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Bintrafusp Alfa Versus Pembrolizumab in Patients With Treatment-Naive, Programmed Death-Ligand 1–High Advanced NSCLC: A Randomized, Open-Label, Phase 3 Trial

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ABSTRACT

Introduction: Bintrafusp alfa, a first-in-class bifunctional fusion protein composed of the extracellular domain of TGF-βRII (a TGF-β "trap") fused to a human immunoglobulin G1 monoclonal antibody blocking programmed death-ligand 1 (PD-L1), has exhibited clinical activity in a phase 1 expansion cohort of patients with PD-L1–high advanced NSCLC.

Methods: This adaptive phase 3 trial (NCT03631706) compared the efficacy and safety of bintrafusp alfa versus pembrolizumab as first-line treatment in patients with PD-L1–high advanced NSCLC. Primary end points were progression-free survival according to Response Evaluation Criteria in Solid Tumors version 1.1 per independent review committee and overall survival.

Results: Patients (N = 304) were randomized one-to-one to receive either bintrafusp alfa or pembrolizumab (n = 152 each). The median follow-up was 14.3 months (95% confidence interval [CI]: 13.1–16.0 mo) for bintrafusp alfa and 14.5 months (95% CI: 13.1–15.9 mo) for pembrolizumab. Progression-free survival by independent review committee was not significantly different between bintrafusp alfa and pembrolizumab arms (median = 7.0 mo [95% CI: 4.2 mo–not reached (NR)] versus 11.1 mo [95% CI: 8.1 mo–NR]; hazard ratio = 1.232 [95% CI: 0.885–1.714]). The median overall survival was 21.1 months (95% CI: 21.1 mo–NR) for bintrafusp alfa and 22.1 months (95% CI: 20.4 mo–NR) for pembrolizumab (hazard ratio = 1.201 [95% CI: 0.796–1.811]). Treatment-related adverse events were higher with bintrafusp alfa versus pembrolizumab; grade 3-4 treatment-related adverse events occurred in 42.4% versus 13.2% of patients, respectively. The study was discontinued at an interim analysis as it was unlikely to meet the primary end point.

Conclusions: First-line treatment with bintrafusp alfa did not exhibit superior efficacy compared with pembrolizumab in patients with PD-L1–high, advanced NSCLC.

Introduction

NSCLC accounts for approximately 85% of all lung cancers and is the leading cause of cancer deaths worldwide, accounting for 18% of total cancer deaths in 2020.[1,2] Pembrolizumab is a monoclonal antibody targeting programmed death 1 and is a standard of care in the first line for patients with programmed death-ligand 1 (PD-L1)–positive (≥1%) advanced NSCLC.[3] Approval was granted for patients with PD-L1 tumor proportion score (TPS) greater than or equal to 50% on the basis of the phase 3 KEYNOTE-024 trial,[4] in which pembrolizumab had improved median progression-free survival (PFS) versus chemotherapy (10.3 versus 6.0 mo), and objective response rate (45% versus 28%).[5] In an updated analysis, after 5 years of follow-up, the median overall survival (OS) was 26.3 months (95% confidence interval [CI]: 18.3-40.4) with pembrolizumab versus 13.4 months (95% CI: 9.4–18.3) with chemotherapy (hazard ratio [HR] = 0.62; 95% CI: 0.48–0.81).[6] The U.S. Food and Drug Administration approval was later expanded to include patients with PD-L1 TPS greater than or equal to 1%, on the basis of the results of the KEYNOTE-042 study.[7] Besides KEYNOTE-024[5] and KEYNOTE-042,[7] several other phase 3 studies have evaluated the use of immune checkpoint inhibitors in patients with PD-L1–high (assessed per 22C3 assay) advanced NSCLC, such as atezolizumab (IMpower110), and cemiplimab (EMPOWER-Lung 1).[8,9] In these studies, in patients with PD-L1 TPS greater than or equal to 50%, the median OS was 20.0 months with pembrolizumab, 20.2 months with atezolizumab, and not reached (NR) with cemiplimab; the median PFS (mPFS) ranged from 7.1 to 8.2 months, and objective response rates (ORRs) reported for pembrolizumab and cemiplimab were both 39%.[7–9] It is important to note that PD-L1 immunohistochemistry assays have since been compared in studies using clinical samples. Compared with the 22C3 assay, the PD-L1 73-10 assay seemed more sensitive for PD-L1 staining, with a cutoff value of 80% PD-L1–positive tumor being most similar to the cutoff value of at least 50% for the 22C3 assay.[10]

