ORIGINAL ARTICLE

Bintrafusp Alfa With CCRT Followed by Bintrafusp Alfa Versus Placebo With CCRT Followed by Durvalumab in Patients With Unresectable Stage III NSCLC: A Phase 2 Randomized Study

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ABSTRACT

Introduction: Preclinical evaluation of bintrafusp alfa (BA) combined with radiotherapy revealed greater antitumor effects than BA or radiotherapy alone. In a phase 1 study, BA exhibited encouraging clinical activity in patients with stage IIIB or IV NSCLC who had received previous treatment.

Methods: This multicenter, double-blind, controlled phase 2 study (NCT03840902) evaluated the safety and efficacy of BA with concurrent chemoradiotherapy (cCRT) followed by BA (BA group) versus placebo with cCRT followed by durvalumab (durvalumab group) in patients with unresectable stage III NSCLC. The primary end point was progression-free survival according to Response Evaluation Criteria in Solid Tumors version 1.1 as assessed by the investigator. On the basis of the recommendation of an independent data monitoring committee, the study was discontinued before the maturity of overall survival data (secondary end point).

Results: A total of 153 patients were randomized to either BA (n = 75) or durvalumab groups (n = 78). The median progression-free survival was 12.8 months versus 14.6 months (stratified hazard ratio = 1.48 [95% confidence interval: 0.69–3.17]), in the BA and durvalumab groups, respectively. Trends for overall response rate (29.3% versus 32.1%) and disease control rate (66.7% versus 70.5%) were similar between the two groups. Any-grade treatment-emergent adverse events occurred in 94.6% versus 96.1% of patients in the BA versus durvalumab groups, respectively. Bleeding events in the BA group were mostly grade 1 (21.6%) or 2 (9.5%).

Conclusions: BA with cCRT followed by BA exhibited no efficacy benefit over placebo with cCRT followed by durvalumab in patients with stage III unresectable NSCLC.

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Keywords: Bintrafusp alfa; TGF-β; Concurrent chemoradiotherapy; Bifunctional; Non–small cell lung cancer

Introduction

NSCLC is the most prevalent form of lung cancer, accounting for 81% of cases.[1] Approximately 35% of patients with NSCLC have locally advanced stage III disease at diagnosis,[2] with a 5-year survival rate of 13% to 36%.[3] On the basis of the results of the PACIFIC trial,[4] durvalumab consolidation therapy after concurrent chemoradiotherapy (cCRT) has become the standard of care (SoC) in patients with unresectable stage III NSCLC.[4,5]

In the PACIFIC analysis, durvalumab exhibited improved efficacy versus placebo, with a median overall survival (OS) of 47.5 months versus 29.1 months and median progression-free survival (PFS) of 17.2 months versus 5.6 months.[6] There were consistent OS benefits with durvalumab over placebo across all prespecified subgroups except in patients with mutations in the *EGFR* gene and those with programmed death-ligand 1 (PD-L1) expression of less than 1% of tumor cells.[6]

Consistent with the PACIFIC analysis, results from the PACIFIC-R retrospective real-world study revealed numerically longer median real-world PFS with consolidation durvalumab after cCRT (23.7 mo) versus sequential chemoradiotherapy (19.3 mo) and in patients with PD-L1 expression of greater than or equal to 1% versus less than 1% (22.4 mo versus 15.6 mo, respectively).[7] However, many patients treated with the current SoC still experience disease progression or recurrence (5-y PFS, 33.1%; 5-y OS, 42.9%).[8]

Other immune checkpoint inhibitors that have been explored concurrently with cCRT include nivolumab (NICOLAS; NCT02434081),[9] pembrolizumab (NCT02621398),[10] and atezolizumab (NCT02525757)[11]; however, none has been studied as a maintenance agent after cCRT. Therefore, novel treatment options are needed to address the unmet medical needs of this difficult-to-treat population. One approach could be to simultaneously target immunosuppressive networks in the tumor microenvironment (TME) in addition to PD-L1.[12]

Transforming growth factor-β (TGF-β) overexpression is common in several tumor types, including NSCLC. Aberrant TGF-β activity is associated with an immunosuppressive TME and has been implicated in promoting the progression and metastasis of NSCLC.[13] Studies have found that radiation and chemotherapy can induce TGF-β[14] and enhance PD-L1 expression[15] and that TGF-β signaling in the TME is associated with resistance to anti–PD-L1 treatment.[12] In addition, TGF-β signaling is the primary driver of radiation-induced fibrosis, which is implicated in resistance to radiotherapy and tissue injury.[16,17]

Bintrafusp alfa (BA) was designed to block TGF-β (by "trapping" all TGF-β isoforms) and its trap function is physically linked to PD-L1 blockade; the bifunctional nature of BA might allow for colocalized, simultaneous inhibition of these two nonredundant immunosuppressive pathways (TGF-β and PD-L1) within the TME.[12,16] In preclinical models, BA exhibited enhanced suppression of metastasis and tumor growth compared with the inhibition of TGF-β or PD-L1 alone. Furthermore, adding BA to radiotherapy revealed synergistic antitumor activity, beyond that achieved with BA or radiotherapy alone.[16]

In a phase 1 study, BA exhibited a manageable safety profile and encouraging clinical activity in patients who were previously treated for stage IIIB or IV NSCLC.[18] Because of its mechanism of action, BA is a potentially suitable combination agent for CRT. In this study, we report the efficacy and safety of BA with cCRT followed by BA compared with placebo with cCRT followed by durvalumab in patients with unresectable stage III NSCLC.

