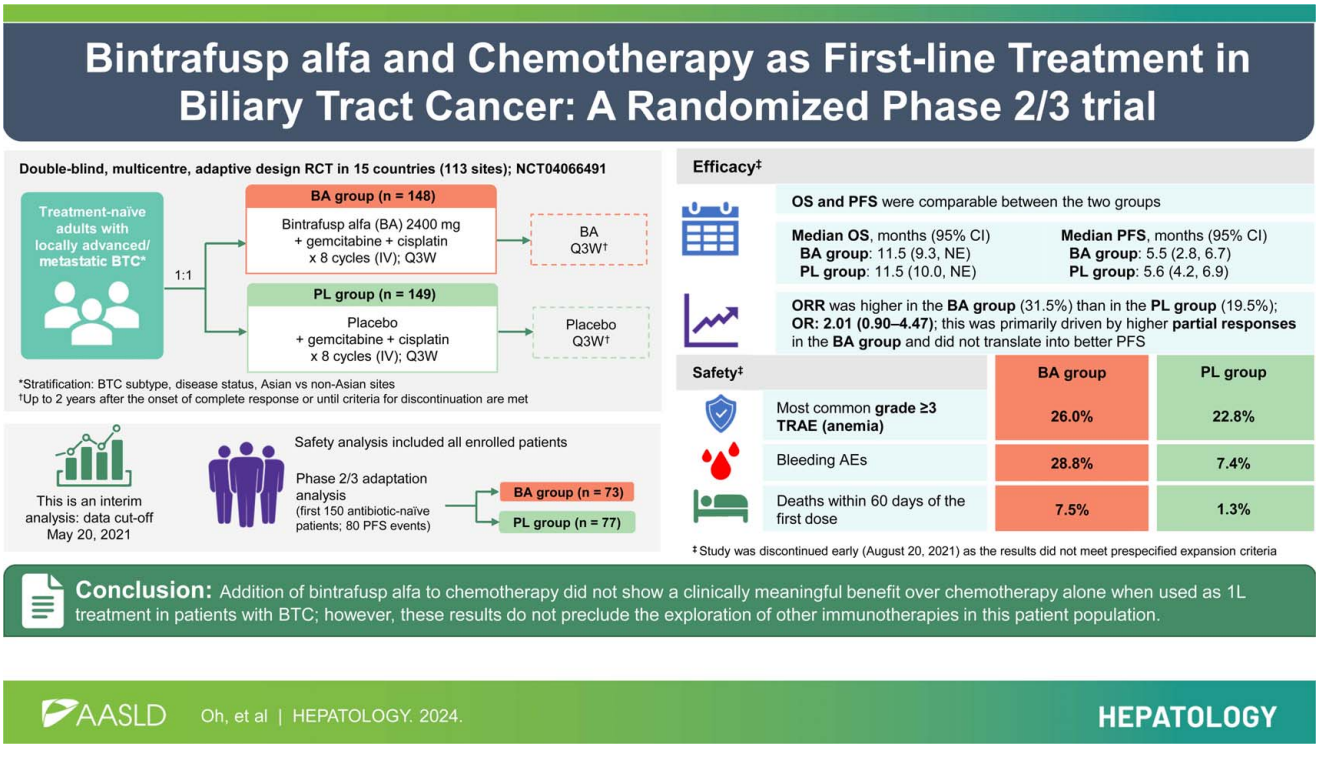
Bintrafusp alfa and chemotherapy as first-line treatment in biliary tract cancer: A randomized phase 2/3 trial

VISUAL ABSTRACT



Received: 23 January 2024 | Accepted: 30 April 2024

DOI: 10.1097/HEP.0000000000000965

ORIGINAL ARTICLE

OPEN

Bintrafusp alfa and chemotherapy as first-line treatment in biliary tract cancer: A randomized phase 2/3 trial

Do-Youn Oh[1,2] | Masafumi Ikeda[3] | Choong-kun Lee[4] | Carlos Rojas[5] | Chih-Hung Hsu[6] | Jin Won Kim[7] | Lin Shen[8] | Junji Furuse[9] | Joon Oh Park[10] | Mitesh Borad[11] | Filippo de Braud[12] | John Bridgewater[13] | Sunyoung S. Lee[14] | Markus Moehler[15] | Francois Audhuy[16] | Motonobu Osada[17] | Masashi Sato[17] | Changhoon Yoo[18]

[1]Division of Medical Oncology, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

[2]Integrated Major in Innovative Medical Science, Seoul National University Graduate School, Seoul, Republic of Korea

[3]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

[4]Division of Medical Oncology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

[5]Department Medical Oncology, Bradford Hill Centro de Investigación Clínica, Santiago, Chile

[6]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan

[7]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea

[8]Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China

[9]Department of Gastroenterology, Kanagawa Cancer Center, Yokohama, Japan

[10]Department of Medicine, Samsung Medical Centre, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

[11]Department of Hematology-Oncology, Mayo Clinic, Phoenix, Arizona, USA

[12]Department Medical Oncology, University of Milan, Fondazione IRCCS Istituto Nazionale del Tumori, Milan, Italy

[13]Department of Oncology, University College London Cancer Institute, London, UK

[14]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

[15]Department of Gastrointestinal Oncology, Mainz University Hospital, Mainz, Germany

[16]Global Medical Affairs Oncology, Merck Serono S.A.S., Lyon, France, an affiliate of Merck KGaA, Darmstadt, Germany

[17]Merck Biopharma Co., Ltd., Tokyo, Japan, an affiliate of Merck KGaA, Darmstadt, Germany

[18]Asan Medical Center, Department of Oncology, University of Ulsan College of Medicine, Seoul, Republic of Korea

Correspondence
Do-Youn Oh, Department of Internal Medicine, Division of Medical Oncology, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Email: ohdoyoun@snu.ac.kr

Abstract

Background and Aims: We compared the safety and efficacy of bintrafusp alfa (BA) in combination with gemcitabine+cisplatin (GemCis), to those of GemCis alone, in patients with biliary tract cancer.

Abbreviations: BA, bintrafusp alfa; BTC, biliary tract cancer; DLTs, dose-limiting toxicities; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GemCis, gemcitabine+cisplatin; IDMC, Independent Data Monitoring Committee; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RDI, relative dose intensity; TGF-β, transforming growth factor-beta; TME, tumor microenvironment.

Clinical trial number: NCT04066491.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.hepjournal.com.

Approach and Results: This randomized, double-blind, placebo-controlled, adaptive design phase 2/3 trial (NCT04066491) included adults who are treatment-naive with locally advanced/metastatic biliary tract cancer. Patients (N = 297) were randomized to receive an IV infusion of BA (2400 mg once/3 wk) plus GemCis (gemcitabine 1000 mg/m^2+cisplatin 25 mg/m^2 on days 1 and 8/3 wk; 8 cycles) (BA group, n = 148) or placebo+GemCis (placebo group, n = 149). The primary end point was overall survival (OS). For adaptation analysis (phase 2-phase 3; data cutoff: May 20, 2021), efficacy was assessed in the first 150 patients who were antibiotic-naive when 80 progression-free survival events had occurred and ≥ 19 weeks of follow-up had been completed (BA, n = 73; placebo, n = 77). Median OS (95% CI) for the BA (11.5 mo [9.3–not estimable]) and placebo (11.5 mo [10.0–not estimable]) groups was comparable (hazard ration 1.23 [95% CI 0.66–2.28]; p = 0.7394); OS data maturity was 27.2% (41 events/151 patients). The most common grade ≥3 treatment-related adverse event was anemia (BA, 26.0%; placebo, 22.8%). Bleeding adverse events were reported more frequently in the BA group (28.8%) versus the placebo group (7.4%). Deaths within 60 days of the first dose were reported in 7.5% and 1.3% of patients in the BA and placebo groups, respectively.

Conclusions: BA+GemCis did not provide a clinically meaningful benefit compared with GemCis alone as first-line treatment for biliary tract cancer, and the study was discontinued early (terminated: August 20, 2021).

INTRODUCTION

Biliary tract cancers (BTCs) are a rare, heterogeneous group of aggressive hepatic and perihepatic malignancies that include gallbladder cancer, cholangiocarcinoma of the intrahepatic and extrahepatic bile ducts, and cancers of the ampulla and the papilla of Vater.[1,2] The incidence of BTC is higher in Asian and Latin American countries than in the United States and the European Union[3–5]; however, prognosis remains poor across geographies, with an average 5-year survival rate of ~10% in advanced-stage disease.[6] Most patients present with advanced-stage disease at diagnosis due to a delay in clinical manifestation of BTCs, thereby precluding the option of curative surgical resection.[1] Moreover, even in patients who undergo surgery, high rates of metastasis and tumor recurrence have been reported.[7] Hence, palliative chemotherapy with gemcitabine+cisplatin (GemCis) has remained the first-line standard of care for locally advanced/metastatic disease for over a decade.[8,9] However, the median overall survival (OS) in patients treated with GemCis is < 1 year,[10] which highlights the need for improving patient outcomes using more effective treatment strategies.