Despite improvements in treatment outcomes after the introduction of immune checkpoint inhibitors in patients with advanced NSCLC, an unmet need remains for effective treatments in this population, as many patients develop resistance to anti–PD-(L)1 therapies.[11] Transforming growth factor β (TGF-β) is expressed in NSCLC tissue and is associated with tumor progression, metastasis, and resistance to anticancer treatments.[12,13] TGF-β overexpression in cancer has been associated with metastasis in the tumor microenvironment because of suppressed immunosurveillance.[14] Moreover, increased expression of TGF-β can contribute to the lack of response to PD-L1 blockade because of restriction of T-cell infiltration in the tumor microenvironment.[15,16] Combining immune checkpoint inhibition with blockade of TGF-β signaling could, therefore, be a promising treatment strategy.[14]

Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of the human TGF-β receptor II (TGF-βRII or TGF-β "trap") fused by means of a flexible linker to the C-terminus of each heavy chain of an immunoglobulin G1 antibody blocking programmed death-ligand 1 (anti–PD-L1).[17,18] Preclinical data have revealed that bintrafusp alfa can simultaneously inhibit both PD-L1 and TGF-β pathways.[18,19] A phase 1 study of second-line treatment with bintrafusp alfa 1200 mg reported that bintrafusp alfa had a manageable safety profile and exhibited promising clinical activity in a subset of patients with PD-L1–high advanced NSCLC, with a confirmed ORR of 85.7% in PD-L1–high (≥80% PD-L1–positive tumor cells using the PD-L1 73-10 assay) patients (ORR of 37.0% in PD-L1-positive [≥1%] patients).[20] The mPFS for PD-L1–positive and PD-L1–high patients was 9.5 months and 15.2 months, respectively; the median OS was NR for either population after a median follow-up of 51.9 weeks.[20] The median duration of response (assessed by the independent review committee [IRC]) was NR.[20] On the basis of these results, we conducted this phase 3 trial comparing bintrafusp alfa with pembrolizumab in the first-line treatment of patients with advanced NSCLC and high PD-L1 expression.

Materials and methods

Study Design and Participants

The adaptive INTR@PID LUNG 037 trial (NCT03631706) was a global, randomized, open-label, phase 3 trial comparing the efficacy and safety of bintrafusp alfa with pembrolizumab in the first-line treatment of patients with advanced, PD-L1–high NSCLC. PD-L1 high expression was defined as greater than or equal to 80% PD-L1–positive tumor cells, as determined by the PD-L1 immunohistochemistry 73-10 assay (Dako North America, Inc., Carpinteria, CA).

Additional PD-L1 expression analyses were also conducted, which included centralized laboratory testing with the Ventana PD-L1 SP263 assay (Ventana Medical Systems) and localized laboratory testing using the 22C3 pharmDx test (Dako North America, Inc., Carpinteria, CA). For these two assays, PD-L1 high expression was defined

as greater than or equal to 50% PD-L1–positive tumor cells. Of note, previous studies have reported that the cutoff value of at least 50% PD-L1–positive tumor cells using the 22C3 assay was similar to the cutoff value of at least 80% PD-L1–positive tumor cells using the 73-10 assay.[10]

Patients were recruited from 115 sites across 18 countries and four regions: North America (Canada and United States), Europe (Belgium, France, Germany, Greece, Italy, Netherlands, Spain, Turkey, and Ukraine), Asia (People's Republic of China, Hong Kong, Japan, Republic of Korea, and Taiwan), and South America (Argentina and Brazil). Key inclusion criteria included the following: (1) age 18 years and older; (2) no previous systemic treatment for advanced NSCLC; (3) measurable disease on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; (4) availability of tumor archival material (<6 mo old) or fresh biopsies collected not later than 28 days before the first dose; (5) Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate organ function and life expectancy of at least 3 months. Key exclusion criteria included the following: (1) patients with tumors containing actionable mutations for which targeted therapy was locally approved (e.g., *EGFR*, *ALK*, *ROS1*, *BRAF* V600E); (2) previous malignant disease within the past 3 years; (3) major surgery not later than 4 weeks before enrollment or thoracic radiotherapy of greater than 30 Gy within 6 months before the first dose of study treatment; (4) previous immunotherapy; and (5) active brain metastases. Full eligibility criteria are available in the Supplementary Methods.

This study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines, including the Declaration of Helsinki, Council for International Organizations of Medical Sciences, International Ethical Guidelines, applicable International Conference on Harmonisation Good Clinical Practice guidelines, the Japanese Ministerial Ordinance on Good Clinical Practice, and other applicable laws and regulations.

Randomization

Patients were randomized one-to-one to receive either bintrafusp alfa or pembrolizumab using an interactive web response system. Randomization was stratified by histologic diagnosis and smoking history: (1) squamous histologic structure; (2) nonsquamous histologic structure and never smoked; and (3) nonsquamous histologic structure with a smoking history.