Materials and Methods

Study Design and Participants

This global, multicenter, randomized, double-blind, controlled phase 2 study (NCT03840902) evaluated BA use in patients with unresectable stage III NSCLC according to the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology version 8. As per the final protocol (additional details in Supplementary Methods) the study comprised a safety run-in phase (n = 42) that stratified patients according to ethnicity (12 Japanese and 30 non-Japanese patients) and an expansion phase (n = 118) that stratified patients according to chemotherapy regimen and PD-L1 expression.

Randomized (1:1) patients received either 1200 mg BA every 2 weeks with cCRT followed by BA every 2 weeks or placebo with cCRT followed by durvalumab (10 mg/kg every 2 wk). Radiotherapy was administered to all participants 5 days a week at a dose of 60 Gy (30 fractions [2 Gy/fraction]) along with a chemotherapy regimen. Delineation of targets and organs at risk and plan quality metrics followed a study Radiotherapy Guidelines Manual (additional details in Supplementary Methods). Radiotherapy plan data (known as Digital Imaging and Communications in Medicine–Radiation Therapy)[19] was submitted digitally, peer-reviewed, and scored per the manual. Sites were encouraged but not required to submit revised plans that did not meet passing criteria (Supplementary Table 1). Three standard chemotherapy regimens were selected according to the National Comprehensive Cancer Network guidelines: cisplatin (50 mg/m^2) on days 1, 8, 29, and 36 or etoposide (50 mg/m^2) on days 1 to 5 and 29 to 33 during cCRT; carboplatin (area under concentration 2) or paclitaxel (45 mg/m^2) on days 1, 8, 15, 22, 29, 36, and 43 during cCRT; and cisplatin (75 mg/m^2) or pemetrexed (500 mg/m^2) on days 1, 22, and 43 during cCRT.

The primary objective of this trial was to evaluate PFS according to the Response Evaluation Criteria in Solid Tumors version 1.1 as assessed by the investigator. Secondary objectives included the evaluation of safety, OS, and objective response rate (ORR). Exploratory end points included the evaluation of biomarkers, pulmonary function, and patient-reported outcomes.

Methodology

Patients aged 18 years and older with histologically confirmed, locally advanced, unresectable stage III NSCLC; adequate renal, hepatic, and hematologic function; an Eastern Cooperative Oncology Group performance status of 0 or 1; and a life expectancy of at least 12 weeks were included. Additional eligibility criteria include the following: (1) patients with *EGFR* mutations;

(2) ALK translocation; (3) ROS-1 rearrangement; (4) ongoing postobstructive pneumonia because of the tumor; and (5) minimal pleural effusion with cytologically negative pleural fluid. Exclusion criteria included the following: (1) the presence of mixed small cells with NSCLC histologic diagnosis; (2) greater than minimal, exudative, or cytologically positive pleural effusion(s); (3) any major surgery in the 4 weeks before study entry; (4) previous treatment with chemotherapy or immunotherapy; (5) previous radiotherapy as an adjuvant or neoadjuvant regimen; (6) autoimmune disease; (7) use of immunosuppressive medications within 28 days of the first dose of the study drug; and (8) concurrent enrollment in another trial (a full list of the inclusion and exclusion criteria is provided in the Supplementary Methods).

After patients received the initial dose, antitumor responses were monitored by means of contrast-enhanced computed tomography or magnetic resonance imaging every 8 weeks for 24 months unless disease progression occurred, or the patient withdrew from the study. All adverse events (AEs) were classified by worst severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 using the latest version of the Medical Dictionary for Regulatory Activities. The study protocol was approved by the ethics committees of all participating institutions. The study was conducted in accordance with all applicable regulatory requirements. All patients provided written informed consent before enrollment. The study complied with international standards of Good Clinical Practice and the Declaration of Helsinki.

Statistical Analysis

A maximum of 160 eligible patients (safety run-in, n = 42 and expansion phase, n = 118) were planned for enrollment to observe 70 PFS events in the primary analysis. An independent data monitoring committee (IDMC) periodically reviewed the safety data during the safety run-in and expansion phases. PFS, the primary end point, was defined as the time from randomization to the date of the first documentation of objective progressive disease, as assessed by the investigator, according to Response Evaluation Criteria in Solid Tumors version 1.1, or death because of any cause in the absence of documented progressive disease, whichever occurred first. OS was defined as the time from randomization to the date of death because of any cause. The Kaplan-Meier method was used to estimate the survival rates and 95% confidence intervals (CIs) of PFS and OS. Stratified log-rank tests were used to evaluate PFS and OS differences between the treatment groups. A Cox proportional hazards model was used to estimate hazard ratios (HRs). The objective responses and safety end points are presented using descriptive statistics. Analyses were performed using the statistical software Statistical Analysis System (Windows Version 9.4 or higher; SAS Institute, Cary, NC).

