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Bintrafusp Alfa for Recurrent or Metastatic Cervical Cancer After Platinum Failure

A Nonrandomized Controlled Trial

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IMPORTANCE Cervical cancer is a common and lethal cancer worldwide. Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of the human transforming growth factor β receptor II (or transforming growth factor β trap) fused via a flexible linker to the C-terminus of each heavy chain of an immunoglobulin G1 antibody blocking programmed cell death 1 ligand 1.

OBJECTIVE To evaluate the safety and response rates of bintrafusp alfa in patients with recurrent or metastatic cervical cancer.

DESIGN, SETTING, AND PARTICIPANTS This phase 2 nonrandomized controlled trial evaluated bintrafusp alfa monotherapy in patients with recurrent or metastatic cervical cancer with disease progression during or after platinum-based chemotherapy. Data were collected from March 2020 to February 2022.

INTERVENTION Patients received bintrafusp alfa, 1200 mg, intravenously once every 2 weeks.

MAIN OUTCOMES AND MEASURES The primary end point was confirmed objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1 by an independent review committee.

RESULTS At data cutoff, 146 of 203 screened patients received 1 or more doses of bintrafusp alfa; of these, the median (range) age was 53 (24-79) years. The study met its primary end point of a 95% CI above the objective response rate benchmark of 15%, with a confirmed objective response rate of 21.9% (95% CI, 15.5-29.5) per the independent review committee. Of these patients, 19 (59.4%) had a durable response of 6 months or more. At data cutoff, responses were ongoing in 13 of 32 responders (40.6%). The most common treatment-related adverse events were anemia (25 [17.1%]), rash (21 [14.4%]), hypothyroidism (15 [10.3%]), and pruritus (15 [10.3%]). Any-cause adverse events of special interest included anemia (82[56.2%]), bleeding events (81 [55.5%]), and immune-related adverse events (49 [33.6%]).

CONCLUSIONS AND RELEVANCE This phase 2 nonrandomized controlled trial of bintrafusp alfa met its primary end point, which may support the potential of a bispecific therapy targeting transforming growth factor β and programmed cell death 1 ligand 1 in patients with recurrent or metastatic cervical cancer.

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Supplemental content

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Globally, cervical cancer is one of the most common and lethal gynecologic cancers.[1] Most cervical cancers are driven by the human papillomavirus (HPV),[2] which has been linked to the upregulation of transforming growth factor β (TGF-β) signaling.[3]

The preferred first-line treatment for patients with persistent, recurrent, or metastatic cervical cancer whose tumors express programmed cell death 1 ligand 1 (PD-L1) is pembrolizumab plus platinum-based chemotherapy, with or without bevacizumab, based on the results of the KEYNOTE-826 trial.[4] However, as pembrolizumab is restricted to those whose tumors express PD-L1, most patients with recurrent or metastatic disease are typically treated with chemotherapy, often with poor response rates and a short duration of response (DOR).[5]

For patients with recurrent or metastatic cervical cancer with disease progression during or after platinum-based chemotherapy, second-line treatment options include cytostatic agents, such as vinorelbine, topotecan, gemcitabine, pemetrexed, or nanoparticle albumin-bound paclitaxel; however, response rates are low (5% to 29%), with short DORs ranging from 2.1 to 5 months.[5] As a result, there is no established consensus for second-line treatment, and better treatment options are needed.[5]

While there is no globally accepted standard-of-care treatment for recurrent or metastatic cervical cancer after first-line systemic therapy, the therapeutic landscape is rapidly evolving. Immunotherapy agents, such as pembrolizumab[6] and cemiplimab,[7] have shown clinical activity in patients with recurrent or metastatic cervical cancer. Despite the promise of immunotherapies, the limited response rates (particularly in monotherapy) as well as first-line treatment eligibility being restricted to PD-L1 expression leave significant room for improvement.

Recent studies have investigated the potential of dual-inhibition approaches and bispecific immunotherapies for recurrent or metastatic cervical cancer. Ipilimumab plus nivolumab has shown promising clinical activity compared with nivolumab monotherapy,[8] while cadonilimab—a bispecific antibody against programmed cell death 1 (PD-1) and cytotoxic lymphocyte-associated antigen 4—was shown to be effective and safe as second-line treatment for patients with recurrent or metastatic cervical cancer, regardless of PD-L1 status.[9]

Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of the human TGF-β receptor II (or TGF-β trap) fused via a flexible linker to the C-terminus of each heavy chain of an IgG1 antibody blocking PD-L1.[10,11] TGF-β has a multifunctional role in the development and progression of cancer[12] and has been shown to promote immune escape of tumor cells, as well as the cell intrinsic interaction of PD-L1 and PD-1.[13-16] Further, preclinical models have shown that TGF-β signaling promotes epithelial-mesenchymal transition, angiogenesis, and fibrosis in cervical cancer, which result in resistance to anticancer therapies, including immunotherapies, and worse survival outcomes.[14,15,17-19] Together, these data suggest that simultaneous inhibition of 2 nonredundant immunosuppressive pathways (TGF-β and PD-L1) might improve outcomes in patients with cervical cancer.