Procedures

The study included a 28-day screening period. Eligible patients received intravenous infusions of bintrafusp alfa 1200 mg every 2 weeks or pembrolizumab 200 mg every 3 weeks until confirmed disease progression, unacceptable toxicity, or for up to 24 months. Though this study was discontinued at an interim analysis, patients could remain on study treatment at the investigator's discretion and on previous evaluation of benefit and risk.

Tumor evaluation by contrast-enhanced computed tomography or magnetic resonance imaging was performed every 6 weeks up to 18 months, then every 12 weeks. Tumor responses were assessed according to RECIST 1.1. Responses were confirmed by imaging at or after more than 4 weeks from the first documentation of response.

Safety follow-up continued up to 12 weeks after the last dose of study treatment. Safety assessments included the occurrence of adverse events (AEs), clinical laboratory tests (hematology and serum chemistry), physical examination, and skin assessment. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Outcomes

The primary end points for the study were PFS according to RECIST 1.1 as adjudicated by the IRC, and OS. Secondary end points included ORR and duration of response (DOR) by RECIST 1.1 as adjudicated by the IRC, safety per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, the pharmacokinetic profile of bintrafusp alfa, immunogenicity (antidrug antibodies at baseline and on treatment) and biomarkers.

Statistical Analysis

The study had an adaptive phase 3 study design with dual primary end points (PFS and OS), which were evaluated in a confirmatory analysis with the aim to illustrate the superiority of bintrafusp alfa over pembrolizumab using one-sided stratified log-rank tests, taking the randomization strata into account and controlling the overall significance at a target alpha level of 2.5% one-sided.

The sample-size calculation was planned for the primary analysis population (full analysis set) and on the basis of the following assumptions: (1) the exponential distribution of PFS and OS in each arm and stratum; (2) one-to-one randomization; (3) a constant hazard ratio for OS and PFS in all strata; and (4) accrual of 15 patients per month over a period of 20 months to reach an N of 300.

After guidance from the independent data monitoring committee, on 20 January 2021, the decision was made
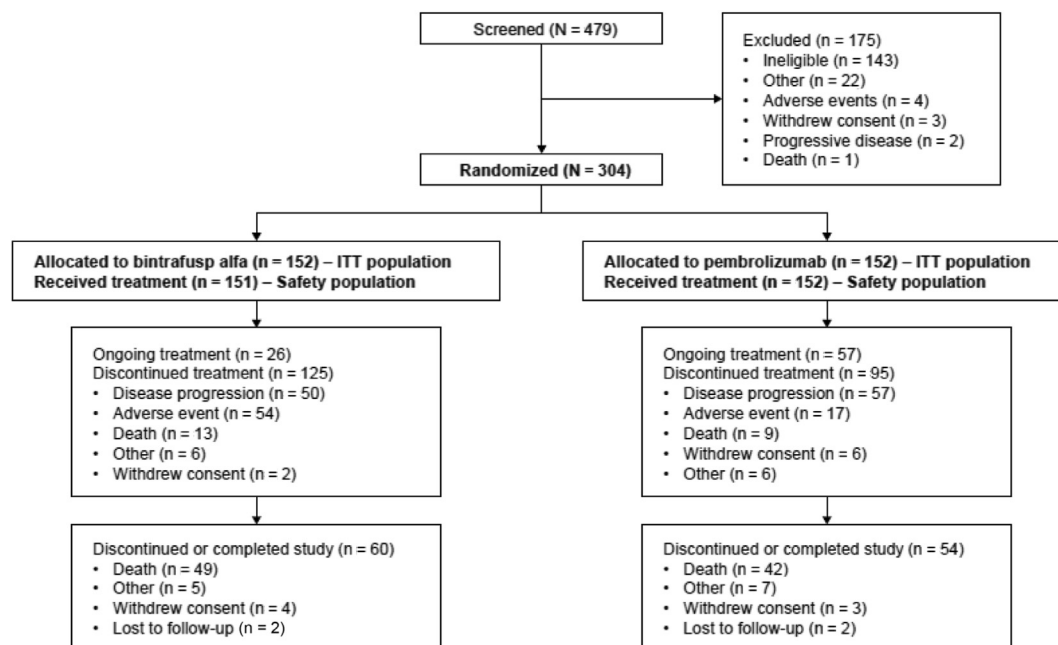
Figure 1. Patient disposition. ITT, intention-to-treat.

to discontinue the study early as it was unlikely to meet its primary end point. Therefore, the study included two data cutoff dates: (1) all efficacy analyses (except OS) were performed on the basis of data for the PFS interim analysis with a cutoff date of 15 October 2020; and (2) safety and OS analyses were performed on the basis of data with a cutoff date of 20 January 2021. OS analyses were, therefore, considered exploratory because of the early discontinuation of the study. PFS and OS analyses were performed using Kaplan-Meier methods on the full analysis set. The treatment effect was estimated using Cox's proportional hazard model stratified by the randomization strata to calculate hazard ratios. Safety was tabulated using descriptive statistics.