Results

Patients and Treatment

Between April 2019 and July 2021, 153 patients were randomized either to BA with cCRT followed by BA (n = 75) or placebo with cCRT followed by durvalumab (n = 78; full analysis set) (Fig. 1). Study discontinuation rates were 18.7% in the BA group and 10.3% in the durvalumab group. Death was the most frequently reported reason for study discontinuation in both treatment groups (BA versus durvalumab: 85.7% versus 62.5%).

Baseline characteristics were generally well-balanced between the treatment groups. The median age was 65 years (range: 37–89) and 66 (41–81) years in the BA and durvalumab groups, respectively (Table 1). The proportion of patients with PD-L1 expression greater than or equal to 1% was similar in both groups (BA versus durvalumab group: 62.7% versus 61.5%). Of note, the proportion of patients with adenocarcinomas was higher in the BA group (61.3%) than in the durvalumab group (39.7%).

The median duration of treatment was 12.6 (range: 2.0–64.1) weeks with BA and 16.3 (range: 2.0–76.4) weeks with durvalumab. The proportions of patients who received a relative dose intensity of greater than 90% of BA, placebo, and durvalumab were 66.2%, 92.2%, and 67.5%, respectively. The median duration of radiotherapy was similar between the BA (6.1 [0.1–12.9] weeks) and durvalumab (6.1 [1.0–8.1] wk) groups. The median duration of chemotherapy was comparable between the groups (cisplatin/etoposide, 9 wk; carboplatin/paclitaxel, 7 wk; and cisplatin/pemetrexed, 9 wk).

Efficacy

After a median follow-up duration of 3.7 months in both treatment groups (data cutoff date: July 21, 2021), the median PFS was 12.8 months (95% CI: 7.5–not estimable [NE]) in the BA group and 14.6 months (95% CI: 7.3–NE) in the durvalumab group (stratified HR = 1.48; 95% CI: 0.69–3.17) (Table 2 and Fig. 2*A*). PFS benefit with durvalumab was observed across most subgroups (Supplementary Fig. 1). The ORR was 29.3% in the BA group (complete response [CR], n = 3; partial response [PR], n = 19 [25.3%]) versus 32.1% in the durvalumab group (CR, n = 1; PR, n = 24 [30.8%]) (Supplementary Fig. 2). The disease control rates (DCRs) were 66.7% and 70.5% in the BA and durvalumab

