<1%	43 (50)	68 (56.7)
≥1%	43 (50)	52 (43.3)
Metastatic disease, No. (%)[a]	n = 93	n = 155
Yes	82 (88.2)	128 (82.6)
No	11 (11.8)	27 (17.4)
Anatomic location of primary tumor, No. (%)		
iCCA	50 (52.6)	89 (54.9)
eCCA	16 (16.8)	30 (18.5)
GBC	29 (30.5)	43 (26.5)

Abbreviations: BEP, biomarker evaluable population; eCCA, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder cancer; iCCA, intrahepatic cholangiocarcinoma; ITT, intention-to-treat; TAP, tumor area positivity score.
[a]Per electronic case report form.
[b]Per VENTANA SP263 PD-L1 assay.

slower tumor growth and faster tumor shrinkage rates in the bevacizumab-containing arm relative to the control arm, despite no difference in ORR.[33] Thus, ORR assessed according to RECIST criteria may not be the optimal surrogate measure of clinical benefit in patients with BTC. IMbrave151 was not powered to detect a difference in OS, but OS in the ITT population did not differ between treatment arms. No clear trend for improved OS was observed in any subgroup analyzed.

The TOPAZ-1 and KEYNOTE-966 phase III studies have recently validated the role of PD-1 or PD-L1 inhibitors in combination with chemotherapy as first-line treatment for advanced BTC.[17,18] The BTC patient populations enrolled in IMbrave151, TOPAZ-1, and KEYNOTE-966 were largely similar. Outcomes with respect to PFS, OS, and ORR in the atezolizumab/chemotherapy arm of IMbrave151 were largely comparable with those reported in experimental arms of TOPAZ-1 and KEYNOTE-966 (Appendix Table A4). However, these chemoimmunotherapy data are similar to previous studies of CisGem alone, indicating that the benefit of adding a PD-1 or PD-L1 inhibitor to CisGem is modest.[4] A consistent finding in IMbrave151, TOPAZ-1, and KEYNOTE-966 is the lack of association between higher PD-L1 expression and outcomes. Although acknowledging the use of different PD-L1 assays and the presence of atezolizumab in both arms of IMbrave151, PD-L1 status does not appear to be a useful biomarker in BTC.

By binding to VEGFA, bevacizumab prevents the interaction of VEGFA with VEGFR1 and VEGFR2, thereby inhibiting the activation of VEGF signaling—primarily through VEGFR2.[34] In this context, an intriguing observation from the post hoc exploratory correlative biomarker analysis in IMbrave151 is the association between high *VEGFA* gene expression and enhanced PFS benefit in the bevacizumab arm. Of note, high expression of an angiogenesis gene signature did not differentiate PFS benefit, suggesting that in BTC, bevacizumab may augment anticancer immunity specifically through VEGFA-mediated mechanisms. This exploratory finding suggests that VEGFA expression could be a biomarker to enrich patient selection for anti-VEGF/PD-L1 treatment. Interestingly, *VEGFA* gene expression was highest in iCCA and GBC compared with eCCA, which may account in part for the trend toward improved bevacizumab benefit in iCCA and GBC versus the eCCA subgroup. To our knowledge, an association between *VEGFA* gene expression and clinical outcomes is a novel finding in BTC in the context of antiangiogenic therapy. *VEGF* gene expression was not associated with clinical benefit of first-line ramucirumab plus CisGem in a randomized phase II study.[6] In HCC, high *VEGFR2*, but not *VEGFA*, gene expression was associated with enhanced clinical benefit of bevacizumab in combination with atezolizumab compared with atezolizumab alone.[35]

The observation of an association between PI3K/AKT mutations and worse outcome in the bevacizumab arm is limited by the small numbers but is consistent with a similar observation made in an ad hoc analysis of a breast cancer trial with bevacizumab.[36] Our trial does not allow for a mechanistic explanation of this potential association.

The safety profile of the atezolizumab, bevacizumab, and chemotherapy combination was consistent with previous experience with this type of triplet regimen.[25,37,38] The most common adverse events were blood count–related abnormalities, nausea, and constipation, events known to be associated with chemotherapy. The rates of grade 3 or 4 adverse events and treatment discontinuation were very similar between treatment arms, indicating that bevacizumab did not add significant additional toxicity. Consistent with previous studies, most of the toxicity in both treatment arms occurred during the induction phase of treatment when chemotherapy was being administered.[25,39] The need for corticosteroids to manage immune-mediated adverse events was higher in the bevacizumab arm, perhaps indicating enhanced immune activation.

The work presented here has several limitations, including the size and hypothesis-generating (noncomparative) design of