Until recently, the potential of immune checkpoint inhibitors for treating BTCs had not been extensively explored, and the few early-phase clinical trials for which data were available had shown limited efficacy. In the first-line setting, a phase 1 study of nivolumab plus GemCis in patients with unresectable and recurrent BTC reported a median progression-free survival (PFS) of 4.2 months (90% CI, 2.8–5.6) and median OS of 15.4 months (90% CI, 11.8–not estimable [NE]).[11] Only recently have immune checkpoint inhibitors, especially programmed death-ligand 1 (PD-L1)/programmed death-1 blockers such as durvalumab and pembrolizumab, shown promising outcomes as first-line treatment for advanced BTCs.[12–14] After the completion of the study described here, the US Food and Drug Administration approved durvalumab plus GemCis for the treatment of locally advanced/metastatic BTC (September 2022) based on the encouraging survival benefits observed in the first-line setting of the TOPAZ-1 study,[12,15] while pembrolizumab plus GemCis was approved by the Food and Drug Administration for locally advanced unresectable or metastatic BTC (October 2023) based on the KEYNOTE-966 trial.[14,16] Furthermore, both durvalumab plus GemCis and pembrolizumab plus GemCis have been included as the preferred treatment options for advanced/metastatic BTC in the most recent version of the National Comprehensive Cancer Network (NCCN)® guidelines,[8] thus providing additional support for the use of immunotherapy in such patients.

Transforming growth factor-beta (TGF-β) has been shown to modulate immune responses in the tumor microenvironment (TME) and has been linked to immune evasion and immune checkpoint inhibitor resistance.[17–21] In late-stage cancers, TGF-β signaling has been implicated in inducing epithelial-mesenchymal transition, thereby promoting tumor metastasis.[19] Moreover, TGF-β signaling is one of the primary pathways associated with cholangiocarcinoma progression.[22] Thus, the simultaneous blockade of TGF-β and programmed death-1/PD-L1 may constitute an important therapeutic strategy for BTC.

Bintrafusp alfa is a first-in-class bifunctional fusion protein that is composed of the extracellular domain of the TGF-β RII receptor (a TGF-β trap) fused to a human IgG1 monoclonal antibody blocking PD-L1. In a phase 1 trial of patients with refractory BTC, bintrafusp alfa showed a promising objective response rate (ORR) of 20% and an OS of > 1 year (12.7 mo [95% CI 6.7–15.7]) when used as monotherapy.[23] Additionally, the encouraging clinical efficacy signals observed in the second-line setting indicated that treatment with bintrafusp alfa, in combination with chemotherapy, had the potential to improve standard first-line treatment in BTC. Thus, we conducted a phase 2/3 adaptive study to compare the safety and efficacy of bintrafusp alfa in patients with advanced BTC who were chemotherapy- and immunotherapy-naive in combination with GemCis versus that of GemCis alone. After the completion of our study, results from a phase 2 trial of bintrafusp alfa monotherapy in patients with locally advanced/metastatic BTC were published—the trial did not meet its prespecified primary end point of ORR being > 10% as the lower bound of the 95% CI was < 10% (reported ORR: 10.7% [95% CI: 6.4–16.6%]).[24]

METHODS

Study design and participants

This multicenter study was conducted at 113 sites across 15 countries (United States, Argentina, Australia, Brazil, Chile, China, France, Germany, Italy, Japan, Republic of Korea, Poland, Spain, Taiwan, and the United Kingdom) and included an open-label, safety run-in phase followed by a randomized, double-blind, placebo-controlled phase 2/3 (phase 2/3). Adults with histologically or cytologically confirmed, locally advanced/metastatic BTC (including intrahepatic and extrahepatic cholangiocarcinoma, gallbladder cancer, and cancers of the ampulla and the papilla of Vater) who had not undergone chemotherapy, immunotherapy, or interventional radiological treatment, were included. Additional eligibility criteria were the presence of at least 1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors version 1.1[25] (not required in the safety run-in phase), Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, life expectancy of at least 12 weeks, and adequate hematological, hepatic, and renal function at baseline. The study did not enroll patients with previous and/or intercurrent cancers; exceptions were those with curatively treated cancers and no recurrence in > 3 years or early cancers with curative intent. Additionally, patients who used systemic antibiotics during the screening period, that is, within 30 days before randomization, were deemed ineligible. In a few recent studies, the use of antibiotics before immune checkpoint inhibitors has been associated with worse treatment response and survival outcomes, possibly due to modulation of the gut microbiota.[26,27] Consequently, the original study protocol was amended to exclude patients treated with systemic antibiotics at screening, and the criterion of being “antibiotic-naive” was added to the definition of the efficacy analysis set used for the expansion decision from phase 2 to phase 3 to have a patient population that was more representative of the anticipated population in phase 3. Full details of the study design, interventions, inclusion/exclusion criteria, guidelines for treatment discontinuation, and dose reductions to manage adverse events are in the protocol (appendix).

This study was conducted in accordance with the ethical principles of the International Council for Harmonization Guideline for Good Clinical Practice, the Council for International Organizations of Medical Sciences, the Japanese ministerial ordinance on Good Clinical Practice (study centers in Japan only), and the Declaration of Helsinki, as well as applicable local regulations. All patients provided written informed consent before screening. The study was approved by the Institutional Review Board/Independent Ethics Committee before initiation. The complete study protocol is available as Supplemental Material, http://links.lww.com/HEP/I511.

Randomization and masking

During phase 2/3 of the study, patients were randomly assigned 1:1 to receive either bintrafusp alfa combined with GemCis (bintrafusp alfa+GemCis; bintrafusp alfa group) or placebo combined with GemCis (placebo +GemCis; placebo group). Randomization was stratified according to type of BTC (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma including cancers of the ampulla of Vater, and gallbladder cancer), disease status at diagnosis (metastatic versus locally advanced), and Asian versus non-Asian sites. An interactive response system was used for randomization and was based on a computer-generated randomization list. In addition to patients and investigators, the entire study team, including sponsor personnel, were blinded to the administration of bintrafusp alfa or placebo; in contrast, chemotherapy was open-label.

Procedures

During the safety run-in phase, patients received an IV infusion of bintrafusp alfa (2400 mg) once every 3 weeks, in combination with gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) on days 1 and 8 of the 3-week cycle, for a maximum of 8 cycles. The same dosing regimen was used in phase 2/3, with matched placebo administration. Both phases included a 28-day screening period, a treatment period, along with long-term survival follow-up. Treatment was continued until either disease progression or unacceptable toxicity occurred. In patients with complete response, bintrafusp alfa/placebo was to be continued for 2 years after the onset of the first complete response.

An Independent Review Committee evaluated tumor response according to Response Evaluation Criteria in Solid Tumors 1.1. All patients in the randomized phase 2/3 of the study who received any dose of any study intervention were included in the safety analysis set; the severity of adverse events and laboratory results were graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events 5.0. Any adverse event that was potentially immune- or TGF-β-related was classified as an adverse event of special interest (infusion-related reactions including immediate hypersensitivity, immune-related adverse events, TGF-β inhibition mediated skin reactions, anemia, and bleeding adverse events). Immune-related adverse events were identified using a 2-level approach that was based on a preselected list of terms from the Medical Dictionary for Regulatory Activities (version 23.1).

Outcomes

The primary end point of the safety run-in phase of the study was the occurrence of dose-limiting toxicities (DLTs), which was evaluated in the first 21 days after the first dose of bintrafusp alfa. The secondary end points included safety assessment, clinical laboratory parameters, vital signs, physical examination, electrocardiogram parameters, and ECOG PS.

The primary efficacy end point of phase 2/3 was OS; secondary efficacy end points included PFS, ORR, response duration, durable response rate (Response Evaluation Criteria in Solid Tumors 1.1 and Independent Review Committee), and safety.

Statistical analyses

The study aimed to enroll a total of 524 patients (12–24 patients in the open-label, safety run-in phase and up to 300 or 500 patients in phase 2/3, if expanded). The sample size for the randomized, double-blind phase of the study was calculated to provide an overall power of 90% in phase 3 and 67% in phase 2 to achieve a hazard ration (HR) of 0.70 (corresponding to an increase in median OS from 11.7 months in the placebo group to 16.7 mo in the bintrafusp alfa group, with an expected dropout rate of 5% at 40 mo) and a 1-sided α-level of 0.025.

Efficacy analyses were to be conducted in the intent-to-treat population, which included all patients randomized to any study intervention and when the last patient in the open-label phase of the study had reached a minimum follow-up time of 12 months. The DLTs in the safety run-in phase of the study were assessed in the DLT analysis set, which included all patients who completed the safety run-in, that is, the 21-day evaluation period (without missing a dose or withdrawal during this period for reasons other than toxicity). DLTs were evaluated separately in the Asian and the non-Asian cohorts. Safety analyses were performed in the safety run-in analysis set and the safety analysis set (randomized phase 2/3).