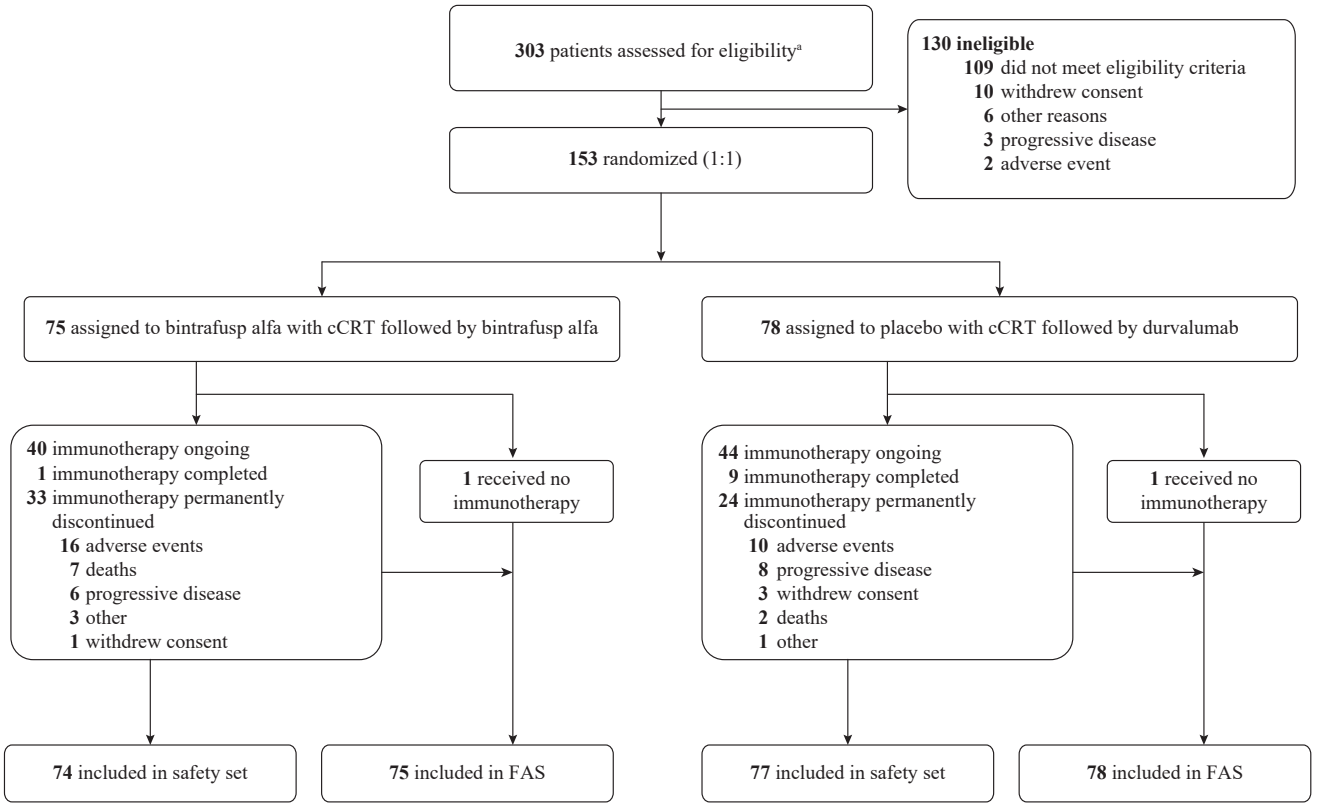

Figure 1. CONSORT diagram. [a]At data cutoff July 21, 2021, 20 patients were rescreened but not randomized. cCRT, concurrent chemoradiotherapy; FAS, full analysis set.

groups, respectively. The proportions of nonevaluable patients in the BA (26.7%) and durvalumab (25.6%) groups were similar (Table 2). The median follow-up duration for OS was also similar between both the groups (BA, 4.6 mo [95% CI: 2.9–7.0] and durvalumab, 4.3 mo [95% CI: 2.9–6.0]). The median OS was not evaluable using the Kaplan-Meier method in both groups (stratified HR = 3.28 [95% CI: 1.15–9.38]). At the time of data cutoff, more patients had died in the BA group than in the durvalumab group (17.3% versus 6.4%, respectively) (Fig. 2*B*).

Safety

The safety cohort consisted of 74 patients in the BA group and 77 patients in the durvalumab group; any-grade treatment-emergent AEs (TEAEs) were reported in 94.6% and 96.1% of patients, respectively (Table 3). The most common any-grade TEAEs (≥30%) were anemia (51.4% versus 41.6%), constipation (31.1% versus 44.2%), nausea (36.5% versus 39.0%), esophagitis (20.3% versus 31.2%), and decreased white blood cell count (32.4% versus 37.7%) in the BA and durvalumab groups, respectively. The proportion of patients who experienced grade 3 or higher TEAEs, grade 4 or higher TEAEs, and any serious TEAEs are provided in Table 3. The rates of TEAEs leading to permanent discontinuation of any treatment occurred in 35.1% of patients in the BA group versus 15.6% of patients in the durvalumab group. The rate of TEAEs leading to death was higher in the BA group (10.8%; one patient each with death, disease progression, coronavirus disease 2019, pulmonary sepsis, septic shock, brain stem hemorrhage, atelectasis, and bronchial hemorrhage) than in the durvalumab group (3.9%; one patient each with cardiac arrest, pneumonia, and hemoptysis). The proportions of patients with treatment-related AEs (TRAEs) of grade 3 or higher due to immunotherapy (32.4% versus 15.6%), radiotherapy (35.1% versus 27.3%), and chemotherapy (64.9% versus 49.4%) were higher in the BA group than in the durvalumab group (Table 3). The categorization of AEs with respect to timing (during, immediately after, and late-onset) of radiotherapy administration is provided in Supplementary Table 1. The most common any-grade AE (≥10%) resulting during radiotherapy administration was esophagitis (18.9% versus 29.9%), anemia (17.6% versus 13.0%), radiation esophagitis (16.2% versus 13.0%), decreased neutrophil count (10.8% versus 15.6%), and neutropenia (10.8% versus 3.9%) in the BA and durvalumab groups, respectively. The proportion of patients with AEs (≥1%) resulting immediately after radiotherapy administration were 8.1% and 5.2% in the BA versus

Table 1. Baseline Patient and Disease Characteristics

Characteristics	BA With cCRT Followed by BA (n = 75)	Placebo With cCRT Followed by Durvalumab (n = 78)
Sex, n (%)		
Male	55 (73.3)	62 (79.5)
Age		
Median (range), y	65 (37-89)	66 (41-81)
<65 y	37 (49.3)	33 (42.3)
≥65 y	38 (50.7)	45 (57.7)
Race n (%)		
Caucasian	48 (64.0)	41 (52.6)
Asian	25 (33.3)	34 (43.6)
Others/not collected at the site	2 (2.7)	3 (3.8)
Ethnicity - Japanese, n (%)		
Yes	10 (13.3)	17 (21.8)
No	65 (86.7)	60 (76.9)
Smoking history		
Never smokers	10 (13.3)	4 (5.1)
Ever smokers	65 (86.7)	73 (93.6)
Former	57 (76.0)	61 (78.2)
Current	8 (10.7)	12 (15.4)
Missing	0	1 (1.3)
ECOG performance status		
0	39 (52.0)	47 (60.3)
≥1	36 (48.0)	31 (39.7)
PD-L1 status at screening[a], n (%)		
≥1%	47 (62.7)	48 (61.5)
<1%	27 (36.0)	29 (37.2)
Missing	1 (1.3)	1 (1.3)
EGFR, n (%)		
Wild-type	22 (29.3)	17 (21.8)
Mutated	2 (2.7)	3 (3.8)
Not assessed	51 (68.0)	58 (74.4)
Tumor histologic diagnosis, n (%)		
Adenocarcinoma	46 (61.3)	31 (39.7)
Squamous cell carcinoma	24 (32.0)	43 (55.1)
Others	5 (6.7)	4 (5.2)
NSCLC stage at study entry (according to IASLC staging manual version 8), n (%)		
IIIa	34 (45.3)	31 (39.7)
IIIb	26 (34.7)	34 (43.6)
IIIc	15 (20.0)	13 (16.7)
Time since initial cancer diagnosis by means of biopsy[b]		
Median (range), mo	1.1 (0.4-4.3)	1.1 (0.5-3.5)
Time since documented, locally advanced, or inoperable disease[c]		1.0 (0.0-3.5)
Median (range), mo	1.0 (0.0-4.3)	