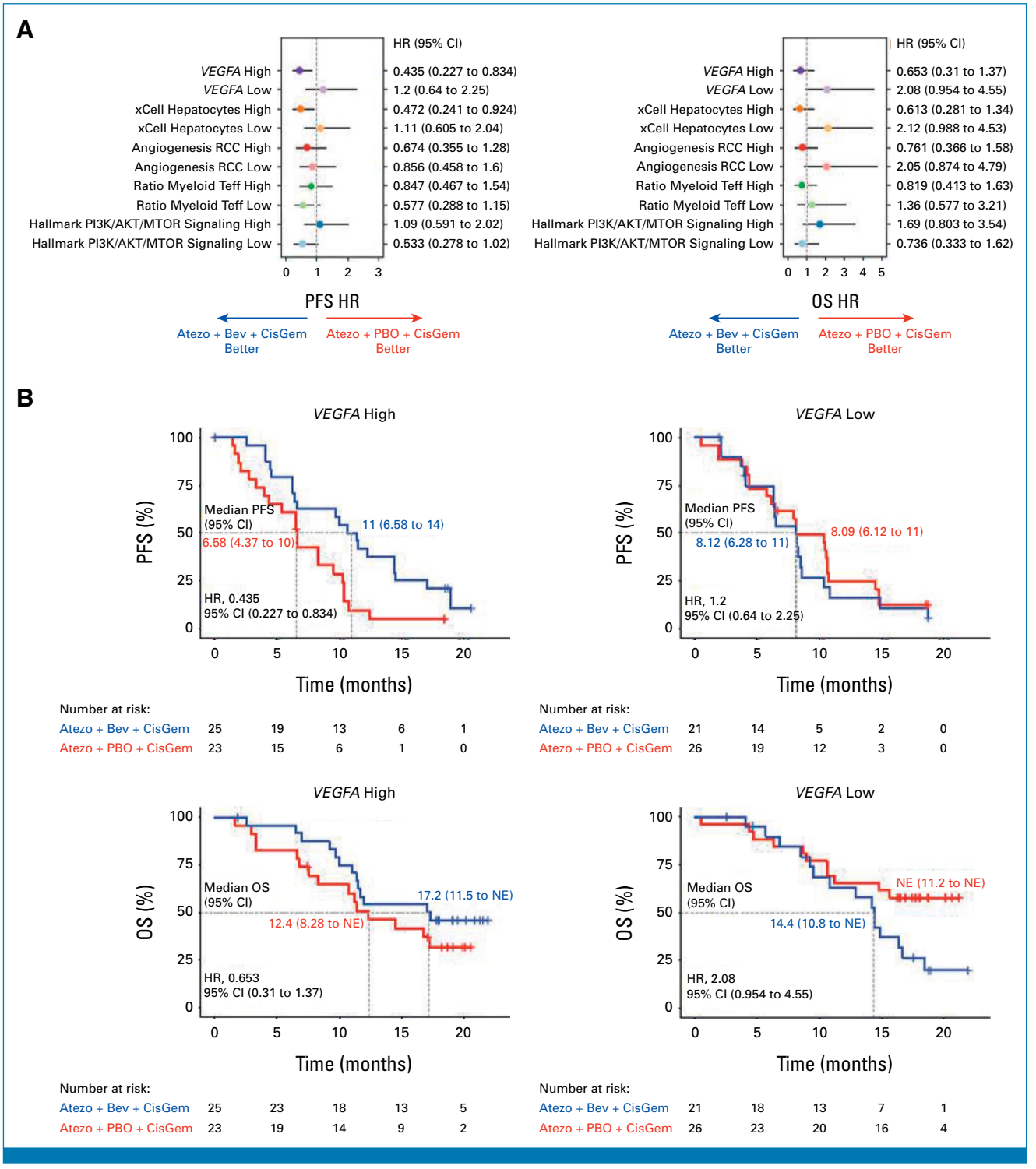

FIG 4. (A) Top gene signature forest plot (PFS and OS) and (B) outcomes by *VEGFA* gene expression. (A) Forest plot shows *VEGFA* gene and other biologic pathways in association with PFS (left) and OS (right) in the bevacizumab arm (n = 46) compared with the placebo arm (n = 49). The effect measure used is HR with 95% CI. (B) Kaplan-Meier plots of PFS and OS stratified by treatment arms (atezolizumab + bevacizumab and cisplatin and gemcitabine *v* atezolizumab + placebo and cisplatin and gemcitabine) in patients with high or low (split by median) expression score of *VEGFA* (BEP, n = 95). Atezo, atezolizumab; BEP, biomarker evaluable population; Bev, bevacizumab; CisGem, cisplatin plus gemcitabine; HR, hazard ratio; NE, not estimable; OS, overall survival; PBO, placebo; PFS, progression-free survival.

the study. The study also did not include a chemotherapy with bevacizumab arm. Correlative biomarker studies are exploratory in nature and further prospective evaluation is needed.

The results of IMbrave151 suggest that the addition of bevacizumab to a first-line chemoimmunotherapy platform in an unselected population of patients with advanced BTC is associated with modest PFS improvement but no benefit in OS. These results should be interpreted with caution within the limitations of the size and noncomparative design of the study, which limit the power to detect modest but significant differences. Exploratory correlative biomarker analyses suggest that high *VEGFA* gene expression may be a predictive marker of benefit with atezolizumab/bevacizumab. Although this study did not allow the identification of a clear winner to evaluate in a phase III study, it does provide evidence of potential benefit from the combination of PD-L1/VEGF inhibition in a subset of patients with BTC, which could be explored further. Furthermore, this study may provide a rationale to explore the atezolizumab/bevacizumab with chemotherapy combination in the setting of mixed cholangiocarcinoma-HCC, which is an area of unmet need.

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REFERENCES

1. Valle JW, Kelley RK, Nervi B, et al: Biliary tract cancer. Lancet 397:428-444, 2021
2. Banales JM, Marin JJG, Lamarca A, et al: Cholangiocarcinoma 2020: The next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol 17:557-588, 2020
3. Florio AA, Ferlay J, Znaor A, et al: Global trends in intrahepatic and extrahepatic cholangiocarcinoma incidence from 1993 to 2012. Cancer 126:2666-2678, 2020
4. Valle J, Wasan H, Palmer DH, et al: Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 362:1273-1281, 2010
5. Shroff RT, Guthrie KA, Scott AJ, et al: SWOG 1815: A phase III randomized trial of gemcitabine, cisplatin, and nab-paclitaxel versus gemcitabine and cisplatin in newly diagnosed, advanced biliary tract cancers. J Clin Oncol 41:LBA490, 2023