An Independent Data Monitoring Committee (IDMC) analyzed the data for potential adaptation from phase 2 to 3 in the first 150 patients who were antibiotic-naive when 80 PFS events had occurred and $\geq$ 19 weeks of follow-up had been completed. Expansion into phase 3 was planned if the OR of a confirmed ORR was $\geq$ 1.6 or PFS HR was $<$ 0.75 and if the probability of the trial being successful exceeded 60%; trial success was defined as the predictive probability of observing an OS HR of $<$ 0.70 at primary analysis (when 334 deaths from 500 patients were observed). The IDMC determined that the study did not meet these protocol-specified expansion criteria and the trial was discontinued early.

Survival analyses were performed using Kaplan-Meier curves and are presented as median PFS and OS duration (95% CI). ORRs are expressed as a percent change in tumor diameter from baseline, and two-sided 95% CIs were calculated using the Clopper–Pearson method. Subgroup analyses were conducted for OS, PFS, and ORR. Adverse events are summarized as the number and proportion of patients reporting each event.

Analyses were performed using the statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, Windows Version 9.4 or higher). The study was registered at ClinicalTrials.gov (NCT04066491).

RESULTS

Between September 20, 2019, and May 20, 2021, 309 patients were enrolled in the study; of these, 12 patients were included in the safety run-in phase, while 297 patients were randomly assigned to 1 of 2 groups during phase 2/3, that is, bintrafusp alfa (n = 148) or placebo (n = 149; Figure 1). As the study did not meet its prespecified expansion criteria and was discontinued

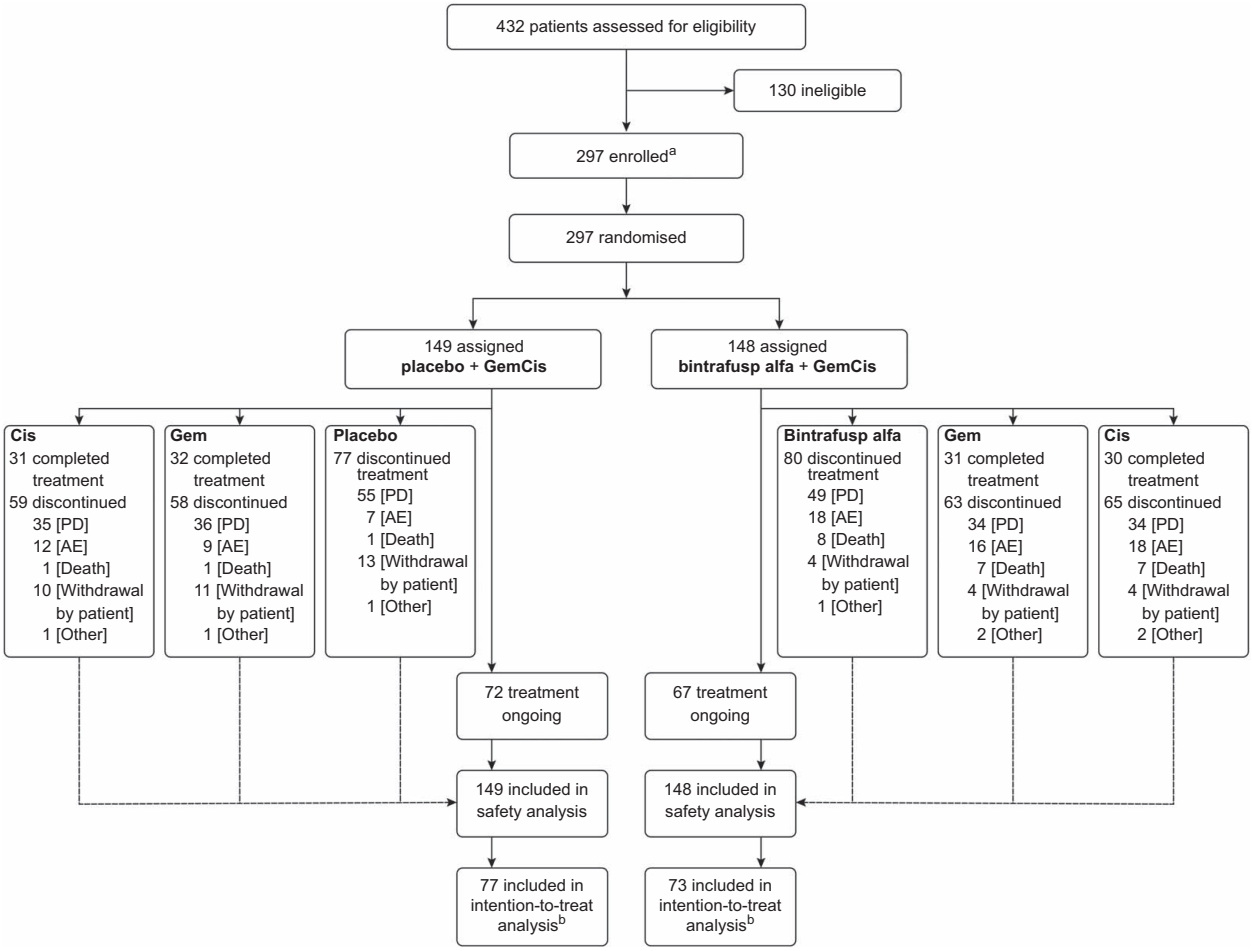


FIGURE 1 Trial profile. Abbreviations: AE, adverse event; GemCis, gemcitabine+cisplatin; PD, progressive disease.

early, we report here the results of the interim analysis conducted for adaptation from phase 2 to phase 3 (data cutoff: May 20, 2021).

In the open-label run-in phase, the median age of patients was 68.0 years (range: 39.0–80.0), 5 (41.7%) were women and 4 (33.3%) had an ECOG PS of 1. In phase 2/3, median age was 65.0 years (range: 29.0–84.0), and demographic characteristics were generally well-balanced between the treatment groups (Table 1). The median duration of bintrafusp alfa treatment in the open-label run-in phase was 19.5 weeks (range: 3.0–84.3), with a relative dose intensity (RDI) of >90% reported in 7 (58.3%) patients. For gemcitabine and cisplatin, the median duration of exposure was 18.0 weeks (range: 3.0–51.1) and 19.5 weeks (range: 3.0–51.1), respectively, with an RDI of > 75% reported in 5 (41.7%) and 6 (50.0%) patients, respectively. In phase 2/3, the median duration of treatment was lower for bintrafusp alfa than for placebo (12.1 wk [range: 3.0–59.9] versus 17.9 wk [range: 3.0–60.0]) and a similar proportion of patients in both groups exhibited an RDI of > 90% (79.5% vs. 81.2%). The median treatment duration was lower in the bintrafusp alfa group than in the placebo group for both gemcitabine (12.1 wk [range: 3.0–35.6] vs. 18.0 wk [range: 2.9–36.0]) and cisplatin (12.1 wk [range: 3.0–35.6] vs 16.6 wk [range: 2.9–36.0]), respectively. A similar proportion of patients had an RDI of > 75% for gemcitabine (65.1% vs 64.4%) and cisplatin (60.3% vs 67.1%) in both groups.

The primary end point analysis in the safety run-in phase did not reveal any DLTs in either the Asian or the non-Asian patient cohorts. Median OS was estimated to be 11.6 months (95% CI 6.0–not estimable) during a median follow-up duration of 18.7 months (range: 1.3 – 19.4).

In phase 2/3, efficacy data were assessed for the first 150 antibiotic-naive patients when ≥ 19 weeks of follow-up had been completed and when 80 PFS events had occurred (bintrafusp alfa, n = 73; placebo, n = 77). The primary end point of median OS (95% CI) in the bintrafusp alfa (11.5 mo [9.3–not estimable]) and placebo (11.5 mo [10.0–not estimable]) groups was comparable (HR 1.23 [95% CI, 0.66–2.28; $p = 0.7394$]; Figure 2, Table 2); however, OS data maturity was 27.2% (41 events/151 patients). The median follow-up duration for OS was 8.4 months (range: 0.2–13.9) and 7.6 months (range: 0.9–15.2) in the bintrafusp alfa and