Results

A total of 479 patients were screened and 304 patients were randomly assigned to bintrafusp alfa or pembrolizumab (n = 152 each) (Fig. 1). As of January 20, 2021, the median follow–up was 14.3 months (95% CI: 13.1–16.0 mo) for the bintrafusp alfa arm and 14.5 months (95% CI: 13.1–15.9) for the pembrolizumab arm. All but one patient randomized to bintrafusp alfa received at least one treatment dose and were included in the safety population (n = 151). Treatment was ongoing in 26 patients (17.1%) in the bintrafusp alfa arm and 57 patients (37.5%) in the pembrolizumab arm at the time of the January 20, 2021, data cutoff. The median duration of treatment was 26.0 months (range: 2.0–90.6 mo) with bintrafusp alfa and 37.6 months (range: 3.0–96.0 mo) with pembrolizumab. Patient demographics

and baseline disease characteristics were generally well-balanced between treatment arms (Table 1). Most patients were men; the median age in both cohorts was 68 years. In both cohorts, most patients were White or Asian and most had adenocarcinoma. The proportion of patients who experienced dose delays was high in both treatment arms (bintrafusp alfa: 75.5%; pembrolizumab: 75.0%); the longest dose delay of at least 16 days occurred in 35.8% and 28.3% of patients treated with bintrafusp alfa and pembrolizumab, respectively.

Efficacy

PFS by IRC was not significantly different between the bintrafusp alfa and pembrolizumab treatment arms (median = 7.0 mo [95% CI: 4.2–NR] versus 11.1 months [95% CI: 8.1–NR]; HR for PFS was 1.232 [95% CI: 0.885–1.714], $p = 0.89$) (Fig. 2A). Results were similar for investigator-assessed PFS (Supplementary Fig. 1). The mPFS for the PD-L1–high group for the bintrafusp alfa arm was almost identical when analyzed with three different PD-L1 assays (73-10, SP263, and 22C3), and the mPFS was similar for the pembrolizumab arm using two of the PD-L1 assays (73-10 and SP263) (Supplementary Table 1). The median OS was comparable between the bintrafusp alfa and pembrolizumab treatment arms; the median OS was 21.1 months (95% CI: 21.1–NR) with bintrafusp alfa, compared with 22.1 months (95% CI: 20.4–NR) with pembrolizumab (HR for OS was 1.201 [95% CI: 0.796–1.811]; $p = 0.81$) (Fig. 2B).

The unconfirmed ORR by IRC was similar in the bintrafusp alfa and pembrolizumab treatment arms

Table 1. Demographics and Baseline Characteristics

Characteristic	Bintrafusp Alfa n = 152	Pembrolizumab n = 152
Sex, n (%)		
Male	110 (72.4)	116 (76.3)
Female	42 (27.6)	36 (23.7)
Race, n (%)		
White	91 (59.9)	79 (52.0)
Asian	50 (32.9)	55 (36.2)
Black or African American	1 (0.7)	0 (0.0)
Other[a]	10 (6.6)	18 (11.8)
Age, y		
Median (Q1--Q3)	68 (62-73)	68 (61-75)
Age categories, y, n (%)		
<65	51 (33.6)	62 (40.8)
≥65	101 (66.4)	90 (59.2)
Smoking history, n (%)		
Never-smoker	12 (7.9)	13 (8.6)
Ever smoker	140 (92.1)	139 (91.4)
Former	110 (72.4)	105 (69.1)
Current	30 (19.7)	34 (22.4)
Histologic diagnosis, n (%)		
Adenocarcinoma	100 (65.8)	102 (67.1)
Squamous cell carcinoma	45 (29.6)	44 (28.9)
Sarcomatoid carcinoma	3 (2.0)	0
Adenosquamous carcinoma	1 (0.7)	1 (0.7)
Other	3 (2.0)[b]	5 (3.3)[c]
Time since initial cancer diagnosis, months		
Median (Q1-Q3)	1.6 (1.2-2.5)	1.6 (1.2-2.4)
Time since documented locally advanced, inoperable or metastatic disease, months		
Median (Q1-Q3)	1.4 (1.1-2.0)	1.4 (1.1-2.0)
PD-L1 expression (central 73-10 assay), n		
High (≥80%)	138	141
Not high (<80%)	13	8
Unevaluable	1	3
PD-L1 expression (central SP263 assay), n		
High (≥50%)	107	104
Not high (<50%)	15	13
Unevaluable	2	4
Missing	28	31
PD-L1 expression (local 22C3 IHC assay), n		
High (≥50%)	104	98
Not high (<50%)	3	0
Missing	45	54