6. Valle JW, Vogel A, Denlinger CS, et al: Addition of ramucirumab or merestinib to standard first-line chemotherapy for locally advanced or metastatic biliary tract cancer: A randomised, double-blind, multicentre, phase 2 study. Lancet Oncol 22:1468-1482, 2021
7. Valle JW, Wasan H, Lopes A, et al: Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): A randomised phase 2 trial. Lancet Oncol 16:967-978, 2015
8. Lamarca A, Barriuso J, McNamara MG, et al: Molecular targeted therapies: Ready for "prime time" in biliary tract cancer. J Hepatol 73:170-185, 2020
9. Abou-Alfa GK, Macarulla T, Javle MM, et al: Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): A multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 21:796-807, 2020
10. Abou-Alfa GK, Sahai V, Hollebecque A, et al: Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: A multicentre, open-label, phase 2 study. Lancet Oncol 21: 671-684, 2020
11. Tomlinson JL, Valle JW, Ilyas SI: Immunobiology of cholangiocarcinoma. J Hepatol 79:867-875, 2023
12. Greten TF, Schwabe R, Bardeesy N, et al: Immunology and immunotherapy of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol 20:349-365, 2023
13. Ilyas SI, Affo S, Goyal L, et al: Cholangiocarcinoma—Novel biological insights and therapeutic strategies. Nat Rev Clin Oncol 20:470-486, 2023
14. Yarchoan M, Cope L, Ruggieri AN, et al: Multicenter randomized phase II trial of atezolizumab with or without cobimetinib in biliary tract cancers. J Clin Invest 131:e152670, 2021
15. Piha-Paul SA, Oh D-Y, Ueno M, et al: Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: Results from the KEYNOTE-158 and KEYNOTE-028 studies. Int J Cancer 147:2190-2198, 2020
16. Salas-Benito D, Pérez-Gracia JL, Ponz-Sarvisé M, et al: Paradigms on immunotherapy combinations with chemotherapy. Cancer Discov 11:1353-1367, 2021
17. Oh D-Y, Ruth He A, Qin S, et al: Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evid 1:EVIDoa2200015, 2022
18. Kelley RK, Ueno M, Yoo C, et al: Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 401:1853-1865, 2023
19. Rimini M, Casadei-Gardini A: Angiogenesis in biliary tract cancer: Targeting and therapeutic potential. Expert Opin Investig Drugs 30:411-418, 2021
20. Yoshikawa D, Ojima H, Iwasaki M, et al: Clinicopathological and prognostic significance of EGFR, VEGF, and HER2 expression in cholangiocarcinoma. Br J Cancer 98:418-425, 2008
21. Hack SP, Zhu AX, Wang Y: Augmenting anticancer immunity through combined targeting of angiogenic and PD-1/PD-L1 pathways: Challenges and opportunities. Front Immunol 11:598877, 2020
22. Finn RS, Qin S, Ikeda M, et al: Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 382:1894-1905, 2020
23. Cheng AL, Qin S, Ikeda M, et al: Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol 76:862-873, 2022
24. Hack SP, Verret W, Mulla S, et al: IMbrave 151: A randomized phase II trial of atezolizumab combined with bevacizumab and chemotherapy in patients with advanced biliary tract cancer. Ther Adv Med Oncol 13:17588359211036544, 2021
25. Socinski MA, Jotte RM, Cappuzzo F, et al: Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 378:2288-2301, 2018
26. Wu TD, Nacu S: Fast and SNP-tolerant detection of complex variants and splicing in short reads. Bioinformatics 26:873-881, 2010
27. Lawrence M, Huber W, Pagès H, et al: Software for computing and annotating genomic ranges. PLoS Comput Biol 9:e1003118, 2013
28. Ritchie ME, Phipson B, Wu D, et al: Limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res 43:e47, 2015
29. Aran D, Hu Z, Butte AJ: xCell: Digitally portraying the tissue cellular heterogeneity landscape. Genome Biol 18:220, 2017
30. U.S. Department of Health and Human Services: Common terminology criteria for adverse events (CTCAE), Version 5.0. November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf
31. Lamarca A, Hubner RA, David Ryder W, et al: Second-line chemotherapy in advanced biliary cancer: A systematic review. Ann Oncol 25:2328-2338, 2014
32. Eckel F, Schmid RM: Chemotherapy in advanced biliary tract carcinoma: A pooled analysis of clinical trials. Br J Cancer 96:896-902, 2007
33. Shemesh CS, Chan P, Marchand M, et al: Early decision making in a randomized phase II trial of atezolizumab in biliary tract cancer using a tumor growth inhibition-survival modeling framework. Clin Pharmacol Ther 114:644-651, 2023
34. Ferrara N, Adamis AP: Ten years of anti-vascular endothelial growth factor therapy. Nat Rev Drug Discov 15:385-403, 2016
35. Zhu AX, Abbas AR, de Galarreta MR, et al: Molecular correlates of clinical response and resistance to atezolizumab in combination with bevacizumab in advanced hepatocellular carcinoma. Nat Med 28:1599-1611, 2022
36. Vidal M, Di Cosimo S, Torrejon D, et al: P5-13-01: Survival outcome with bevacizumab: Activation of the phosphatidylinositol-3 kinase (PI3K) pathway due to PIK3CA mutations or PTEN loss makes a difference. Cancer Res 71:P5-13-01, 2011
37. Antoniotti C, Rossini D, Pietrantonio F, et al: Upfront FOLFOXIRI plus bevacizumab with or without atezolizumab in the treatment of patients with metastatic colorectal cancer (AtezoTRIBE): A multicentre, open-label, randomised, controlled, phase 2 trial. Lancet Oncol 23:876-887, 2022
38. Moore KN, Bookman M, Sehouli J, et al: Atezolizumab, bevacizumab, and chemotherapy for newly diagnosed stage III or IV ovarian cancer: Placebo-controlled randomized phase III trial (IMagyn050/GOG 3015/ENGOT-OV39). J Clin Oncol 39:1842-1855, 2021
39. Reck M, Wehler T, Orlandi F, et al: Safety and patient-reported outcomes of atezolizumab plus chemotherapy with or without bevacizumab versus bevacizumab plus chemotherapy in non–small-cell lung cancer. J Clin Oncol 38:2530-2542, 2020
40. McDermott DF, Huseni MA, Atkins MB, et al: Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. Nat Med 24:749-757, 2018
41. MacParland SA, Liu JC, Ma X-Z, et al: Single cell RNA sequencing of human liver reveals distinct intrahepatic macrophage populations. Nat Commun 9:4383, 2018
42. Subramanian A, Tamayo P, Mootha VK, et al: Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles. Proc Natl Acad Sci USA 102: 15545-15550, 2005
43. Liberzon A, Birger C, Thorvaldsdóttir H, et al: The Molecular Signatures Database (MSigDB) hallmark gene set collection. Cell Syst 1:417-425, 2015

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Atezolizumab Plus Chemotherapy With or Without Bevacizumab in Advanced Biliary Tract Cancer: Clinical and Biomarker Data From the Randomized Phase II IMbrave151 Trial