TABLE 1 Baseline patient and disease characteristics

Characteristic[a]	Safety run-in phase (n = 12)	Randomized phase 2	
		Placebo plus GemCis (n = 149)	Bintrafusp alfa plus GemCis (n = 148)
Gender			
Male	7 (58.3)	71 (47.7)	80 (54.1)
Geographic region			
Asia	6 (50.0)	91 (61.1)	90 (60.8)
Europe	2 (16.7)	24 (16.1)	24 (16.2)
Latin America	0 (0.0)	18 (12.1)	23 (15.5)
Race			
Asian	6 (50.0)	93 (62.4)	90 (60.8)
White	6 (50.0)	51 (34.2)	51 (34.5)
Others/data not collected	0 (0.0)	5 (3.4)	7 (4.8)
Age (y)			
Median (min, max)	68.0 (39.0, 80.0)	65.0 (34.0, 81.0)	64.0 (29.0, 84.0)
≥ 65 y	8 (66.7)	79 (53.0)	70 (47.3)
ECOG PS			
0	8 (66.7)	64 (43.0)	72 (48.6)
1	4 (33.3)	85 (57.0)	76 (51.4)
BTC subtype classification			
Intrahepatic cholangiocarcinoma	5 (41.7)	65 (43.6)	67 (45.3)
Extrahepatic cholangiocarcinoma	3 (25.0)	34 (22.8)	32 (21.6)
Gallbladder cancer	4 (33.3)	39 (26.2)	39 (26.4)
Cancer of the ampulla of Vater	0 (0.0)	11 (7.4)	10 (6.8)
Extent of disease			
Metastatic	NA	102 (68.5)	101 (68.2)
Locally advanced	NA	47 (31.5)	47 (31.8)
Histology grade			
Well-differentiated	1 (8.3)	12 (8.1)	6 (4.1)
Moderately differentiated	3 (25.0)	61 (40.9)	59 (39.9)
Poorly differentiated	5 (41.7)	29 (19.5)	32 (21.6)
Time since documented, locally advanced or metastatic disease (mo)			
Median (range)	1.2 (0.6–20.6)	1.3 (0.0–13.1)	1.2 (0.2–178.8)

[a]Unless otherwise specified, all data are presented as n (%).
Abbreviations: BTC, biliary tract cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GemCis, Gemcitabine + Cisplatin.

placebo groups, respectively. The OS results in the various subgroups (defined based on BTC subtypes, disease status at study entry, ECOG PS at baseline, etc.) were consistent with the overall results (Supplemental Figure S2, http://links.lww.com/HEP/I511).

Median PFS for the bintrafusp alfa and placebo groups was comparable (5.5 mo [95% CI 2.8–6.7] versus 5.6 mo [95% CI 4.2–6.9]; HR 1.08 [95% CI 0.70–1.66], $p > 0.05$) (Figure 3, Table 2). The results of the PFS subgroup analyses supported overall findings and are summarized in Supplemental Figure S3, http://links.lww.com/HEP/I511.

ORR was higher in the bintrafusp alfa group (31.5% [95% CI 21.1–43.4]) than in the placebo group (19.5% [95% CI 11.3–30.1]; OR: 2.01 [0.90–4.47]; Figure 4, Table 2); similarly, partial response was observed in a greater proportion of the patients in the bintrafusp alfa group (31.5% vs 18.2%). One patient in the placebo group achieved a complete response, while there were none in the bintrafusp alfa group. Compared to the placebo group, the proportion of patients with stable disease was lower (30.1% vs. 57.1%), while that of patients with progressive disease was higher (27.4% vs 19.5%) in the bintrafusp alfa group. Subgroup analysis showed that patients with a baseline ECOG PS ≥ 1 who received bintrafusp alfa had higher odds of response compared to those who received placebo (OR, 3.45 [95% CI 1.16–10.29]; Supplemental Figure S4, http://links.lww.com/HEP/I511).

Disease control rate was 61.6% (95% CI 49.5–72.8) and 76.6% (95% CI 65.6–85.5) in the bintrafusp alfa and placebo groups, respectively (Table 2), but more

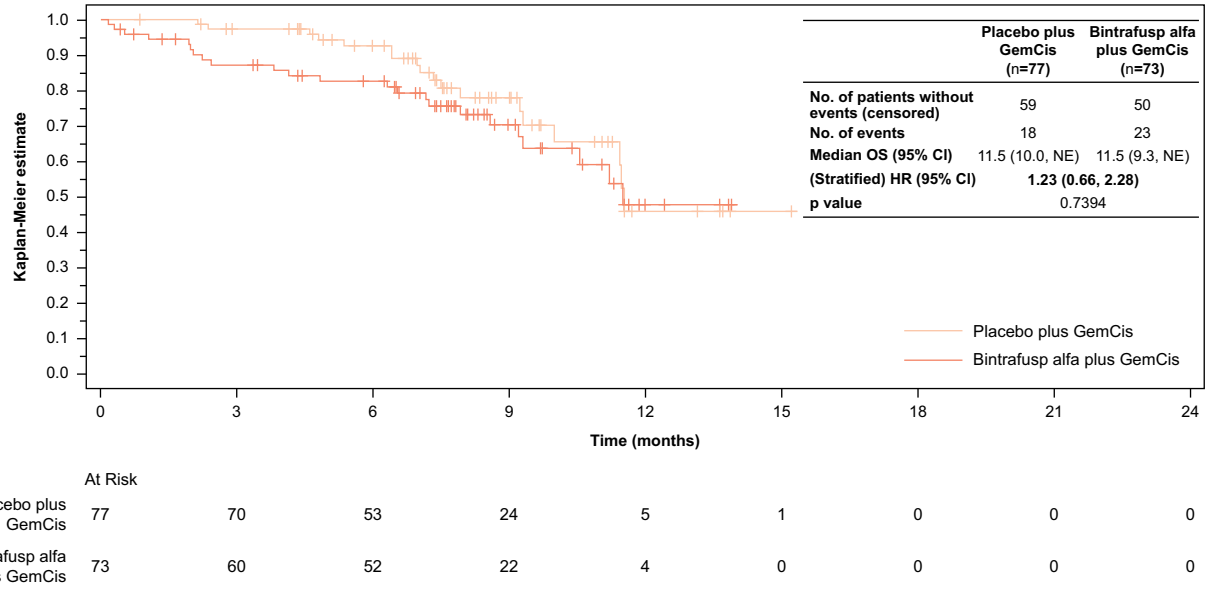


FIGURE 2 Overall survival (primary end point)—randomized double-blind phase. Abbreviations: GemCis, gemcitabine+cisplatin; NE, not estimable; OS, overall survival.

patients in the bintrafusp alfa group showed both confirmed and ongoing responses than those in the placebo group (60.9% vs. 53.3%). However, the bintrafusp alfa group had a shorter median duration of confirmed response (7.0 mo [range: 1.4–8.3]) than the placebo group (12.5 mo [range: 2.7–12.5]).

Data from 295 (99.3%) patients were included in the safety analysis set (n = 146 and n = 149 in the

TABLE 2 Summary of efficacy analyses

Outcome measure	Randomized phase 2	
	Placebo plus GemCis (n = 77)	Bintrafusp alfa plus GemCis (n = 73)
OS		
Median (95% CI), mo	11.5 (10.0–NE)	11.5 (9.3–NE)
HR[a] (95% CI)	—	1.23 (0.66, 2.28)
p value	—	0.7394
PFS		
Median (95% CI), mo	5.6 (4.2–6.9)	5.5 (2.8–6.7)
HR[a] (95% CI)	—	1.08 (0.70–1.66)
p value	—	0.6378
Objective response		
Best overall response, n (%)		
CR	1 (1.3)	0 (0.0)
PR	14 (18.2)	23 (31.5)
Stable disease	44 (57.1)	22 (30.1)
Non-CR/non-PD	0 (0.0)	1 (1.4)
PD	15 (19.5)	20 (27.4)
Nonevaluable	3 (3.9)	7 (9.6)
ORR, n (%)	15 (19.5)	23 (31.5)
Common OR adjusted by strata (95% CI)	—	2.01 (0.90–4.47)
DCR, n (%)	59 (76.6)	45 (61.6)
Duration of response		
Median (range), mo	12.5 (2.7–12.5)	7.0 (1.4–8.3)

[a]Stratified.

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; GemCis, Gemcitabine + Cisplatin; NE, not estimable; OS, overall survival; ORR, objective response rate; PD, progressive disease; PR, partial response; PFS, progression-free survival.