[a]PD-L1 data was obtained from two sources: as per protocol, PD-L1 expression was tested prospectively (results provided in IWRS) for participants enrolled during the expansion phase and retrospectively (results provided by central laboratory) for those enrolled during the safety run-in phase.
[b]Time since initial cancer diagnosis by biopsy (mo) = (date of randomization − date of initial cancer diagnosis)/30.4375.
[c]Time since documentation of locally advanced or inoperable disease diagnosis (mo) = (date of randomization − date of documentation of locally advanced or inoperable disease diagnosis)/30.4375.
BA, bintrafusp alfa; cCRT, concurrent chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; IASLC, International Association for the Study of Lung Cancer; IWRS, Interactive/Web Response System; PD-L1, programmed death-ligand 1.

durvalumab groups, respectively. The most common AEs (≥10%) that were late-onset after radiotherapy administration were anemia (13.5% versus 9.1%) and febrile neutropenia (10.8% versus 9.1%) in the BA and durvalumab groups, respectively (Supplementary Table 2). The proportion of patients with immune-related AEs of special interest (AESIs) and any-grade bleeding events were 21.6% and 40.5%, respectively, in the BA group and 20.8% and 9.1%, respectively, in the durvalumab group (Table 4). Skin-related AESIs occurred only in the BA group, of which the most common was keratoacanthoma (5.4%; n = 4) (Table 4). The proportion of

Table 2. Summary of Efficacy Analyses

Outcome Measure	BA With cCRT Followed by BA (n = 75)	Placebo With cCRT Followed by Durvalumab (n = 78)
Progression-free survival		
Median (95% CI), mo	12.8 (7.5-NE)	14.6 (7.3-NE)
HR (stratified), 95% CI	1.48 (0.69-3.17)	-
Overall survival		
Median (95% CI), mo	NE (15.8-NE)	NE (NE-NE)
HR (stratified), 95% CI	3.28 (1.15-9.38)	-
Objective response[a], n (%)		
CR	3 (4.0)	1 (1.3)
Partial response	19 (25.3)	24 (30.8)
Stable disease	28 (37.3)	30 (38.5)
PD	3 (4.0)	3 (3.8)
Non-CR/non-PD	2 (2.7)	0
Not evaluable	20 (26.7)	20 (25.6)
Objective tumor response, n (%)		
Objective response rate[b]	22 (29.3)	25 (32.1)
Disease control, n (%)		
Disease control rate[c]	50 (66.7)	55 (70.5)

[a]Objective response rate on the basis of confirmed responses according to RECIST version 1.1 as assessed by the investigator.
[b]Best overall response assessment of CR or partial response.
[c]Best overall response assessment of CR, partial response, or stable disease.
BA, bintrafusp alfa; cCRT, concurrent chemoradiotherapy; CI, confidence interval; CR, complete response; HR, hazard ratio; NE, not estimable; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors.

bleeding events observed in the BA group was mostly grade 1 (21.6%) and grade 2 (9.5%); there were 6.8% and 2.7% grade 3 and grade 5 bleeding events, respectively, but no grade 4 bleeding events. A total of 17.6% of patients in the BA group and 6.5% in the durvalumab group died. Most deaths in the BA group were attributed to the progression of underlying disease and disease-related conditions (6.8%). More deaths occurred within 60 days of study treatment initiation in the BA group than in the durvalumab group (4.1% versus 2.6%). On the basis of the IDMC review of the cumulative data of 153 randomized participants and the total efficacy and safety data available until the data cutoff date, the IDMC recommended that the study be discontinued (September 2021) because of an unfavorable risk-benefit ratio and the low probability of achieving the proposed efficacy end points.

Discussion

This study was discontinued before the maturity of the OS data. At the time the study was discontinued, the PFS (median PFS, 12.8 mo versus 14.6 mo; HR = 1.48) and OS (median OS, NE in both groups; HR = 3.28) outcomes were numerically less favorable for BA than for durvalumab. The ORR and DCR were similar but numerically lower for BA than for durvalumab (29.3% versus 32.1% and 66.7% versus 70.5%). As this study did not include an arm evaluating BA consolidation therapy after cCRT alone, the effect of BA consolidation therapy without the initial combination regimen of BA with cCRT could not be assessed.