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APPENDIX

TABLE A1. Gene Expression Signatures

Pathway	Genes	Sources and References
T effector	*CXCL9, PRF1, GZMB*	36
Angiogenesis RCC	*VEGFA, KDR, ESM1, PECAM1, FLT1, ANGPTL4, CD34*	40
Myeloid inflammation RCC	*CXCL1, CXCL2, CXCL3, CXCL8, IL6, PTGS2*	40
High in hepatocyte-like	*ADH1C, ALDH1A1, ALDH3A1, AOC3, AQP7, ARG1, CA2, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP3A4, GPD1, HMGCS2, HPGD, IDH1, MAOA, TDO2*	Facile Explorer DGE analysis of TCGA HCC (370) *v* cirrhosis (50) and associated with good prognosis
Hepatocytes	*BCHE, G6PC, GHR, ALDH6A1, RCAN1, AR, RPP25L, HSD11B1, HAMP, APOM*	41
Hallmark PI3K/AKT/MTOR signaling	*MAPK8, PIK3R3, GRB2, NFKBIB, MAP2K6, MAPK9, AKT1, MAPK1, PLCG1, TRIB3, GSK3B, MAP2K3, CDKN1A, RAC1, RIPK1, AKT1S1, ACTR2, PRKAR2A, YWHAB, HRAS, PDK1, PIKFYVE, TBK1, ACTR3, E2F1, MYD88, ITPR2, SQSTM1, RPS6KA1, PTPN11, MAPKAP1, PLCB1, RAF1, CAMK4, RPTOR, CFL1, CDK4, TRAF2, GNGT1, UBE2N, ADCY2, CDKN1B, VAV3, FGF6, ECSIT, RALB, ARF1, MKNK1, CDK1, PTEN, ARHGDIA, GRK2, FGF17, DDIT3, IRAK4, TIAM1, CDK2, SFN, PRKCB, GNA14, EIF4E, CLTC, TSC2, FGF22, PPP1CA, DUSP3, HSP90B1, IL4, STAT2, SLA, EGFR, PLA2G12A, MAPK10, CALR, THEM4, RIT1, MKNK2, PPP2R1B, CAB39L, ARPC3, PITX2, NCK1, IL2RG, PFN1, FASLG, NOD1, DAPP1, UBE2D3, CAB39, AP2M1, MAP3K7, PRKAG1, CSNK2B, PRKAA2, ATF1, SLC2A1, PIN1, TNFRSF1A, LCK, RPS6KA3, NGF, CXCR4, ACACA, SMAD2, PAK4*	42,43

Abbreviations: DGE, differential gene expression; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; TCGA, The Cancer Genome Atlas.

TABLE A2. Prespecified Analyses

Analysis	Events	CCOD	Minimum Follow-Up,[a] Months
Interim PFS	First 100 patients randomly assigned with ≥6 months of follow-up	January 10, 2022	4.1
Final PFS	≈90 PFS events	May 16, 2022	8.3
Final OS	≈90 OS events	January 16, 2023	16.3

Abbreviations: CCOD, clinical cutoff date; OS, overall survival; PFS, progression-free survival.
[a]Calculated from the last patient enrollment date to the respective CCOD of each analysis.

TABLE A3. Treatment Exposure

	Atezo + Bev + Gem/Cis (n = 78)				Atezo + PBO + Gem/Cis (n = 81)			
Exposure	Atezo	Bev	Cis	Gem	Atezo	PBO	Cis	Gem
Median treatment duration, months (range)	7.6 (0-21)	7.4 (0-21)	5.1 (0-7)	5.1 (0-7)	6.7 (0-21)	6.4 (0-21)	5.1 (0-7)	5.1 (0-7)
Treatment duration, No. (%)								
0-3 months	9 (11.5)	11 (14.1)	8 (10.3)	8 (10.3)	20 (24.7)	22 (27.2)	21 (25.9)	19 (23.5)
>3-6 months	22 (28.2)	24 (30.8)	62 (79.5)	62 (79.5)	16 (19.8)	16 (19.8)	53 (65.4)	54 (66.7)
>6-9 months	20 (25.6)	19 (24.4)	8 (10.3)	8 (10.3)	17 (21)	16 (19.8)	7 (8.6)	8 (9.9)
>9 months	27 (34.6)	24 (30.8)	0	0	28 (34.6)	27 (33.3)	0	0
Median dose intensity, % (range)	100 (60-117)	100 (59-128)	85.2 (45-106)	88.9 (50-106)	100 (60-133)	NE (NE-NE)	89.9 (45-120)	89.4 (45-114)
Median No. of cycles (range)	11 (1-32)	10 (1-32)	8 (1-8)	8 (1-8)	10 (1-30)	9 (1-30)	8 (1-8)	8 (1-8)

Abbreviations: Atezo, atezolizumab; Bev, bevacizumab; Cis, cisplatin; Gem, gemcitabine; NE, not estimable; PBO, placebo.

TABLE A4. PFS, OS, and ORR in the Atezolizumab/Chemotherapy Arm of IMbrave150 Versus the Experimental Arms of TOPAZ-1 and KEYNOTE-966

	TOPAZ-1 (N = 685)		KEYNOTE-966 (N = 1,069)		IMbrave151 (N = 162)	
End Point	CisGem + PBO (n = 344)	D + CisGem (n = 341)	CisGem + PBO (n = 536)	P + CisGem (n = 533)	Atezo + CisGem (n = 83)	Atezo + Bev + CisGem (n = 79)
ORR, %	18.7	26.7	29	29	26.5	26.6
DCR, %	82.6	85.3	76	75	79.7	75.9
Median DOR, months	6.2	6.4	6.9	9.7	6.2	10.3
Ongoing response, %						
≥6 months	54.2	59.3	56	67	52.5	90
≥12 months	15	26.1	28	41	9.6	47.8
Median PFS, months	5.7	7.2	5.6	6.5	7.9	8.3
PFS rate, %						
6 months			46	52	63.4	78.1
12 months			20	25	19.6	33.5
Median OS, months	11.5	12.8	10.9	12.7	14.6	14.9
12-month OS rate, %	48	54.1	44	52	54.6	59

Abbreviations: Atezo, atezolizumab; Bev, bevacizumab; CisGem, cisplatin plus gemcitabine; D, durvalumab; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; OS, overall survival; P, pembrolizumab; PBO, placebo; PFS, progression-free survival.