Key Points

Question What are the safety and response rates of bintrafusp alfa in patients with recurrent or metastatic cervical cancer?

Findings In this phase 2 nonrandomized controlled trial of 146 patients with recurrent or metastatic cervical cancer with disease progression during or after platinum-based chemotherapy who received bintrafusp alfa monotherapy, the confirmed objective response rate was 21.9%, meeting its primary end point. The most common treatment-related adverse events were anemia (17.1%), rash (14.4%), hypothyroidism (10.3%), and pruritus (10.3%).

Meaning These findings support the potential of a bispecific therapy targeting transforming growth factor β and programmed cell death 1 ligand 1 in patients with recurrent or metastatic cervical cancer.

In a previous phase 1 study and single-institution phase 2 studies in patients with HPV-associated tumors (including cervical cancer) treated with bintrafusp alfa, the total clinical response was 30.0%.[11] This phase 2 nonrandomized controlled trial examined bintrafusp alfa in patients with recurrent or metastatic cervical cancer with disease progression during or after platinum-containing chemotherapy.

Methods

Study Design

This was a multicenter, open-label, international, single-arm phase 2 nonrandomized controlled trial to further investigate the clinical efficacy of bintrafusp alfa monotherapy (in terms of response rates and survival) in patients with recurrent or metastatic cervical cancer with disease progression during or after platinum-containing chemotherapy. Tumor response evaluation was based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and was performed every 8 weeks until 12 months after the first dose of bintrafusp alfa and then every 12 weeks until confirmed disease progression per RECIST 1.1, death, unacceptable toxic effects, or study withdrawal. Safety follow-up continued up to 12 weeks after the last dose of study treatment, and long-term follow-up was performed every 12 weeks after the safety follow-up. Survival follow-up continued until the end of the study.

The study protocol was approved by the institutional review board/international ethics committee before the study was initiated and was conducted in accordance with the Declaration of Helsinki, the Council for International Organizations of Medical Sciences, the International Ethical Guidelines, applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, the Guideline for Good Clinical Practice, The Japanese Ministerial Ordinance on Good Clinical Practice, and other applicable laws and regulations. The trial protocol can be found in Supplement 1, and the statistical analysis plan can be found in Supplement 2. This study followed the Transparent Reporting of Evaluations With Nonrandomized Designs (TREND)

reporting guideline. All patients provided written informed consent before enrolling in the study.

Patient Eligibility Criteria

Key inclusion criteria were recurrent or metastatic cervical cancer (irrespective of PD-L1 tumor expression) with disease progression during or after the prior platinum-containing chemotherapy, measurable disease, an Eastern Cooperative Oncology Group performance status of 0 or 1, and a life expectancy of 12 weeks or more. Key exclusion criteria were active central nervous system metastases causing clinical symptoms or requiring therapeutic intervention, interstitial lung disease, or a history of pneumonitis that required oral or intravenous steroids. There was no limit on the number of previous courses of therapy allowed, but prior PD-1 inhibitor therapy was not permitted.

Outcomes

The primary study end point was the confirmed objective response rate (ORR) per RECIST 1.1 by the independent review committee (IRC). The ORR will be determined as the proportion of participants with a confirmed objective response of complete response (disappearance of all target lesions) or partial response (30% or more decrease in the sum of diameters of target lesions, relative to baseline). Secondary study end points included ORR per RECIST 1.1 by the investigator, DOR (measured from the time measurement criteria are first met for complete response or partial response, whichever is first recorded, until the first date that recurrent or progressive disease [20% or more increase in the sum of diameters of target lesions, relative to the smallest sum on study] is objectively documented), durable response rate (DRR; defined as a response of 6 months or more), progression-free survival (PFS) per RECIST 1.1 (defined as time from first administration of study intervention until date of first documentation of progressive disease or death due to any cause in the absence of documented progressive disease, whichever comes first) by the investigator and IRC, safety (treatment-emergent adverse events [AEs], treatment-related AEs [TRAEs], and AEs of special interest [AESIs]), overall survival (OS), pharmacokinetic profile of bintrafusp alfa (trough concentration and concentration at the end of infusion), immunogenicity (antidrug antibodies) from screening through the safety follow-up visit (up to 28 days after last treatment), and efficacy end points by PD-L1 tumor expression.