Phase 1 trials of BA in solid tumors have predominantly reported anemia and skin lesions as TRAEs.[18,20–23] A safety run-in data from a phase 2/3 study of BA in biliary tract cancer has revealed both anemia (grade $\geq$3, 41.7%) and bleeding events (grade $\geq$3, 16.3%) as AESIs (NCT04066491; D.Y. Oh, unpublished and submitted data). Bleeding events and anemia were considered potential risks at the time of study initiation, given the importance of TGF-β in angiogenesis and vasculogenesis.[24] Ongoing safety surveillance during the study confirmed these risks, and all clinical study documents were updated to include these events as important identified risks, and appropriate risk mitigation measures were added to the study protocol. This ensured appropriate, timely identification, and management of anemia and bleeding events throughout the study. Anemia AEs were observed in 51.4% of patients treated with BA, which could be related to the high incidence of bleeding. Any-grade bleeding events that occurred in the BA group were epistaxis (17.6%), hemoptysis (9.5%), and rectal hemorrhage (5.4%). Grade 3 bleeding events were gastrointestinal vascular malformation hemorrhage, hematemesis, hemorrhoidal hemorrhage, small intestinal hemorrhage, upper gastrointestinal hemorrhage, and hematuria (each 1.4%). Two fatal events (grade 5) were brain stem hemorrhage and bronchial hemorrhage (each 1.4%). The safety findings of the present study were consistent with the known safety profile of BA.[18] No new

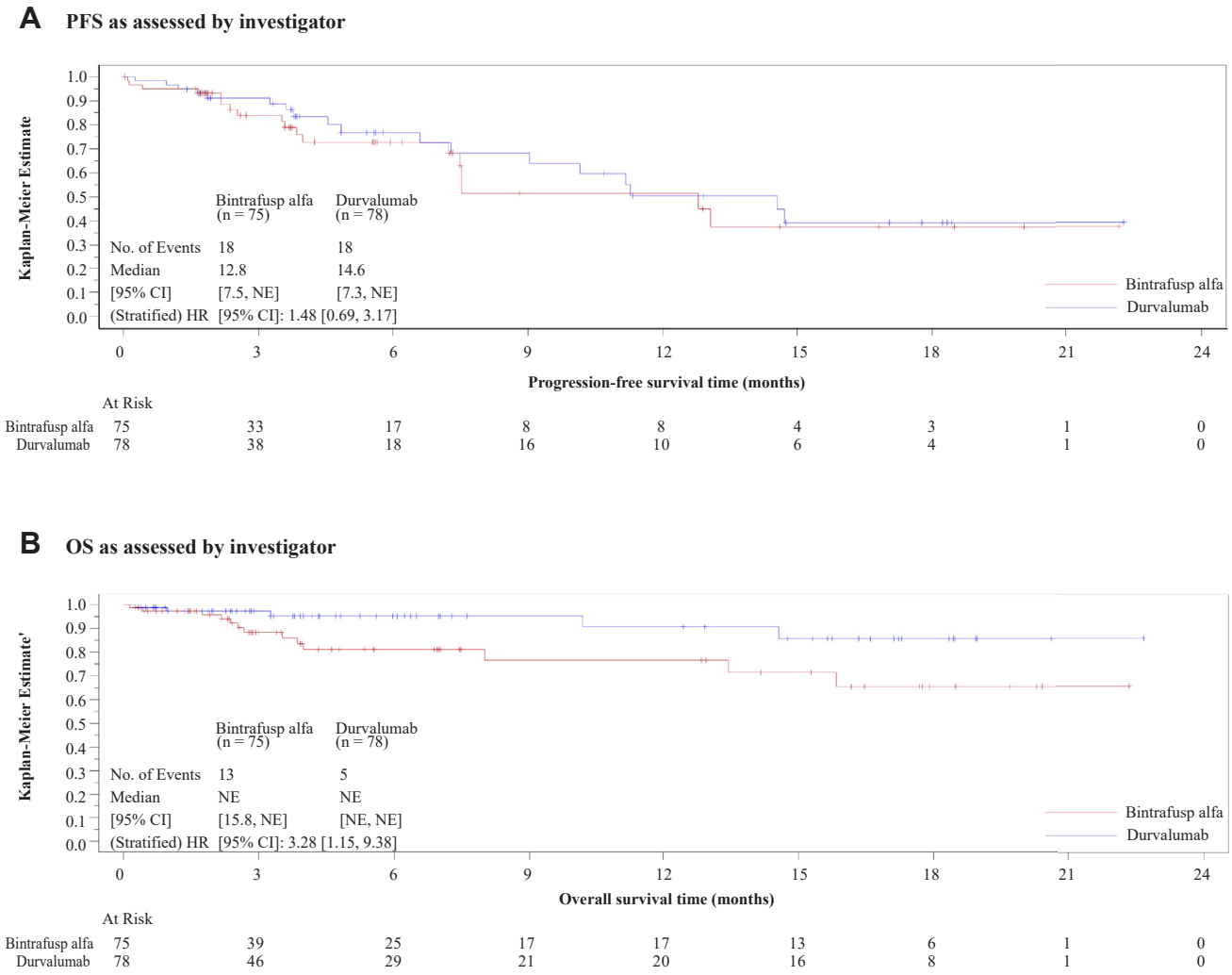

Figure 2. Kaplan-Meier curves for (*A*) progression-free survival and (*B*) overall survival according to RECIST 1.1. CI, confidence interval, HR, hazard ratio, NE, not estimable; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

or unexpected safety signals were identified. The incidence of radiation/immune-mediated pneumonitis was similar in both groups (BA versus durvalumab: 21.6% versus 26.0%).