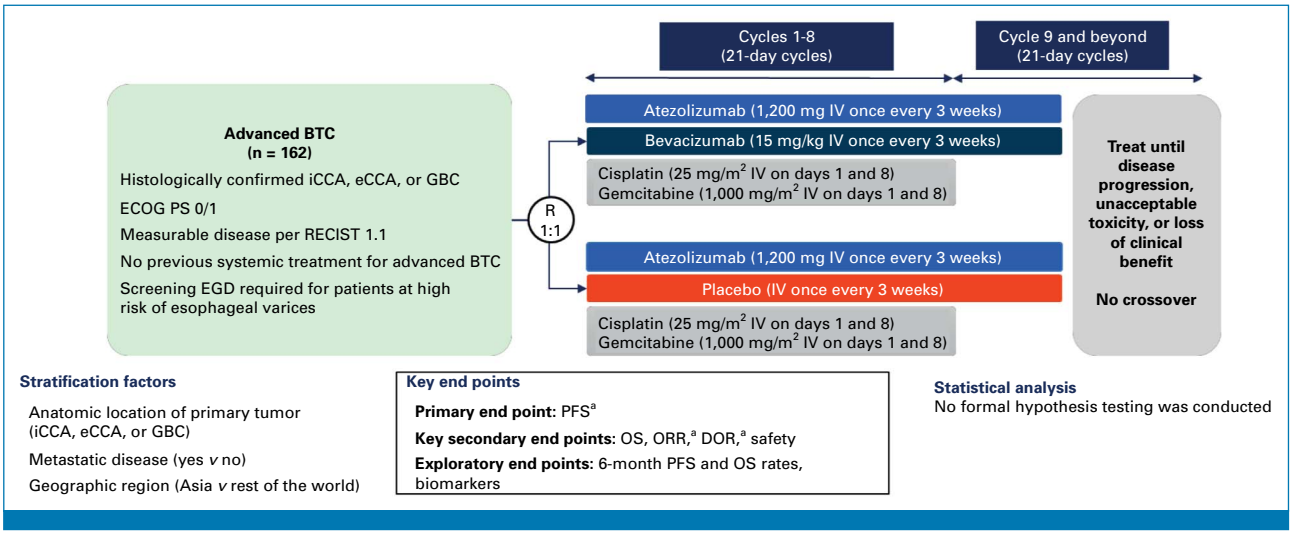

FIG A1. IMbrave151 study design. [a]Per investigator assessment by RECIST 1.1. BTC, biliary tract cancer; DOR, duration of response; eCCA, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EGD, esophagogastroduodenoscopy; GBC, gallbladder carcinoma; iCCA, intrahepatic cholangiocarcinoma; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomly assigned.

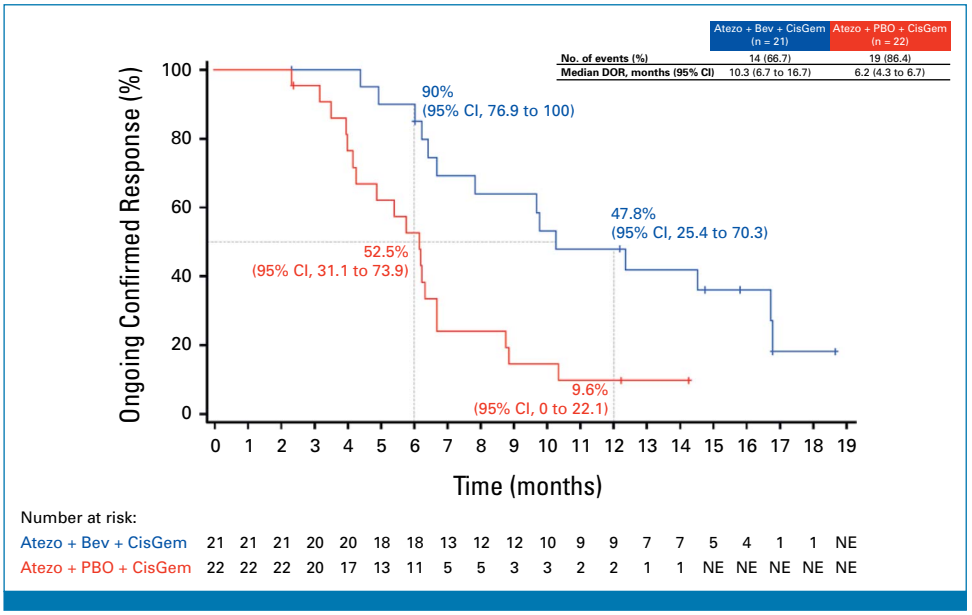

FIG A2. DOR. Atezo, atezolizumab; Bev, bevacizumab; CisGem, cisplatin plus gemcitabine; DOR, duration of response; NE, not evaluable; PBO, placebo.