Statistical Analysis

The analysis cutoff was February 15, 2022. The planned total sample size was 135 patients to address the primary objective and further efficacy and safety assessments. Assuming a true ORR of 25%, the probability of observing a lower bound of the exact 95% CI above 15% would be 80% when analyzing 135 patients and 57% when analyzing 81 patients. For the ORR and DRR, 95% CIs were calculated using the Clopper-Pearson method. Median DOR, PFS, and OS were calculated according to the Brookmeyer and Crowley method, and Kaplan-Meier analyses were performed. Continuous variables were summarized using counts with frequencies, means with SDs, and medians with ranges. Categorical variables were summarized using counts with frequencies. All analyses were performed using SAS version 9.04.01 (SAS Institute).

Results

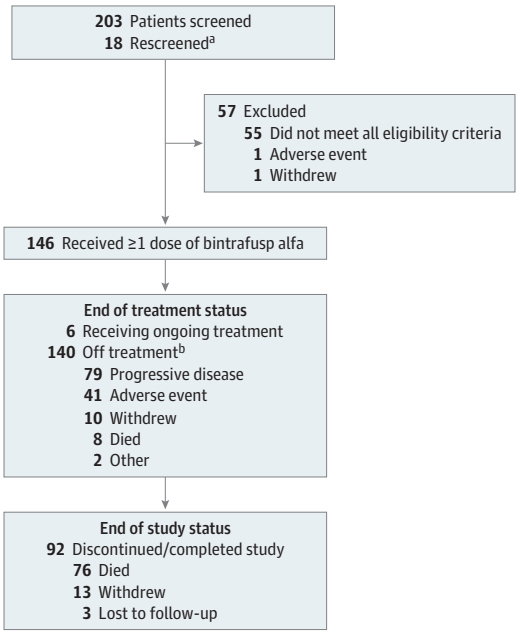
As of February 15, 2022, a total of 146 of 203 screened patients received 1 or more doses of bintrafusp alfa (**Figure 1**). The median (range) age was 53 (24-79) years, and the median follow-up duration was 14.9 months (95% CI, 14.3-15.8) for OS. At data cutoff, the median (range) duration of treatment was 10.0 (2-90) months, treatment was ongoing for 6 patients (4.1%), and 140 patients (95.9%) had discontinued treatment. The most common reasons for treatment discontinuation were progressive disease (79 [54.1%]) and AEs (41 [28.1%]).

Baseline disease characteristics of the enrolled patients were representative of the intended target population (patients with recurrent or metastatic cervical cancer). Most patients had squamous cell carcinoma (SCC) histology (92 [63.0%]), were positive for high-risk HPV (102 [69.9%]) based on central laboratory assessment and were positive for PD-L1 (combined positive score [CPS] of 1 or more; 86 [58.9%]) in tumor tissue (archival or newly obtained excisional or core biopsies) as measured by the 22C3 assay at a central laboratory (**Table 1**). Most patients were younger than 65 years (123 [84.2%]), and 88 patients (60.3%) were treated at centers in Asia, 41 (28.1%) in Europe, 9 (6.2%) in South America, 4 (2.7%) in North America, and 4 (2.7%) in Australia. A total of 51 patients (34.9%) had received 2 or more prior courses of anticancer therapies for recurrent or metastatic disease (excluding concurrent chemoradiation), and 73 patients (50.0%) had received prior treatment with bevacizumab. The median (range) duration of bintrafusp alfa treatment was 10.0 (2.0-90.0) weeks.

Response Rates

The study met its primary end point, with a 95% CI above the ORR benchmark of 15%; 32 patients (21.9%; 95% CI, 15.5-29.5) achieved a confirmed objective response per IRC assessment according to RECIST 1.1 (complete response, 10 patients [6.8%]; partial response, 22 patients [15.1%]) (**Table 2**). Disease control was achieved in 56 patients (38.4%; 95% CI, 30.4-46.8) based on the IRC assessment. Most responses occurred at the first or second assessment; however, several late responses at 6 months or later were observed (eFigures 1 and 2 in Supplement 3). Confirmed objective response by investigator assessment was reported in 25 patients (17.1%; 95% CI, 11.4-24.2) (eTable 1 in Supplement 3), while disease control was reported in 57 patients (39.0%; 95% CI, 31.1-47.5). Median DOR (per the IRC) was not reached (95% CI, 7.4 months to not reached) (Table 2; eFigure 3 in Supplement 3). A DRR of 6 months or more was reported in 19 of 146 patients (13.0%; 95% CI, 8.0-19.6) and in 19 of 32 patients (59.4%) who achieved an objective response. At data cutoff, responses were ongoing in 13 of 32 responders (40.6%). The confirmed ORRs analyzed by number of prior courses of therapy (12 patients with 0 prior courses; 55 with 1; 48 with 2; 16 with 3; and 15 with 4

Figure 1. Patient Disposition



[a]Rescreened patients are counted once in the set of screened patients.