Safety outcomes of BA are in line with those reported for vascular endothelial growth factor inhibitors, bevacizumab, and ramucirumab, which are approved for use in patients with NSCLC. The proportion of patients with grade 3 bleeding events in the E4599 trial of bevacizumab plus chemotherapy (4.4% [epistaxis, 0.7%; hemoptysis, 0.5%; melena or gastrointestinal bleeding, 0.7% and other hemorrhage, 0.2%]]) was lower compared with that reported with BA in the present study (6.8%); there were a total of five treatment-related deaths because of pulmonary hemorrhage with bevacizumab plus chemotherapy.[25] The rates of anemia (grade $\geq$3) and bleeding (severe AEs of interest) in the AVAiL trial of bevacizumab were 10% and 4%, respectively.[26] AEs associated with bevacizumab include neutropenia, vomiting, hypertension, proteinuria, and bleeding.[25,26] The REVEL trial reported lower rates of bleeding or hemorrhage (AESI) in the ramucirumab plus chemotherapy group as compared with that seen with BA in this study (any-grade, 29.0% versus 40.5% and grade $\geq$3, 2% versus 6.8%). Deaths from grade 3 or higher pulmonary hemorrhage with ramucirumab were reported in 8 (1%) patients and the most common grade 3 or higher TEAEs ($\geq$5%) were neutropenia (49%), febrile neutropenia (16%), fatigue (14%), leucopenia (14%), hypertension (6%), and diarrhea (5%).[27] PFS and OS outcomes observed in this study were consistent with earlier studies of durvalumab.[4,6,28,29] The median PFS observed with BA with cCRT in this study (12.8 mo) was similar to the median PFS reported in the NICOLAS (nivolumab with cCRT, 12.7 mo)[9] and DETERRED (atezolizumab with cCRT, 13.2 mo)[11]; trials but shorter than

Table 3. Summary of TEAEs and TRAEs

Patients With TEAEs, n (%)	BA With cCRT Followed by BA (n = 74)		Placebo With cCRT Followed by Durvalumab (n = 77)	
Any-grade TEAE	70 (94.6)		74 (96.1)	
Grade ≥3 TEAE	64 (86.5)		51 (66.2)	
Grade ≥4 TEAE	20 (27.0)		6 (7.8)	
Any serious TEAE	43 (58.1)		31 (40.3)	
Any TEAE leading to permanent discontinuation of at least one study intervention	26 (35.1)		12 (15.6)	
TEAE leading to death	8 (10.8)		3 (3.9)	
Patients with TRAEs, n (%)	**Any-grade**	**Grade ≥3**	**Any-grade**	**Grade ≥3**
Immunotherapy-related AEs	**48 (64.9)**	**24 (32.4)**	**48 (62.3)**	**12 (15.6)**
Most common immunotherapy-related TEAEs in ≥15% of patients in any group				
Pruritus	12 (16.2)	1 (1.4)	5 (6.5)	0
Rash	19 (25.7)	0	5 (6.5)	0
Radiotherapy-related AEs	**59 (79.7)**	**26 (35.1)**	**60 (77.9)**	**21 (27.3)**
Most common radiotherapy-related TEAEs in ≥25% of patients				
Esophagitis	15 (20.3)	2 (2.7)	24 (31.2)	4 (5.2)
Decreased white blood cell count	15 (20.3)	7 (9.5)	20 (26.0)	7 (9.1)
Chemotherapy-related AEs	**68 (91.9)**	**48 (64.9)**	**69 (89.6)**	**38 (49.4)**
Most common cisplatin-related TEAEs in ≥15% of patients				
Anemia	13 (17.6)	4 (5.4)	13 (16.9)	2 (2.6)
Decreased neutrophil count	8 (10.8)	6 (8.1)	12 (15.6)	5 (6.5)
Most common etoposide-related TEAEs in ≥10% of patients				
Anemia	4 (5.4)	0	8 (10.4)	2 (2.6)
Most common carboplatin-related TEAEs in ≥20% of patients				
Anemia	19 (25.7)	2 (2.7)	14 (18.2)	2 (2.6)
Decreased white blood cell count	14 (18.9)	6 (8.1)	18 (23.4)	9 (11.7)
Nausea	13 (17.6)	1 (1.4)	17 (22.1)	0
Most common paclitaxel-related TEAEs in ≥20% of patients				
Anemia	19 (25.7)	2 (2.7)	14 (18.2)	2 (2.6)
Decreased white blood cell count	14 (18.9)	6 (8.1)	18 (23.4)	9 (11.7)
Nausea	13 (17.6)	1 (1.4)	16 (20.8)	0
Most common pemetrexed-related TEAEs in ≥10% of patients				
Anemia	8 (10.8)	3 (4.1)	5 (6.5)	0