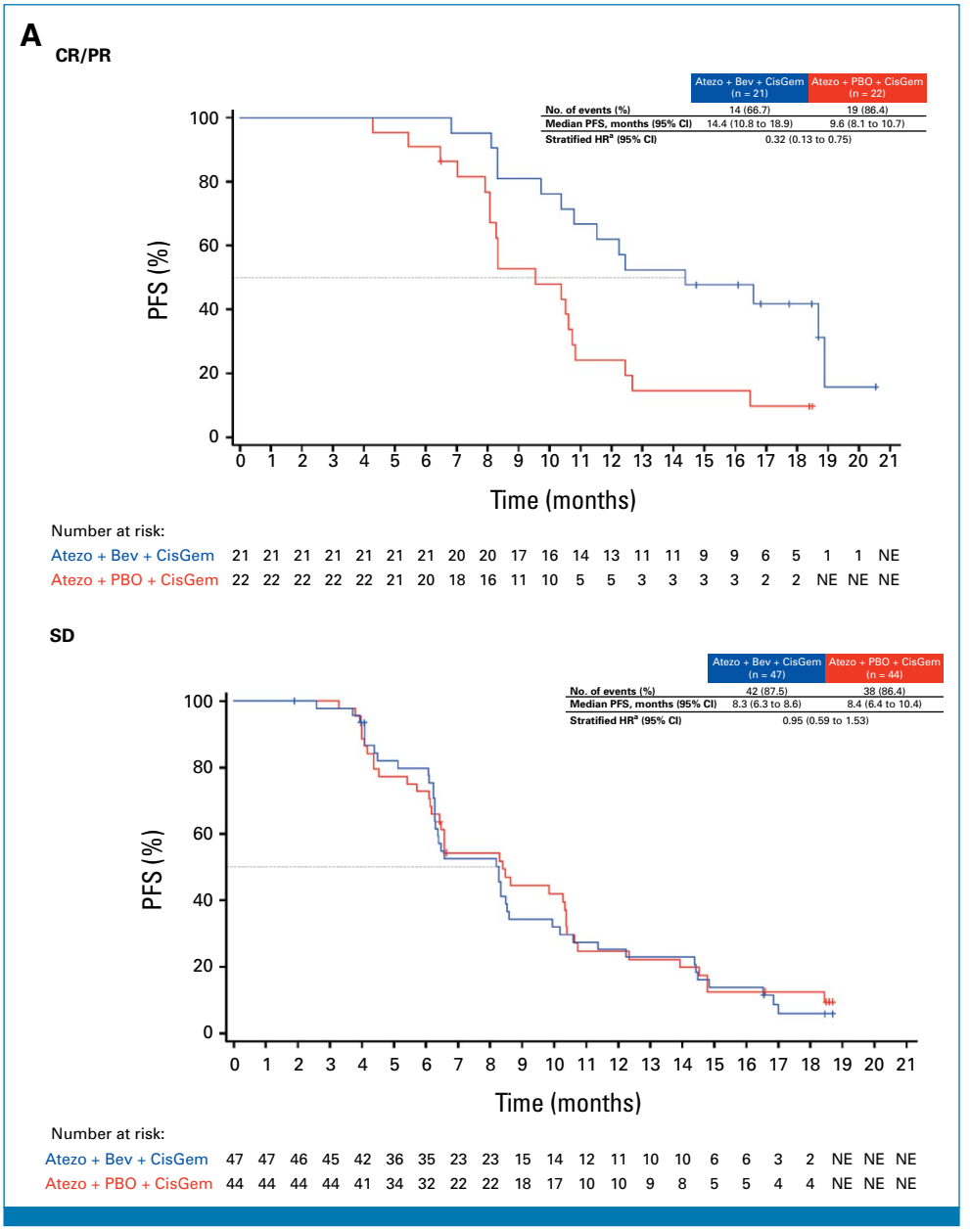

FIG A3. (A) PFS and (B) OS according to CR/PR or SD. Atezo, atezolizumab; Bev, bevacizumab; CisGem, cisplatin plus gemcitabine; CR, complete response; HR, hazard ratio; NE, not evaluable; OS, overall survival; PBO, placebo; PFS, progression-free survival; PR, partial response; SD, stable disease. [a]Stratified analysis. (continued on following page)

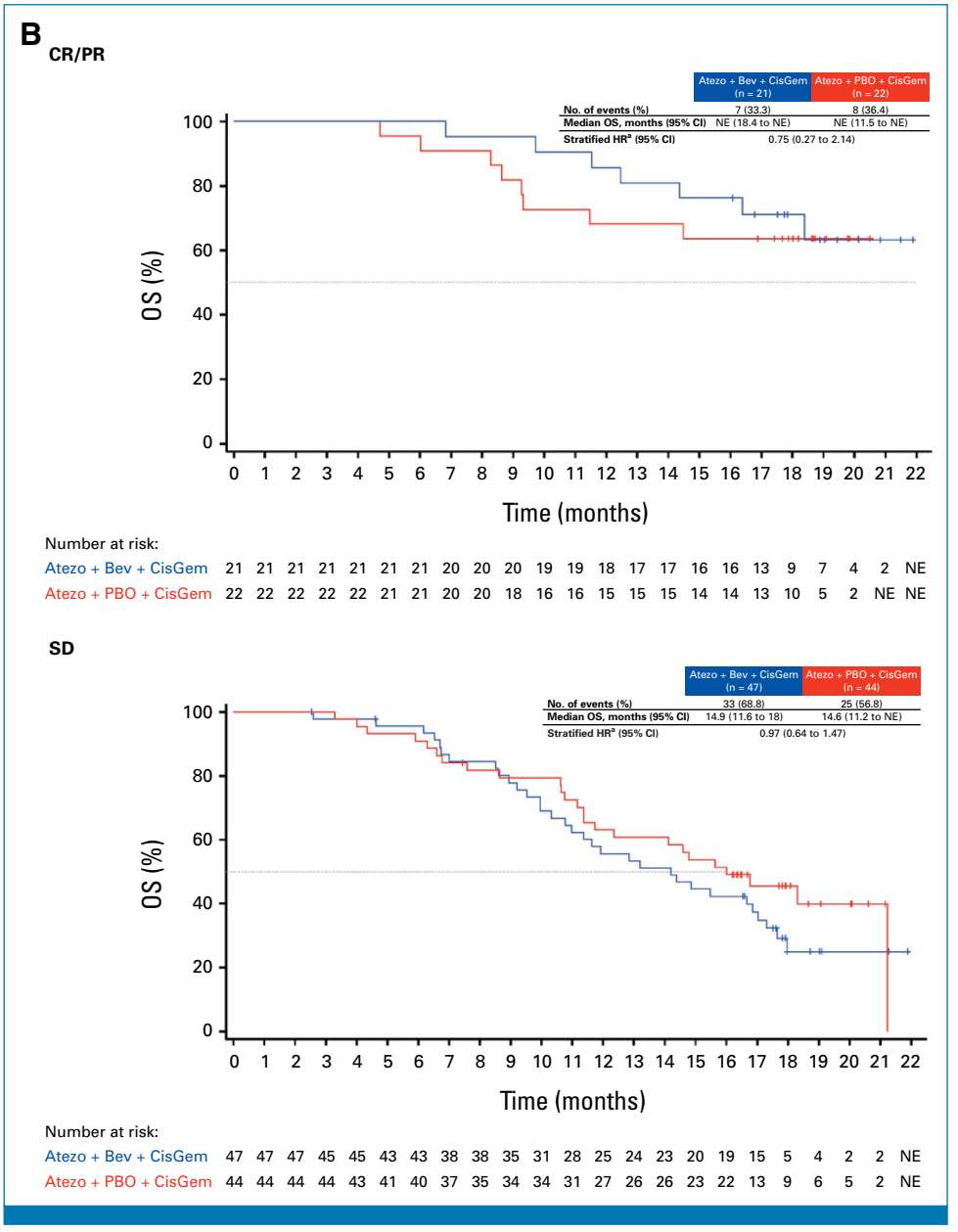

FIG A3. (Continued).