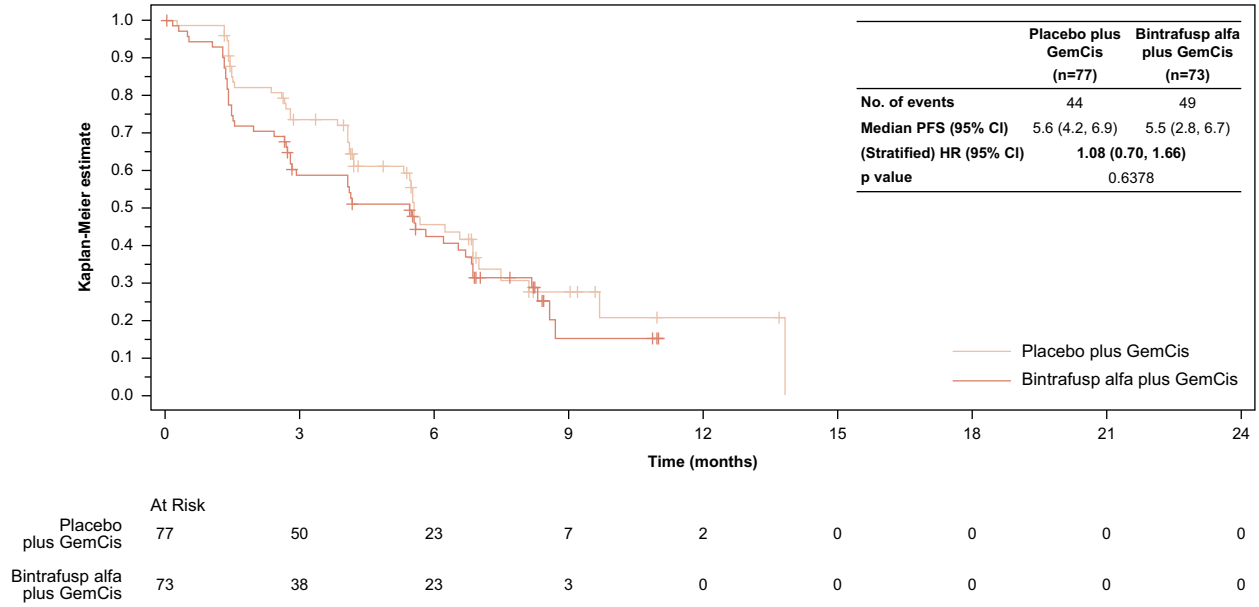


FIGURE 3 Progression-free survival according to RECIST v1.1 (as adjudicated by the IRC). Abbreviations: GemCis, gemcitabine+cisplatin; IRC, Independent Review Committee; RECIST, Response Evaluation Criteria in Solid Tumors.

bintrafusp alfa and placebo groups, respectively). A similar proportion of patients discontinued the study in both groups (26.4% vs 25.5%; Figure 1), and death was the most frequently reported reason (18.9% vs 16.8%). A higher proportion of patients discontinued treatment in the first 60 days in the bintrafusp alfa group than in the placebo group (Supplemental Figure S1, http://links.lww.com/HEP/I511), and the primary reasons for discontinuation included progressive disease (13%), adverse events (4.8%), and death (2.7%).

The safety findings, including most common adverse events and grade ≥ 3 adverse events (Supplemental Tables 1 and 2, http://links.lww.com/HEP/I511), treatment-related adverse events (both bintrafusp alfa/placebo-related and chemotherapy-related adverse events; Table 3, Supplemental Table 2, http://links.lww.com/HEP/I511), and adverse events of special interest (Supplemental Table 2, http://links.lww.com/HEP/I511, Supplemental Table 3, http://links.lww.com/HEP/I511) have been summarized in tabular form. All 12 patients in the safety run-in phase experienced at least 1 adverse event, with bintrafusp-related adverse events reported in 9 (75%) patients. During phase 2, the most common adverse events in the bintrafusp alfa group included anemia (53.4%), nausea (44.5%), constipation (27.4%), pyrexia (24.7%), fatigue (20.5%), pruritus (24.0%), rash (24.7%), and decreased appetite (21.2%) (Supplemental Table 1, http://links.lww.com/HEP/I511). Grade ≥3 adverse events were reported in 68.5% and 74.5% of patients in the bintrafusp alfa and the placebo groups, respectively. Overall, the incidence of treatment-related adverse events was similar in the bintrafusp alfa and the placebo groups (91.1% vs. 91.3%; Table 3; Supplemental Table 2, http://links.lww.com/HEP/I511); however, bintrafusp alfa-related adverse events were observed more frequently than placebo-related adverse events (67.8% vs. 52.3%) (Supplemental Table 2, http://links.lww.com/HEP/I511). The most common treatment-related adverse events in the bintrafusp alfa and the placebo groups were anemia (47.9% vs. 50.3%), nausea (37.7% vs. 45.0%), and decreased neutrophil count (19.2% vs. 40.3%) (Table 3). The most common grade ≥3 treatment-related adverse events in the bintrafusp alfa and the placebo groups were anemia (26.0% vs. 22.8%), neutropenia (11.6% vs. 16.8%), and decreased platelet (7.5% vs. 12.1%) and neutrophil counts (13.7% vs. 34.2%) (Table 3).

A higher rate of bleeding events was reported in the bintrafusp alfa group than in the placebo group (28.8% vs. 7.4%; Supplemental Table 3, http://links.lww.com/HEP/I511). Any TGF-β inhibition mediated skin reactions occurred in 5 (3.4%) patients in the bintrafusp alfa group, with 2 patients requiring surgical intervention. Thirty patients (20.5%) in the bintrafusp alfa group experienced immune-related adverse events, and most of them required steroid treatment for resolution.

Permanent treatment discontinuations were more frequently observed due to bintrafusp alfa-related adverse events compared to placebo-related adverse events (6.8% vs. 2.0%; Supplemental Table 2, http://links.lww.com/HEP/I511). More patients died in the bintrafusp alfa group within 60 days of the first treatment dose than in the placebo group (7.5% vs. 1.3%); however, all the 11 deaths in the bintrafusp alfa group were either unrelated to the drug (n = 6) or caused by progressive disease and/or a disease-related condition (n = 5).

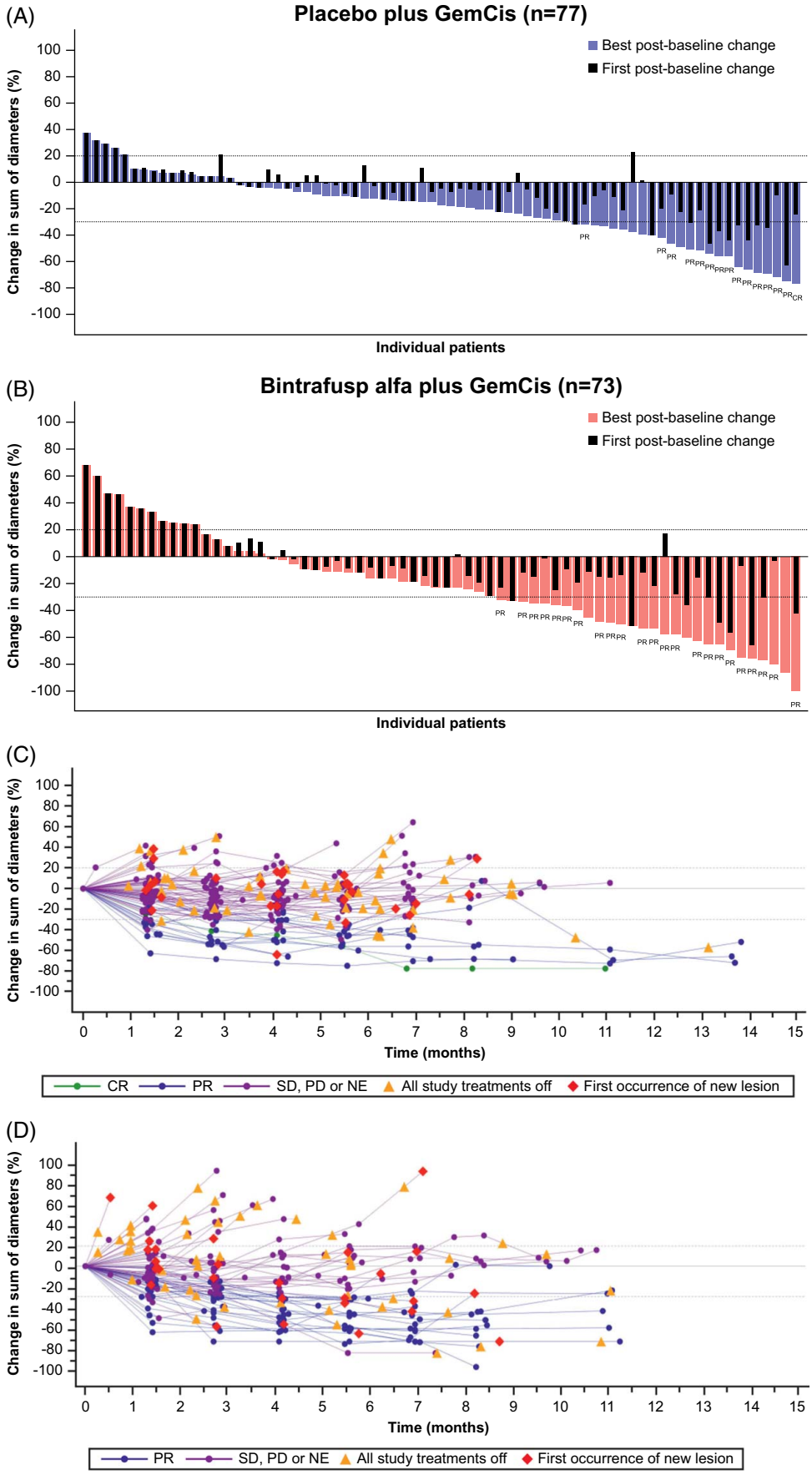

(A)
Placebo plus GemCis (n=77)
Best post-baseline change
First post-baseline change
Change in sum of diameters (%)
Individual patients
(B)
Bintrafusp alfa plus GemCis (n=73)
Best post-baseline change
First post-baseline change
Change in sum of diameters (%)
Individual patients
(C)
Change in sum of diameters (%)
Time (months)
CR
PR
SD, PD or NE
All study treatments off
First occurrence of new lesion
(D)
Change in sum of diameters (%)
Time (months)
PR
SD, PD or NE
All study treatments off
First occurrence of new lesion

FIGURE 4 Waterfall plot (A and B) and Spider plot (C and D) of percent change (from baseline) in the sum of diameters of all target lesions. Abbreviations: CR, complete response; GemCis, gemcitabine+cisplatin; IRC, Independent Review Committee; NE, not estimable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

Based on the IDMC review, the study was discontinued early (August 20, 2021) as the results of the efficacy and safety data analyses did not meet the IDMC-recommended prespecified expansion criteria.