AE, adverse event; BA, bintrafusp alfa; cCRT, concurrent chemoradiotherapy; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Table 4. Summary of AESIs

Patients With AESI of Any-Grade, n (%)	BA With cCRT Followed by BA (n = 74)	Placebo With cCRT Followed by Durvalumab (n = 77)
Any AESI		
Infusion-related reaction	7 (9.5)	7 (9.1)
Anemia	38 (51.4)	32 (41.6)
Radiation/immune-mediated pneumonitis	16 (21.6)	20 (26.0)
Immune-related AESI	**16 (21.6)**	**16 (20.8)**
Skin AESI	**5 (6.8)**	**0**
Keratoacanthoma	4 (5.4)	0
Actinic keratosis	1 (1.4)	0
Bowen's disease	1 (1.4)	0
Bleeding events	**30 (40.5)**	**7 (9.1)**
Gingival bleeding	2 (2.7)	0
Rectal hemorrhage	4 (5.4)	0
Epistaxis	13 (17.6)	2 (2.6)
Hemoptysis	7 (9.5)	4 (5.2)

AESI, adverse event of special interest; BA, bintrafusp alfa; cCRT, concurrent chemoradiotherapy.

the median PFS observed in the PACIFIC (consolidation durvalumab after cCRT, 5-y data: 16.9 mo),[8] and KEYNOTE-799 studies (pembrolizumab with cCRT, 2-y data: 30.6 mo).[30] The ORR observed with BA (29.3%) was considerably lower than the ORR reported in the KEYNOTE-799 (2-y update, 71.4%)[30] and NICOLAS (73.4%)[9] trials.

Several ongoing trials are evaluating anti–PD-L1 and anti–PD-1 (anti–PD-[L]1) agents with cCRT in patients with unresectable stage III NSCLC. PACIFIC-2,[31] CLOVER,[32] and CheckMate 73L[33] will evaluate the safety and efficacy of durvalumab and nivolumab with or without novel agents (e.g., tremelimumab, ipilimumab). Building on the current SoC strategy is the COAST phase 2 study that evaluates durvalumab alone or in combination with oleclumab or monalizumab as consolidation therapy in patients with unresectable stage III NSCLC who had not progressed after cCRT.[34] Although these trials will investigate anti–PD-(L)1 agents in combination with CRT for the treatment of advanced NSCLC, none will evaluate the effects of simultaneous inhibition of the TGF-β and PD-L1 pathways.[35] The results of the present study are consistent with those of an investigation of BA as a first-line therapy in patients with advanced NSCLC with high PD-L1 expression, which failed to exhibit an efficacy advantage over pembrolizumab (in press).[36] Therefore, the development of BA in this context has been discontinued. However, further investigation of dual-targeting agents that localize TGF-β inhibition within the TME is warranted.

Limitations

One major limitation of the study was the early discontinuation and, therefore, immaturity of PFS and OS data; approximately 26% of patients in each treatment group were nonevaluable for efficacy outcomes. Given the early discontinuation of the study, most patients did not experience events by the time of data cutoff and were, therefore, censored for analysis. The median PFS was estimated on the basis of 18 events in each treatment arm and the median OS was estimated on the basis of 13 events in the BA group and five events in the durvalumab group. Furthermore, treatment response for ORR or DCR analysis was not evaluable in 20 patients each treated with BA and durvalumab. Thus, only a limited interpretation of efficacy signals observed in the study is possible. The TGF-β rich TME promotes tumor survival mechanisms and antitumor responses by means of multiple pathways.[11] It is, therefore, possible that the specific inhibition mechanism of TGF-β around so many active pathways cannot alone contribute to clinically relevant efficacy. To date, no response biomarker for TGF-β inhibition has been identified, limiting our understanding of its biology.

In conclusion, BA with cCRT followed by BA exhibited no efficacy benefit over placebo with cCRT followed by durvalumab in patients with stage III unresectable NSCLC. The study highlights the need for further investigation into the pathophysiology of NSCLC to generate insights into future immuno-oncology treatment approaches.

CRediT Authorship Contribution Statement

Everett E. Vokes: Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – Review and Editing, Visualization, Project Administration.

Francoise Mornex: Methodology, Investigation, Data curation, Formal analysis, Writing—original draft, Writing—review and editing.

Ahmet Sezer, Ying Cheng, Jian Fang, David Vicente Baz, Timucin Cil, Alex A. Adjei, Myung-Ju Ahn, Fabrice Barlesi, Enriqueta Felip, Edward B. Garon, Claudio Marcelo Martin, Martin Reck, Clifford G. Robinson: Investigation, Data curation, Formal analysis, Writing—original draft, Writing—review and editing.

Francois Audhuy, Rena Ito, Masashi Sato, S Peter Eggleton: Methodology, Data curation, Formal analysis, Writing—original draft, Writing—review and editing.

Luis G. Paz-Ares: Conceptualization, Investigation, Methodology, Data curation, Formal analysis, Funding acquisition, Writing—original draft, Writing—review and editing.

Data Availability Statement

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.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2023.09.1452.

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