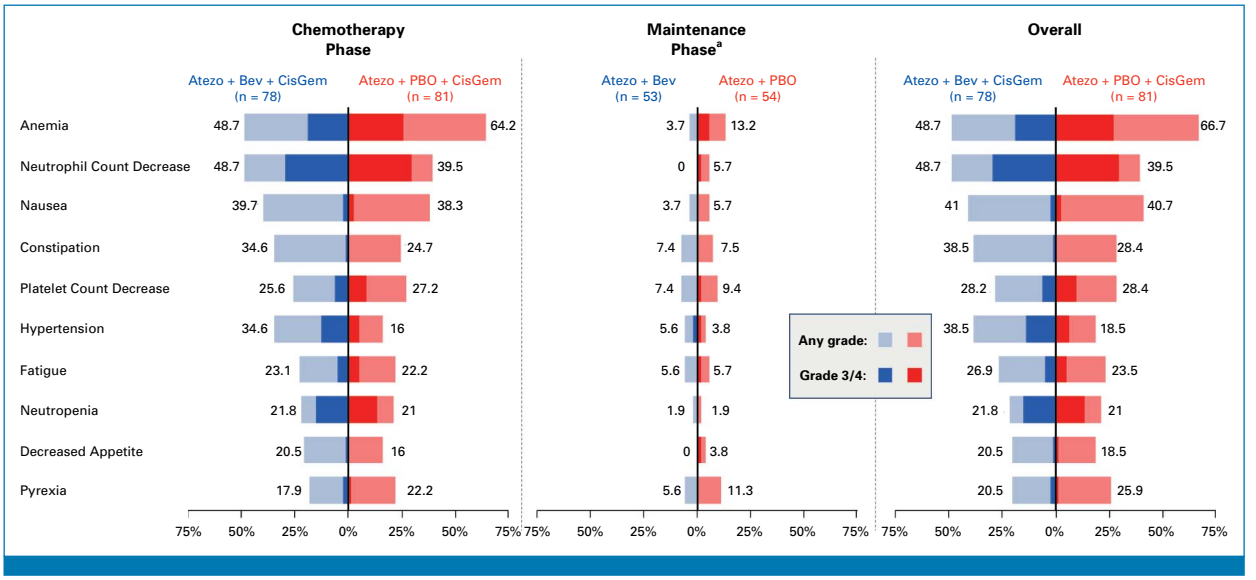

FIG A4. Common adverse events. [a]Maintenance phase started at Cycle 9 after the completion of 8 cycles of combination chemotherapy treatment administered on a 21-day cycle. Atezo, atezolizumab; Bev, bevacizumab; CisGem, cisplatin plus gemcitabine; PBO, placebo.

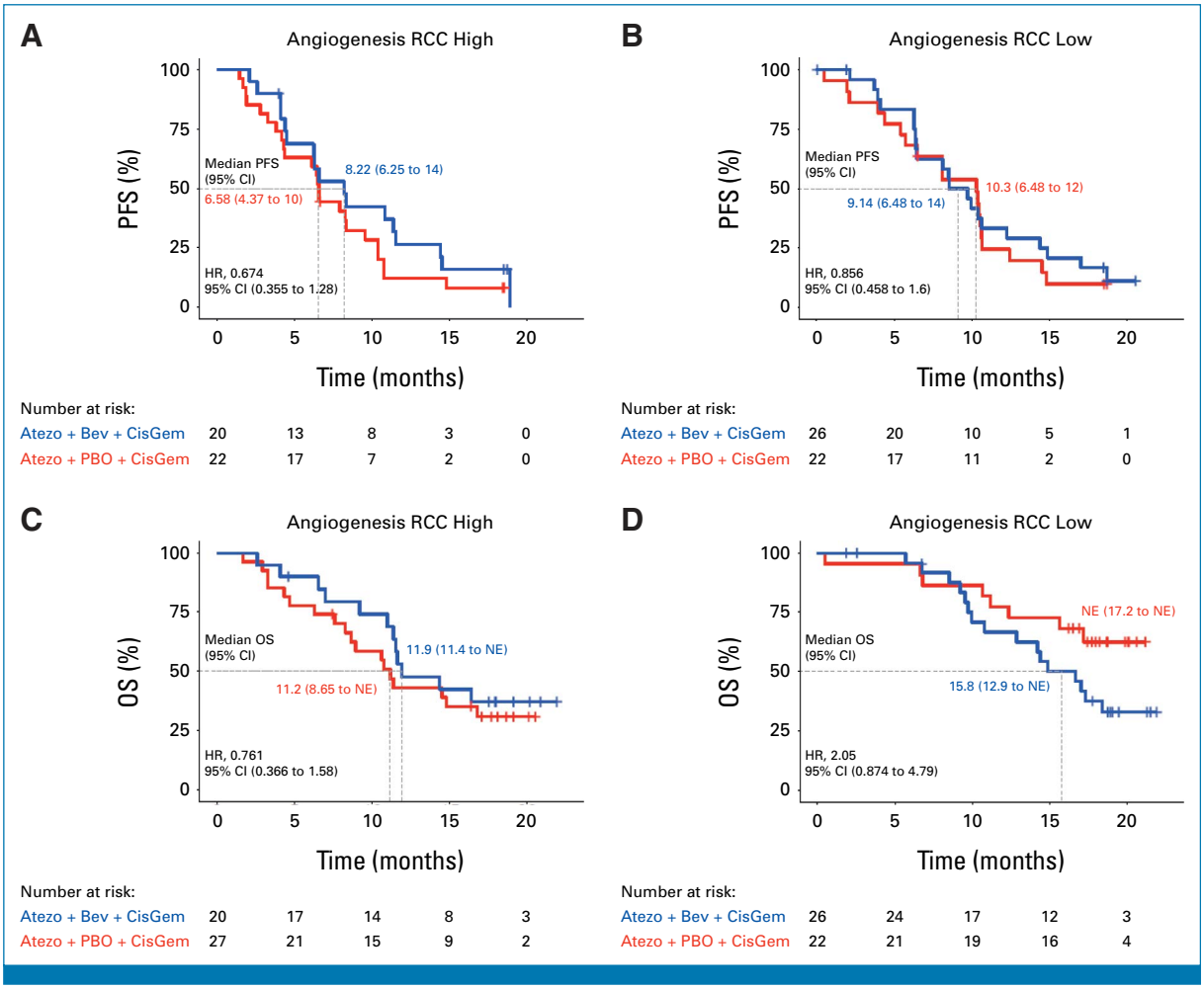

FIG A5. Association between angiogenesis gene signature and clinical outcomes: (A) PFS and angiogenesis RCC high, (B) PFS and angiogenesis RCC low, (C) OS and angiogenesis RCC high, and (D) OS and angiogenesis RCC low. Atezo, atezolizumab; Bev, bevacizumab; CisGem, cisplatin plus gemcitabine; HR, hazard ratio; NE, not evaluable; OS, overall survival; PBO, placebo; PFS, progression-free survival; RCC, renal cell carcinoma.