DISCUSSION

This study investigated the efficacy of bintrafusp alfa plus GemCis treatment in chemotherapy- and immunotherapy-naive, patients with locally advanced/metastatic BTC. At the time the study was recommended for discontinuation, both bintrafusp alfa and placebo groups exhibited similar median OS; however, the OS data were immature. Although the ORR was higher with bintrafusp alfa than with placebo, it was primarily driven by higher partial responses and did not translate into better PFS.

Recently, a phase 2 trial of bintrafusp alfa monotherapy in 149 patients with locally advanced/metastatic BTC who had failed first-line standard chemotherapy reported an ORR of 10.7% (95% CI 6.4–16.6) and a median OS of 7.6 months (95% CI 5.8–9.7); however, this study too did not meet its prespecified primary end point.[24] The limited efficacy of bintrafusp alfa reported in our study could be partly attributed to a higher rate of early treatment discontinuation observed in this group. Further, the lower disease control rate observed with bintrafusp alfa compared to placebo (61.6% vs. 76.6%) suggests that, in certain patients, bintrafusp alfa may have led to the worsening of the disease. Hyperprogressive disease, characterized by accelerated tumor growth during immune checkpoint inhibitor therapy, has been reported in 3.8% to 37% of patients treated with immune checkpoint inhibitors[28]; however, a recent study suggested that that bintrafusp alfa exposure does not drive hyperprogression.[29] Interestingly, the same study showed that the effect of bintrafusp alfa exposure had a significant effect on tumor shrinkage in a BTC model. Given the pleiotropic effects of TGF-β signaling in the TME, wherein it can act as both a tumor suppressor and a tumor promotor in a cell type-dependent and context-dependent manner,[20,21] our study highlights the need to identify effective biomarkers that can reliably predict a robust response with immunotherapies that block TGF-β signaling. The use of TGF-β itself as a biomarker to predict treatment response is constrained by challenges in assessing active levels of the cytokine within the TME.[30,31]

Due to the early termination of the study and the immaturity of OS data, a full biomarker analysis was not performed. A recent review described the importance of predictive biomarkers in immune checkpoint inhibitor therapy and showed that analyzing tumor mutational burden, patterns of tumor immune infiltration, along with transcriptomic profiling of tumors at baseline could provide additional information on the immunophenotype of the tumors—an important factor influencing immunotherapy response rates.[32] In addition, a longitudinal analysis of ctDNA could be used to monitor tumor responses and the evolution of tumor mutations during treatment while also assessing the impact of these changes over time on the treatment response rates.[33]

The immaturity of the OS data was a major limitation of this study. Despite the ORR being higher with bintrafusp alfa (OR 2.01) and meeting the study expansion criteria (OR $\geq$ 1.6), immaturity of OS data meant that the decision to not expand the study to phase 3 had to be primarily based on the limited PFS efficacy outcomes (HR 1.08), which did not meet the specified expansion criteria (HR $<$ 0.75). Other important limitations include restricted follow-up and the small number of patients included for analysis of the prespecified efficacy criteria for study expansion. As the study was discontinued early, further analysis involving other secondary end points, such as pharmacokinetic profile and immunogenicity of bintrafusp alfa, as well as exploratory end points, such as biomarker analyses and patient reported outcomes, were not performed.

Efficacy assessments included only the first 150 patients that are antibiotic-naive who had completed $\geq$ 19 weeks of follow-up and had experienced 80 PFS events, while the safety set included all 297 patients enrolled in phase 2/3. Our approach of including only patients who were antibiotic-naive for efficacy analyses was validated by an ad hoc analysis of the recently published phase 2 trial of bintrafusp alfa as a second-line therapy in patients with locally advanced/metastatic BTC[24] wherein better survival was observed in the antibiotic-naive population than in the patients treated with antibiotics (data not shown). Considering the importance of TGF-β in angiogenesis and vasculogenesis,[34] bleeding events are recognized as important identified risks with bintrafusp alfa treatment. In the phase 2 study of bintrafusp alfa monotherapy in the second-line setting in BTC, treatment-related bleeding events were reported in 5.7% of patients.[24] In this study, bleeding events were reported in ~30% of patients in the bintrafusp alfa group; however, most events were grade 1/2, with grade $\geq$ 3 events reported in 7.5% of patients. Anemia was reported in 53.4% of patients treated with bintrafusp alfa and 53.7% of patients in the placebo group, with grade $\geq$ 3 events reported more frequently in the bintrafusp alfa group

TABLE 3 Incidence of treatment-related adverse events occurring in ≥ 10% of patients in any treatment group

	Safety run-in phase (n = 12)		Randomized phase 2			
			Placebo plus GemCis (n = 149)		Bintrafusp alfa plus GemCis (n = 146)	
Preferred term	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Any treatment-related adverse event	11 (91.7)	10 (83.3)	136 (91.3)	101 (67.8)	133 (91.1)	79 (54.1)
Anemia	5 (41.7)	4 (33.3)	75 (50.3)	34 (22.8)	70 (47.9)	38 (26.0)
Neutropenia	1 (8.3)	1 (8.3)	41 (27.5)	25 (16.8)	25 (17.1)	17 (11.6)
Thrombocytopenia	2 (16.7)	2 (16.7)	12 (8.1)	2 (1.3)	14 (9.6)	4 (2.7)
Constipation	0 (0.0)	0 (0.0)	28 (18.8)	0 (0.0)	18 (12.3)	0 (0.0)
Nausea	5 (41.7)	0 (0.0)	67 (45.0)	2 (1.3)	55 (37.7)	4 (2.7)
Stomatitis	0 (0.0)	0 (0.0)	4 (2.7)	0 (0.0)	16 (11.0)	1 (0.7)
Vomiting	0 (0.0)	0 (0.0)	30 (20.1)	0 (0.0)	26 (17.8)	3 (2.1)
Asthenia	2 (16.7)	0 (0.0)	9 (6.0)	0 (0.0)	19 (13.0)	1 (0.7)
Fatigue	4 (33.3)	0 (0.0)	29 (19.5)	4 (2.7)	24 (16.4)	2 (1.4)
Pyrexia	1 (8.3)	0 (0.0)	6 (4.0)	1 (0.7)	18 (12.3)	2 (1.4)
Neutrophil count decreased	5 (41.7)	5 (41.7)	60 (40.3)	51 (34.2)	28 (19.2)	20 (13.7)
Platelet count decreased	3 (25.0)	2 (16.7)	39 (26.2)	18 (12.1)	33 (22.6)	11 (7.5)
White blood cell count decreased	3 (25.0)	1 (8.3)	36 (24.2)	10 (6.7)	19 (13.0)	3 (2.1)
Decreased appetite	2 (16.7)	0 (0.0)	25 (16.8)	0 (0.0)	23 (15.8)	2 (1.4)
Dysgeusia	2 (16.7)	0 (0.0)	3 (2.0)	0 (0.0)	6 (4.1)	0 (0.0)
Pruritus	4 (33.3)	0 (0.0)	10 (6.7)	0 (0.0)	30 (20.5)	1 (0.7)
Rash	6 (50.0)	0 (0.0)	18 (12.1)	0 (0.0)	33 (22.6)	1 (0.7)

Abbreviation: GemCis, Gemcitabine + Cisplatin.

(31.6% vs. 25.5%). Chemotherapy-associated myelosuppression[35] appeared to be less severe in the bintrafusp alfa arm compared to the placebo, as evidenced by the lower incidence of neutropenia (17.1% vs. 27.5%), which was likely due to the shorter duration of treatment in this group. Thus, the impact of grade ≥ 3 bleeding events on the incidence of anemia seems to be more pronounced in the bintrafusp alfa group. Notably, the safety findings of this study were consistent with the known safety profile of bintrafusp alfa, and no new safety signals were identified.