[a]Other includes patients whose race was not collected at the site or patients of mixed race.
[b]Includes patients with histologies classified as nonsquamous carcinoma, lymphoepithelioma-like carcinoma, and poorly differentiated lung carcinoma mixed with medium and large cells (n = 1 each).
[c]Includes patients with histologies classified as NOS, poorly differentiated, nonsquamous cell carcinoma, pleomorphic carcinoma (adenocarcinoma [20%] and spindle cell sarcomatous area [80%]), and pleomorphic carcinoma + adenocarcinoma (n = 1 each).
IHC, immunohistochemistry; NOS, not otherwise specified; PD-L1, programmed death-ligand 1; Q, quartile.

(46.7% [95% CI: 38.6–55.0] versus 51.3% [95% CI: 43.1–59.5], $p = 0.41$) (Table 2). The median DOR was NR in either treatment arm.

Safety

A higher proportion of patients treated with bintrafusp alfa had any-grade treatment-related AEs (TRAEs) compared with pembrolizumab (82.1% [grade 3-4 42.4%] versus 69.1% [grade 3-4 13.2%]) (Table 3). The most common TRAEs (classified by system-organ class and preferred term) with bintrafusp alfa were pruritus (31.8%), rash (29.1%), diarrhea (12.6%), rash maculopapular (11.3%), aspartate aminotransferase increased (11.3%), asthenia (11.3%), fatigue (11.3%),

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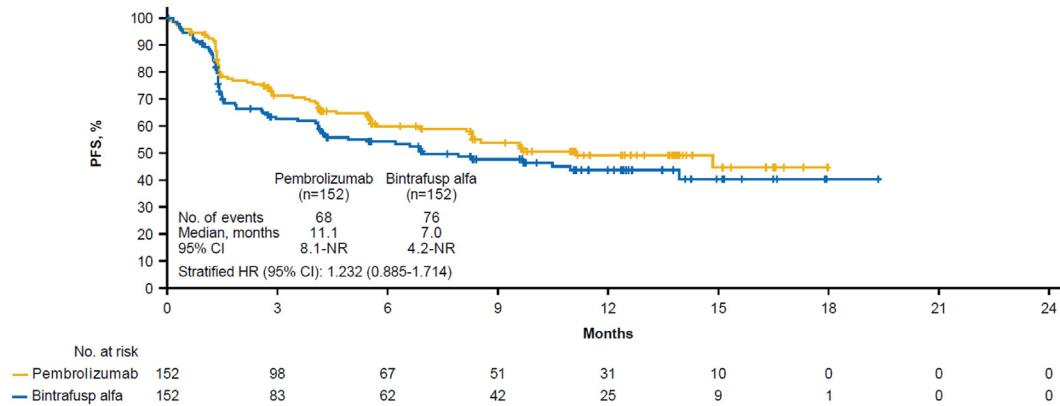
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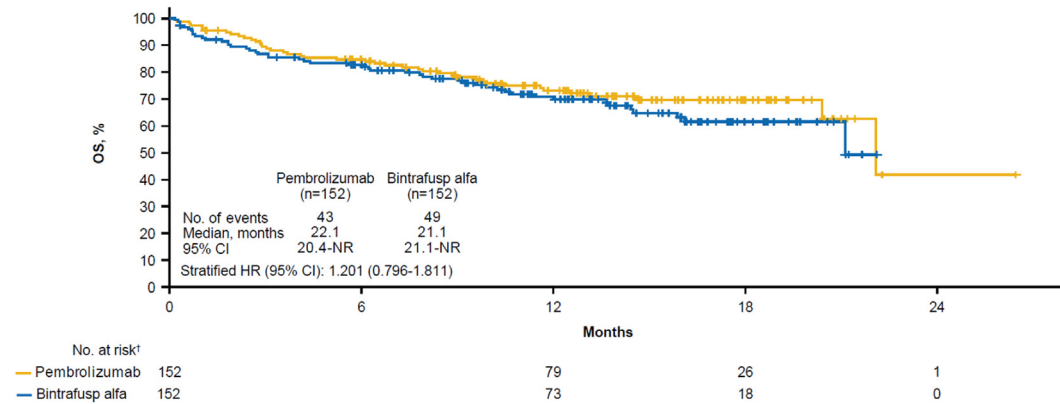
Figure 2. PFS per RECIST 1.1 by IRC and OS. (*A*) PFS primary end point (cutoff date: 15 October 2020). (*B*) OS* exploratory end point (cutoff date: 20 January 2021). *Considered as exploratory analysis because of early discontinuation of the study (cutoff date of January 20, 2021). [†]Number of patients at risk not available for the 6-month time point. CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 2. Summary of Response