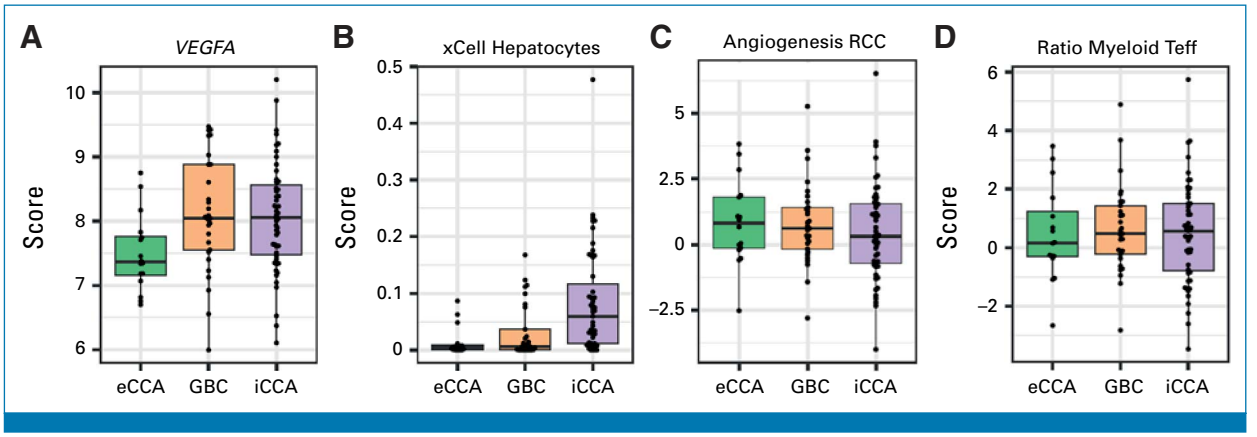

FIG A6. Pathways or gene signatures associated with bevacizumab benefit according to anatomic BTC subtype: (A) *VEGFA*, (B) xCell hepatocytes, (C) angiogenesis RCC, and (D) ratio myeloid Teff. BTC, biliary tract cancer; eCCA, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; iCCA, intrahepatic cholangiocarcinoma; RCC, renal cell carcinoma; Teff, effector T cell.

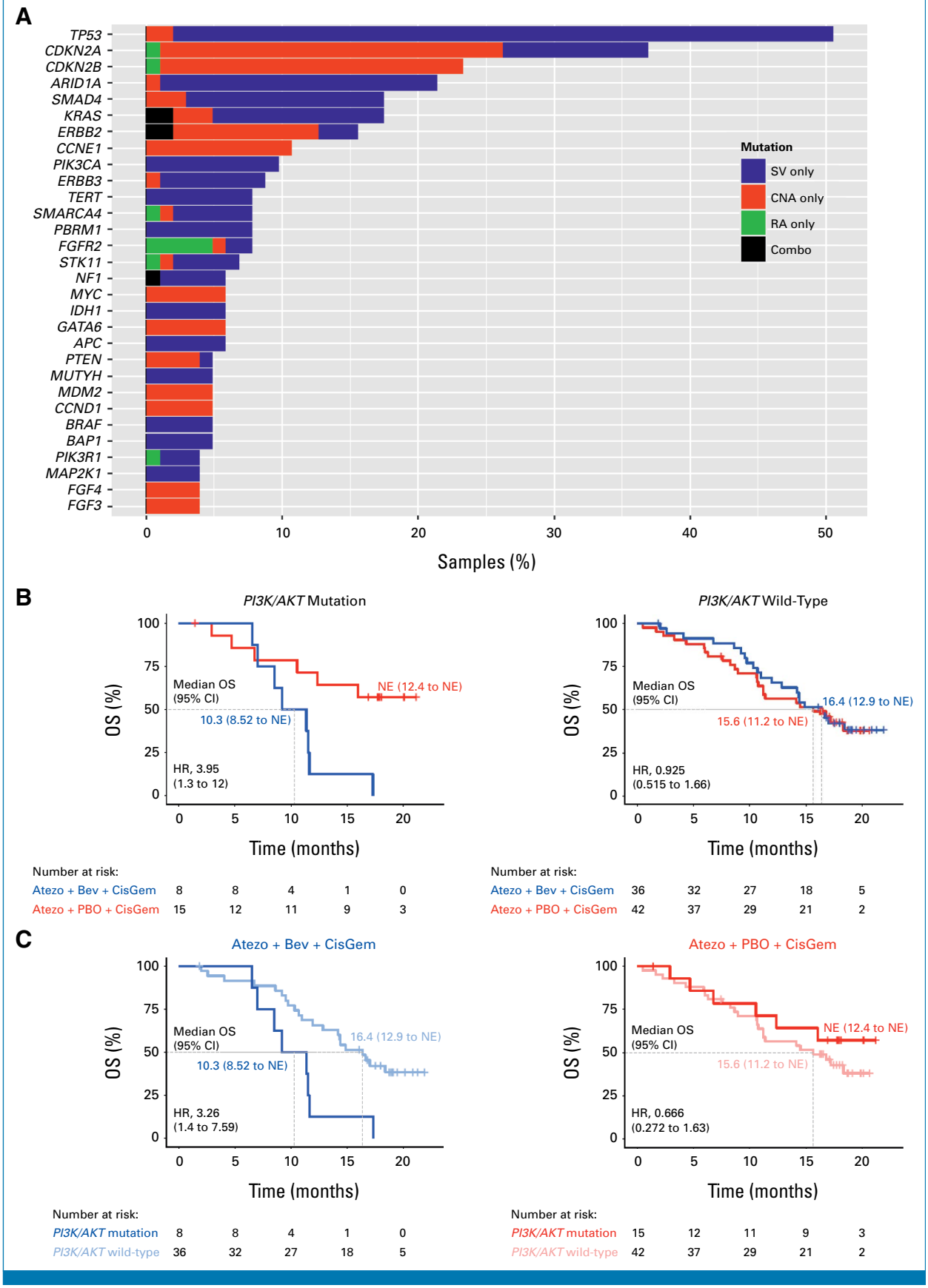

FIG A7. (A) Summary of frequently mutated genes in baseline tumor samples, (B) OS by PI3K/AKT mutation status stratified by treatment arm, and (C) OS by according to PI3K/AKT mutation status within each treatment arm. One patient had missing OS data and was not included in the OS analysis. Atezo, atezolizumab; Bev, bevacizumab; CisGem, cisplatin plus gemcitabine; CNA, copy number alteration; HR, hazard ratio; NE, not evaluable; OS, overall survival; PBO, placebo; RA, rearrangement; SV, short variant.