Overall, the addition of bintrafusp alfa to GemCis did not show a clinically meaningful benefit over GemCis alone when used as a first-line treatment for patients with BTC. The hypotheses proposed for bintrafusp alfa not being effective in the first-line setting include: (1) simultaneous inhibition of TGF-β and anti–PD-L1 may modify the TME in some patients, which results in faster tumor growth due to the activation of oncogenic signaling[36]; (2) TGF-β plays a critical role in epithelial-mesenchymal transition; however, administering anti–TGF-β therapies in advanced cancers where circulating tumor cells may have already undergone epithelial-mesenchymal transition could block one of the most critical molecular pathways that sustain the mesenchymal phenotype of cancer cells, thus, inducing mesenchymal-to-epithelial transition and facilitating the growth of secondary/metastasized tumors[37]; (3) as the ratios of TGF-β and PD-L1 moieties are fixed within the bifunctional fusion molecule, the optimal dosage for both moieties may not have been achieved. Nonetheless, results from our study do not preclude the exploration of other immunotherapies in this patient population. Several recent studies have supported the use of chemoimmunotherapy as a first-line treatment option in patients with locally advanced/metastatic BTC. Results of the phase 3 TOPAZ-1 trial, which reported a median OS of 12.8 months (95% CI: 11.1–14.0) with durvalumab plus GemCis versus 11.5 months (95% CI: 10.1–12.5) with GemCis alone, have prompted an update in the most recent NCCN treatment guidelines.[8,12] The addition of pembrolizumab to GemCis in the first-line setting in patients with advanced/unresectable BTC in phase 3 KEYNOTE-966 trial significantly improved OS (12.7 mo [95% CI 11.5–13.6] vs. 10.9 mo [95% CI 9.9–11.6]; HR 0.83; $p < 0.02$). The regimen has since been added to NCCN treatment guidelines.[8,14] These encouraging results emphasize the potential of immunotherapy in patients with advanced/metastatic BTC and highlight the need to

investigate newer immune modulators in this population while simultaneously aiming to identify optimal biomarkers of response to immunotherapy.

DATA AVAILABILITY

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to the Data Sharing Policy of the healthcare business of Merck KGaA, Darmstadt, Germany. All requests should be submitted in writing to the data sharing portal for the healthcare business of Merck KGaA, Darmstadt, Germany https://www.emdgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. When the healthcare business of Merck KGaA has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, the healthcare business of Merck KGaA will endeavor to gain agreement to share data in response to requests.

AUTHOR CONTRIBUTIONS

Do-Youn Oh, Masafumi Ikeda, Choong-kun Lee, Carlos Rojas, Chih-Hung Hsu, Jin Won Kim, Lin Shen, Junji Furuse, Joon Oh Park, Mitesh Borad, Filippo de Braud, John Bridgewater, Sunyoung S. Lee, Markus Moehler, and Changhoon Yoo recruited patients. Do-Youn Oh, Changhoon Yoo, Francois Audhuy, Motonobu Osada, and Masashi Sato contributed to the conceptualization and design of the study, formal analysis, verifying underlying data, data curation, methodology, and visualization of data. All authors had access to all the data, were responsible for drafting, reviewing, and editing of the manuscript, and had the final responsibility for the decision to submit for publication.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, coinvestigators, and study teams at each of the participating centers. They would also like to thank Dr James L. Gulley, M.D., Ph.D. from the National Cancer Institute for his valuable comments that improved the manuscript. Medical writing support was provided by Anupama Singh, and editorial support was provided by Vasuprada Iyengar, both of Merck Specialities Pvt. Ltd., Bangalore, India, an affiliate of Merck KGaA, Darmstadt, Germany.

Prior presentation: none

FUNDING INFORMATION

This study was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945); the sponsor provided the study drug and collaborated with investigators during trial design and planning, data collection and analysis, and interpretation of results. Medical writing and editorial support were funded by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

CONFLICTS OF INTEREST

Do-Youn Oh advises and received grants from AstraZeneca, BeiGene, Merck & Co, Kenilworth, NJ, and Novartis. She advises Arcus, ASLAN, Basilea, Bayer, Bristol Myers Squibb/Celgene, Genentech/Roche, Halozyme, IQVIA, Taiho, Turning Point, Yuhan, and Zymeworks. She received grants from Array, Eli Lilly, Handok, and Servier. Masafumi Ikeda is on the speakers' bureau and received grants from AstraZeneca, Bayer, Bristol Myers Squibb, Chugai, Eisai, Eli Lilly, Merck & Co, Kenilworth, NJ, NIHON SERVIER, Novartis, Takeda, and Yakult. He is on the speakers' bureau for AbbVie, Abbott, EA Pharma, Fujifilm Toyama Chemical, Incyte, Nippon Kayaku, Otsuka, Teijin, Taiho, and Taisho. He received grants from Chiome, Delta-Fly, Invitae, J-Pharma, Merck KGaA, Merus, Ono, Pfizer, and Syneos Health. Choong-kun Lee is on the speakers' bureau and received grants from Boryung. He consults for Roche. He advises AstraZeneca. He is on the speakers' bureau for Dong-A ST, Servier, and Novartis. He received grants from Celltrion and GC Biopharma. Carlos Rojas consults, advises, and is on the speakers' bureau for Bristol Myers Squibb, Merck & Co, Kenilworth, NJ, Pfizer, and Roche. He consults and advises Tecnofarma. He is on the speakers' bureau AstraZeneca and Knight. He advises Sanofi. Chih-Hung Hsu consults, advises, received grants from AstraZeneca. He consults, is on the speakers' bureau, and received grants from Bristol Myers Squibb, Ono, and Roche. He advises and received grants from Merck KGaA. He is on the speakers' bureau and received grants from Eisai and Merck & Co, Kenilworth, NJ. He consults for Daiichi Sankyo. He received grants from BeiGene, Encure, Ipsen, Johnson & Johnson, MSD, NuCana Biomed, Surface Oncology, and Taiho. Jin Won Kim consults for AstraZeneca, BeiGene, Beyond Bio, Bristol Myers Squibb/Celgene, Eisai, GC Cell, Merck & Co, Kenilworth, NJ, Ono, Sanofi-Aventis, Servier, and TCUBEit. He received grants from HK inno.N and Jeil Pharm. Lin Shen consults for Haichuang, Herbour, and Mingji. He advises AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Merck & Co, Kenilworth, NJ, Merck KGaA, Roche, Sanofi, and Servier. He received grants from Beihai Kangcheng, Beijing Xiantong Biomedical, Jacobio, Qilu, Yaojie Ankang Baiji Shenzhou, and ZaiLab. Junji Furuse advises, is on the speakers' bureau, and received grants from AstraZeneca, Chugai Pharma, Merck & Co, Kenilworth, NJ, and Taiho. He advises and received grants from Astellas, Delta-Fly-Pharma, and J-Pharma. He is on the speakers' bureau and received grants from Daiichi Sankyo, Eisai, Incyte, Ono, and Takeda. He advises Fujifilm, Merck KGaA, Onco Therapy, and Takara Bio. He is on the speakers' bureau for Bayer, EA Pharma, Eli Lilly, Fujifilm,

MSD, Novartis, Servier, Teijin, Terumo, and Yakult. He received grants from Sanofi and Sumitomo Dainippon. Joon Oh Park consults, advises, and received grants from Servier. He consults and advises ImmuneOncia. He advises AstraZeneca, Adicet, Arcus, MediRama, and Merck KGaA. He received grants from ABL Bio, Bristol Myers Squibb, Eutilex, MedPacto, and Minneamrita. Mitesh Borad consults and advises ADC Therapeutics, Excelixis, Inspyr, G1, Genentech, Huya, Immunovative, Lynx Group, Merck & Co, Kenilworth, NJ, OncBioMune, and Western Oncolytics. He received grants from Adaptimmune, Agios, Basilea, Boston Biomed, Celgene, Dicerna, EMD Serona, Halozyme, Incyte, Isis Pharmaceuticals, Merck KGaA, Mirna, Redhill, Senhwa, Sun Biopharma, Taiho, and Toray. Filippo de Braud consults, advises, is on the speakers' bureau, and received grants from Bristol Myers Squibb. He consults, is on the speakers' bureau, and received grants from AstraZeneca, Merck & Co, Kenilworth, NJ, Pfizer, and Roche. He advises, is on the speakers' bureau, and received grants from Sanofi. He consults and advises Pierre Fabre and Taiho. He consults and is on the speakers' bureau for Bayer, Dephaforum, and Ignyta. He consults and received grants from Amgen, Celgene, Incyte, and Novartis. He consults for Daiichi Sankyo, Eli Lilly, Fondazione Menarini, Gentili, IQVIA, Indena, Mattioli 1885, MSD, Menarini, Octimet Oncology, Pharm Research Associated, Servier, and Tiziana Life Sciences. He is on the speakers' bureau for Accmed, Ambrosetti, Biotechespert, Dynamicom Education, Effetti, ESO, Events, Fare Comunicazione, Idea-z, Itanet, Motore Sanità, Nadirex, and Prime Oncology. He received grants from Kymab, Merck KGaA, NMS, and Tesaro. John Bridgewater consults and advises Merck KGaA. He advises and is on the speakers' bureau for Incyte and Servier. He advises Taiho. Markus Moehler is on the speakers' bureau and received grants from Merck KGaA. Francois Audhuy is employed by Merck Serono S.A.S., Lyon, France, an affiliate of Merck KGaA, Darmstadt, Germany. Motonobu Osada is employed by Merck Biopharma Co., Ltd., Tokyo, Japan, an affiliate of Merck KGaA, Darmstadt, Germany. Masashi Sato is employed by Merck Biopharma Co., Ltd., Tokyo, Japan, an affiliate of Merck KGaA, Darmstadt, Germany. Changhoon Yoo consults, advises, and received grants from AstraZeneca, Bayer, Boryung, Celgene, CKD, HK inno.N, Ildong, and Ono. He consults and advises Ipsen and Servier. He consults and received grants from Ipsen, and Servier. He consults for Bristol Myers Squibb, Debiopharm, Eisai, Janssen, Kyowa Kirin, Merck & Co, Kenilworth, NJ, Merck KGaA, Mundipharma, Novartis, and Roche. He received grants from Eisai and MSD. The remaining authors have no conflicts to report.