Outcome	Bintrafusp Alfa n = 152		Pembrolizumab n = 152
Best overall response, n (%)[a]			
Complete response	1 (0.7)		2 (1.3)
Partial response	70 (46.1)		76 (50.0)
Stable disease	24 (15.8)		29 (19.1)
Progressive disease	39 (25.7)		31 (20.4)
Not evaluable	18 (11.8)		14 (9.2)
Unconfirmed ORR (95% CI), %[b]	46.7 (38.6-55.0)		51.3 (43.1-59.5)
p-Value[c]		0.4125	
Median DOR (95% CI), mo	NR (NR-NR)		NR (13.5-NR)

[a]Unconfirmed objective response according to RECIST 1.1 assessed by IRC.
[b]Best overall response assessment of complete response or partial response. 95% exact confidence interval using the Clopper-Pearson method.
[c]p-Value from two-sided Cochran-Mantel-Haenszel test taking into account the randomization strata.
CI, confidence interval; DOR, duration of response; IRC, independent review committee; NR, not reached; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 3. TRAEs Occurring at Any Grade in Greater Than or Equal to 5% of Patients or at Grade 3 or Higher Severity in More Than One Patient

TRAEs	Bintrafusp Alfa n = 151		Pembrolizumab n = 152	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with at least one event, n (%)	124 (82.1)	64 (42.4)	105 (69.1)	20 (13.2)
Pruritus	48 (31.8)	6 (4.0)	39 (25.7)	0
Rash	44 (29.1)	5 (3.3)	20 (13.2)	0
Diarrhea	19 (12.6)	1 (0.7)	12 (7.9)	0
Rash maculopapular	17 (11.3)	4 (2.6)	5 (3.3)	1 (0.7)
Aspartate aminotransferase increased	17 (11.3)	3 (2.0)	13 (8.6)	1 (0.7)
Asthenia	17 (11.3)	1 (0.7)	19 (12.5)	1 (0.7)
Fatigue	17 (11.3)	0	9 (5.9)	0
Anemia	16 (10.6)	7 (4.6)	4 (2.6)	0
Hypothyroidism	16 (10.6)	0	20 (13.2)	0
Keratoacanthoma	15 (9.9)	1 (0.7)	0	0
Alanine aminotransferase increased	14 (9.3)	4 (2.6)	13 (8.6)	1 (0.7)
Decreased appetite	14 (9.3)	0	11 (7.2)	0
Lipase increased	12 (7.9)	6 (4.0)	7 (4.6)	1 (0.7)
Pyrexia	12 (7.9)	0	6 (3.9)	0
Gamma-glutamyltransferase increased	11 (7.3)	8 (5.3)	5 (3.3)	1 (0.7)
Nausea	11 (7.3)	1 (0.7)	6 (3.9)	0
Blood alkaline phosphatase increased	10 (6.6)	3 (2.0)	3 (2.0)	1 (0.7)
Arthralgia	10 (6.6)	0	11 (7.2)	0
Squamous cell carcinoma of skin	9 (6.0)	2 (1.3)	0	0
Amylase increased	8 (5.3)	1 (0.7)	7 (4.6)	0
Rash pruritic	8 (5.3)	1 (0.7)	4 (2.6)	0
Myalgia	8 (5.3)	0	7 (4.6)	0
Eczema	7 (4.6)	2 (1.3)	1 (0.7)	0
Hyperkeratosis	7 (4.6)	2 (1.3)	0	0
Hyperthyroidism	5 (3.3)	0	9 (5.9)	0
Hepatitis	3 (2.0)	3 (2.0)	1 (0.7)	1 (0.7)
Colitis	3 (2.0)	2 (1.3)	0	0
Erythema multiforme	3 (2.0)	2 (1.3)	0	0
Pemphigoid	3 (2.0)	2 (1.3)	0	0
Pneumonia	0	0	5 (3.3)	2 (1.3)
Any TGF-β inhibition-mediated skin AEs, n (%)[a]	32 (21.1)	5 (3.3)	0	0
Any immune-related AEs, n (%)	80 (53.0)	35 (23.2)	53 (34.9)	12 (7.9)

[a]Includes keratoacanthoma, squamous cell carcinoma of skin, hyperkeratosis, actinic keratosis, basal cell carcinoma, lip squamous cell carcinoma, and Bowen disease.

AE, adverse event; TGF-β, transforming growth factor-β; TRAE, treatment-related adverse event.

anemia (10.6%), and hypothyroidism (10.6%). With pembrolizumab, the most common TRAEs were pruritus (25.7%), rash (13.2%), and hypothyroidism (13.2%). TRAEs led to death in one patient (0.7%) in the bintrafusp alfa arm because of pulmonary hemorrhage and in two patients (1.3%) in the pembrolizumab arm because of myocarditis and myositis (n = 1), and pneumonia (n = 1). Serious AEs that were deemed treatment-related occurred in 41 patients (27.2%) treated with bintrafusp alfa and 18 patients (11.8%) treated with pembrolizumab.

TRAEs led to discontinuation in 25.8% of patients in the bintrafusp alfa arm and 6.6% of patients in the pembrolizumab arm. The most common TRAEs (≥2% incidence) leading to permanent discontinuation with bintrafusp alfa treatment were disease progression (2.6%) and increased levels of alanine aminotransferase, blood alkaline phosphatase, dyspnea, gamma-glutamyltransferase, and maculopapular rash (each 2.0%); in the pembrolizumab treatment arm, the most common TRAEs leading to permanent discontinuation were disease progression (2.6%) and pneumonia (2.0%). Temporary treatment discontinuations because of TRAEs occurred at a higher proportion in the bintrafusp alfa arm (67.5%) compared with the pembrolizumab arm (29.6%). The most common TRAEs (≥5% incidence) leading to temporary discontinuation in the bintrafusp alfa arm were the following: (1) pruritus (7.9%); (2) rash (6.6%); (3) maculopapular rash, pneumonia, and aspartate aminotransferase increase (each 6.0%); and (4) increased

alanine aminotransferase (5.3%). In the pembrolizumab treatment arm, the most common TRAE was pneumonia (5.9%).

The AEs of special interest are reported in Supplementary Table 2. Immune-related AEs occurred in 53.0% of patients in the bintrafusp alfa arm and 34.9% of patients in the pembrolizumab arm. TGF-β inhibition–mediated skin AEs occurred in 21.2% of patients treated with bintrafusp alfa, with no patients receiving pembrolizumab reporting these AEs. Events were generally manageable with skin lesion excision, cryotherapy, and skin and subcutaneous tissue therapeutic procedures. Most of the TGF-β inhibition–mediated skin AEs resolved; no patient discontinued because of TGF-β inhibition–mediated skin AE. Overall, the rates of skin and subcutaneous tissue disorders were greater in the bintrafusp alfa arm compared with the pembrolizumab arm (61.6% versus 37.5%; serious: 7.3% versus 0.7%), with 9.9% versus 0% leading to treatment discontinuation, respectively. Despite this, a post hoc analysis of patients with TGF-β inhibition–mediated skin AEs found no difference in median duration of unconfirmed response among patients with and without TGF-β inhibition–mediated skin AEs. Bleeding events and anemia, AEs thought to be associated with TGF-β inhibition, were more common with bintrafusp alfa (36.4% and 31.1%, respectively) than with pembrolizumab (11.8% each). The safety profile in patients with squamous versus nonsquamous histologic structure was comparable; proportions of TRAEs and AESIs were comparable between histologic types (Supplementary Table 3).

Pharmacokinetics and Immunogenicity

Bintrafusp alfa concentrations achieved steady state after day 43, with geometric mean C_{trough} of greater than 90 μg/mL following the 1200 mg every-2-week dosing (Supplementary Table 4), reaching target concentrations for PD-L1 occupancy and TGF-β inhibition in circulation. More than half (53.5%) of patients in the bintrafusp alfa group remained negative for antidrug antibodies throughout the study. A proportion of patients in the bintrafusp alfa group were positive for neutralizing antibodies as assessed by either PD-L1 (22.9%) or TGF-β (16.7%) assays (both assays: 13.9%) (Supplementary Table 5).

Discussion

In this phase 3 study, in a select population of patients with high PD-L1– expressing advanced NSCLC, the primary efficacy end point of superior PFS per RECIST 1.1 with bintrafusp alfa was not met; first-line treatment with bintrafusp alfa did not exhibit efficacy benefit over pembrolizumab (mPFS = 7.0 mo [95% CI: 4.2–NR]

versus 11.1 mo [95% CI: 8.1–NR], respectively). The study was, therefore, discontinued before the accrual of the protocol-defined number of OS events required for the OS primary analysis, although exploratory analysis exhibited similar OS with bintrafusp alfa and pembrolizumab treatment. The ORR was also similar between the two treatment arms.