REFERENCES

1. Valle JW, Kelley RK, Nervi B, Oh DY, Zhu AX. Biliary tract cancer. Lancet. 2021;397:428–44.
2. Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - Evolving concepts and therapeutic strategies. Nat Rev Clin Oncol. 2018;15:95–111.
3. Bridgewater JA, Goodman KA, Kalyan A, Mulcahy MF. Biliary tract cancer: epidemiology, radiotherapy, and molecular profiling. Am Soc Clin Oncol Educ Book. 2016;35:e194–203.
4. Randi G, Malvezzi M, Levi F, Ferlay J, Negri E, Franceschi S, et al. Epidemiology of biliary tract cancers: An update. Ann Oncol. 2009;20:146–59.
5. Matsuda T, Marugame T. International comparisons of cumulative risk of gallbladder cancer and other biliary tract cancer, from Cancer Incidence in Five Continents Vol. VIII. Jpn J Clin Oncol. 2007;37:74–5.
6. Rizzo A, Brandi G. First-line chemotherapy in advanced biliary tract cancer ten years after the ABC-02 Trial: "And Yet It Moves!". Cancer Treat Res Commun. 2021;27:100335.
7. Jung SJ, Woo SM, Park HK, Lee WJ, Han MA, Han SS, et al. Patterns of initial disease recurrence after resection of biliary tract cancer. Oncology. 2012;83:83–90.
8. NCCN Guidelines (Version 3.2023): Biliary Tract Cancers. Accessed March 18, 2024. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1517
9. Vogel A, Bridgewater J, Edeline J, Kelley RK, Klümpen HJ, Malka D, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34:127–40.
10. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362:1273–81.
11. Ueno M, Ikeda M, Morizane C, Kobayashi S, Ohno I, Kondo S, et al. Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: A non-randomised, multicentre, open-label, phase 1 study. Lancet Gastroenterol Hepatol. 2019;4:611–21.
12. Oh D-Y, Ruth He A, Qin S, Chen L-T, Okusaka T, Vogel A, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evidence. 2022;1:EVIDoa2200015.
13. Oh DY, Lee KH, Lee DW, Yoon J, Kim TY, Bang JH, et al. Gemcitabine and cisplatin plus durvalumab with or without tremelimumab in chemotherapy-naive patients with advanced biliary tract cancer: An open-label, single-centre, phase 2 study. Lancet Gastroenterol Hepatol. 2022;7:522–32.
14. Kelley RK, Ueno M, Yoo C, Finn RS, Furuse J, Ren Z, 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. 2023;401:1853–65.
15. FDA D.I.S.C.O. Burst Edition: FDA approval of Imfinzi (durvalumab) for adult patients with locally advanced or metastatic biliary tract cancer. Accessed September 06, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-imfinzi-durvalumab-adult-patients-locally-advanced-or#:~:text=On%20September%202%2C%202022%2C%20FDA,or%20metastatic%20biliary%20tract%20cancer
16. FDA approves pembrolizumab with chemotherapy for biliary tract cancer. Accessed March 18, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-chemotherapy-biliary-tract-cancer
17. Zhao H, Wei J, Sun J. Roles of TGF-beta signaling pathway in tumor microenvirionment and cancer therapy. Int Immunopharmacol. 2020;89:107101.
18. Liu S, Chen S, Zeng J. TGF-beta signaling: A complex role in tumorigenesis (Review). Mol Med Rep. 2018;17:699–704.
19. Colak S, Ten Dijke P. Targeting TGF-beta signaling in cancer. Trends Cancer. 2017;3:56–71.

20. Kim BG, Malek E, Choi SH, Ignatz-Hoover JJ, Driscoll JJ. Novel therapies emerging in oncology to target the TGF-beta pathway. J Hematol Oncol. 2021;14:55.
21. Bai X, Yi M, Jiao Y, Chu Q, Wu K. Blocking TGF-beta signaling to enhance the efficacy of immune checkpoint inhibitor. Onco Targets Ther. 2019;12:9527–38.
22. Papoutsoglou P, Louis C, Coulouarn C. Transforming growth factor-beta (TGFbeta) signaling pathway in cholangiocarcinoma. Cells. 2019;8:960.
23. Yoo C, Oh DY, Choi HJ, Kudo M, Ueno M, Kondo S, et al. Phase I study of bintrafusp alfa, a bifunctional fusion protein targeting TGF-beta and PD-L1, in patients with pretreated biliary tract cancer. J Immunother Cancer. 2020;8:e000564.
24. Yoo C, Javle MM, Verdaguer Mata H, de Braud F, Trojan J, Raoul JL, et al. Phase 2 trial of bintrafusp alfa as second-line therapy for patients with locally advanced/metastatic biliary tract cancers. Hepatology. 2023;78:758–70.
25. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.
26. Pinato DJ, Howlett S, Ottaviani D, Urus H, Patel A, Mineo T, et al. Association of prior antibiotic treatment with survival and response to immune checkpoint inhibitor therapy in patients with cancer. JAMA Oncol. 2019;5:1774–8.
27. Chalabi M, Cardona A, Nagarkar DR, Dhawahir Scala A, Gandara DR, Rittmeyer A, et al. Efficacy of chemotherapy and atezolizumab in patients with non-small-cell lung cancer receiving antibiotics and proton pump inhibitors: Pooled post hoc analyses of the OAK and POPLAR trials. Ann Oncol. 2020;31:525–31.
28. Ferrara R, Mezquita L, Texier M, Lahmar J, Audigier-Valette C, Tessonnier L, et al. Comparison of fast-progression, hyperprogressive disease, and early deaths in advanced non-small-cell lung cancer treated with PD-1/PD-L1 inhibitors or chemotherapy. JCO Precis Oncol. 2020;4:829–40.
29. Milenkovic-Grisic AM, Terranova N, Mould DR, Vugmeyster Y, Mrowiec T, Machl A, et al. Tumor growth inhibition modeling in patients with second line biliary tract cancer and first line non-small cell lung cancer based on bintrafusp alfa trials. CPT Pharmacometrics Syst Pharmacol. 2024;13:143–53.
30. Khan SA, Joyce J, Tsuda T. Quantification of active and total transforming growth factor-beta levels in serum and solid organ tissues by bioassay. BMC Res Notes. 2012;5:636.
31. Gulley JL, Schlom J, Barcellos-Hoff MH, Wang XJ, Seoane J, Audhuy F, et al. Dual inhibition of TGF-beta and PD-L1: A novel approach to cancer treatment. Mol Oncol. 2022;16:2117–34.
32. Bai R, Lv Z, Xu D, Cui J. Predictive biomarkers for cancer immunotherapy with immune checkpoint inhibitors. Biomark Res. 2020;8:34.
33. Ricci AD, Rizzo A, Brandi G. Immunotherapy in biliary tract cancer: Worthy of a second look. Cancer Control. 2020;27:1073274820948047.
34. Goumans MJ, Liu Z, ten Dijke P. TGF-beta signaling in vascular biology and dysfunction. Cell Res. 2009;19:116–27.
35. Rodgers GM, Becker PS, Blinder M, Cella D, Chanan-Khan A, Cleeland C, et al. Cancer-and chemotherapy-induced anemia. J Natl Compr Canc Netw. 2012;10:628–53.
36. Champiat S, Ferrara R, Massard C, Besse B, Marabelle A, Soria JC, et al. Hyperprogressive disease: Recognizing a novel pattern to improve patient management. Nat Rev Clin Oncol. 2018;15:748–62.
37. Teixeira AF, Ten Dijke P, Zhu HJ. On-target anti-TGF-beta therapies are not succeeding in clinical cancer treatments: What are remaining challenges? Front Cell Dev Biol. 2020;8:605.

How to cite this article: Oh D, Ikeda M, Lee C, Rojas C, Hsu C, Kim JW, et al. Bintrafusp alfa and chemotherapy as first-line treatment in biliary tract cancer: A randomized phase 2/3 trial. Hepatology. 2025;81:823–836. https://doi.org/10.1097/HEP.0000000000000965