The efficacy findings from this study are inconsistent with those of previous studies with bintrafusp alfa, though the results with pembrolizumab seem to be similar. Of note, the mPFS for the patients with high PD-L1 expression were generally consistent across the three different commercial assays, and the mPFS reported here (Supplementary Table 1) for pembrolizumab (11.1 mo) using the greater-than-or-equal-to 50% cutoff with the 22C3 assay were also consistent with the results reported from KEYNOTE-24 and KEYNOTE-042 (10.3 mo and 7.1 mo, respectively).[5,7] In other phase 3 trials of immune checkpoint inhibitors in patients with advanced NSCLC, the PFS ranged from 7.2 to 8.2 months,[8,9,21] which is similar to the PFS observed with bintrafusp alfa in this study (7.0 mo [95% CI: 4.2–NR]). However, efficacy findings from the previous phase 1 study of bintrafusp alfa in NSCLC did not translate to the phase 3 study. In the previous study, bintrafusp alfa reported an mPFS of 15.2 months (95% CI:1.3–NR) in patients with high PD-L1 expression (defined as ≥80% expression on tumor cells using the 73-10 assay),[20] although caution should be exercised when interpreting these phase 1 study results, as only seven patients with high PD-L1 expression were evaluated.[20] Notably, despite the early discontinuation of this study, the median OS of 22.1 months for the pembrolizumab treatment arm in the present study was comparable to previous studies; in the KEYNOTE-042 trial the median survival duration was 20.0 months for the PD-L1 high patients (TPS ≥50%) receiving pembrolizumab, whereas in the 5-year follow-up analysis of the KEYNOTE-024 trial, the median OS was 26.3 months for PD-L1 high patients (TPS ≥50%) receiving pembrolizumab.[6,7] Furthermore, the median OS of 21.1 months with bintrafusp alfa in this study was longer than the median OS observed across all patients in the previous phase 1 study (13.6 mo), although median OS was not reached for the PD-L1 high group of patients in that study.[20]

Higher rates of AEs were observed in the bintrafusp alfa treatment arm compared with the pembrolizumab arm. In addition, a higher proportion of patients receiving bintrafusp alfa reported AEs leading to permanent or temporary treatment discontinuation compared with those receiving pembrolizumab. AEs of special interest, including the previously mentioned TGF-β inhibition–mediated skin AEs, bleeding, and anemia, were more common with bintrafusp alfa compared

with pembrolizumab; however, most of these AEs of special interest were grade 1 or 2. The higher incidence of bleeding events observed with bintrafusp alfa in the present study is consistent with other clinical studies of bintrafusp alfa,[22] in which a higher frequency of low-grade bleeding events has been observed than with immune checkpoint inhibitors[23] or targeted agents.[24] Mechanistically, the association of TGF-β inhibition with bleeding events may be related to the inhibition of the TGF-β2 isoform, a hematopoietic regulator.[22] As bintrafusp alfa has a higher affinity for the TGF-β1 and TGF-β3 isoforms,[25] dose reduction may be a feasible management approach to reduce the probability of bleeding events while retaining pharmacologic activity.[22]

Pharmacokinetic data indicated that bintrafusp alfa reached the desired levels of exposure, and therefore, the lack of superior efficacy over pembrolizumab was probably not because of reduced exposure. In addition, bintrafusp alfa did not exceed the desired levels of exposure; thus, the higher occurrence of AEs cannot be explained by higher pharmacokinetic exposures.

Improved efficacy over pembrolizumab may not have been observed in this study because of the pleiotropic nature of TGF-β signaling, which could contribute to drug resistance and tumor escape, weakening clinical response and outweighing the antitumor effect of anti–PD-(L)1 cancer therapy alone.[14] Moreover, higher rates of AEs in the bintrafusp alfa arm, leading to a higher proportion of patients with temporary or permanent treatment discontinuation could potentially also have resulted in this lack of superior efficacy over pembrolizumab. It is also likely that a further preselected population might benefit from treatment with such dual-targeted immunotherapies.[26] Patient selection by PD-L1 status alone is not sufficient; further exploratory biomarker analyses may determine specific patient populations that could benefit from such combination therapies in the future. Currently, no additional biomarker analyses are being done on archival tissue or blood samples from this study.

This is the largest study involving a TGF-β-inhibitor—more specifically, bintrafusp alfa; however, it is not without limitations. First, the open-label nature of the study may have impacted the investigator's judgment on safety events and treatment discontinuation. Second, the interval between treatments was 1 week shorter for bintrafusp alfa compared with pembrolizumab and may have impacted the comparison of safety between both treatment arms. Finally, the TGF-β analysis was only performed in blood; therefore, TGF-β blockade in tumor cells could not be confirmed.

In conclusion, first-line treatment with bintrafusp alfa did not result in superior efficacy benefit over pembrolizumab in patients with high PD-L1–expressing advanced NSCLC. Further investigation may be warranted to identify the optimal sequence and combination and ideal patient population that would benefit from bintrafusp alfa treatment or other TGF-β inhibitors and to perform larger biomarker analyses.

CRediT Authorship Contribution Statement

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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 of 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, Darmstadt, Germany 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, Darmstadt, Germany will endeavor to gain agreement to share data in response to requests.

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.2023.08.018.

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