[b]Treatment termination after reinitiation not considered here.

or more) for metastatic disease were 25.0% (95% CI, 5.5-57.2), 20.0%; (95% CI, 10.4-33.0), 27.1% (95% CI, 15.3-41.8), 18.8% (95% CI, 4.0-45.6), and 13.3% (95% CI, 1.7-40.5), respectively (eFigure 4 in Supplement 3).

Subgroup analyses revealed that responses were observed regardless of PD-L1 expression and histology (eFigure 4 in Supplement 3). Of 86 patients with PD-L1-positive tumors and 55 with PD-L1-negative tumors, the confirmed ORRs were 25.6% (95% CI, 16.8-36.1) and 18.2% (95% CI, 9.1-30.9), respectively. Patients with SCC (n = 92) and adenocarcinoma (n = 49) had confirmed ORRs of 28.3% (95% CI, 19.4-38.6) and 12.2% (95% CI, 4.6-24.8), respectively. Patients with high-risk HPV-positive disease (n = 102) had a confirmed ORR of 25.5% (95% CI, 17.4-35.1), while patients with HPV-negative disease (n = 22) had an ORR of 9.1% (95% CI, 1.1-29.2). Of the 4 patients with low-risk HPV-positive disease, none had a confirmed response.

The median PFS was 1.9 months (95% CI, 1.8-2.2; **Figure 2**A), and the PFS rates at 6 and 12 months were 30.6% (95% CI, 23.1-38.5) and 20.1% (95% CI, 13.3-28.0), respectively. The median PFS was similar between patients with PD-L1-positive tumors (1.9 months; 95% CI, 1.8-4.3) and PD-L1-negative tumors (1.9 months; 95% CI, 1.7-2.0) and between those with SCC (2.0 months; 95% CI, 1.8-5.4) and adenocarcinoma (1.9 months; 95% CI, 1.8-1.9) (eFigure 5 in Supplement 3). However, more patients with PD-L1-negative tumors or adenocarcinoma histology experienced progression at the first assessment.

The median OS was 13.7 months (95% CI, 10.6-17.1), and the OS rate at 12 months was 53.0% (95% CI, 44.2-61.1) (Figure 2B). Longer median OS was observed in patients with PD-L1-positive tumors vs PD-L1-negative tumors (17.5 months [95% CI, 12.5 months to not reached] vs 8.7 months [95% CI, 5.8-11.8]) and SCC vs adenocarcinoma histology (16.8 months [95% CI, 11.8 months to not evaluable] vs 9.1 months [95% CI, 4.6 months to not evaluable]) (eFigure 6 in Supplement 3). At 6 months, patients with high-risk HPV-positive disease had a higher OS rate (76.4%; 95% CI, 66.6-83.6) than patients with low-risk HPV-positive disease (75.0%; 95% CI, 12.8-96.1) and HPV-negative disease (66.6%; 95% CI, 42.4-82.5).

Of the 32 responders, 28 (87.5%) were younger than 65 years, 26 (81.3%) had high-risk HPV-positive disease, and 26 (81.3%) had SCC. A total of 19 patients (59%) had prior bevacizumab treatment (eTable 2 in Supplement 3).

Safety

TRAEs of any grade occurred in 106 patients (72.6%), while TRAEs of grade 3 or higher occurred in 46 patients (31.5%). The most common TRAEs of any grade were anemia (25 [17.1%]), rash (21 [14.4%]), hypothyroidism (15 [10.3%]), and pruritus (15 [10.3%]) (**Table 3**). Serious TRAEs occurred in 38 patients (26.0%). TRAEs that led to the permanent discontinuation of 26 patients (17.8%) included colitis (3 [2.1%]), erythema multiforme (3 [2.1%]), anemia (1 [0.7%]), abnormal hepatic function (1 [0.7%]), diabetic ketoacidosis (2 [1.4%]), immune-mediated dermatitis (2 [1.4%]), and rash (2 [1.4%]). No treatment-related deaths were reported. AESIs included anemia (82 [56.2%]), bleeding events (81 [55.5%]), and immune-related AEs (49 [33.6%]) (Table 3); bleeding events were grade 3 or higher in 25 patients (17.2%), 9 of whom had bintrafusp alfa–related grade 3 or higher bleeding events. TGF-β inhibition–mediated skin AESIs were SCC of the skin in 4 patients (2.7%), keratoacanthoma in 3 patients (2.1%), and hyperkeratosis in 1 patient (0.7%). Most SCCs of the skin and keratoacanthoma resolved with complete excision; some regressed spontaneously following clinical observation.

Pharmacokinetics and Immunogenicity

The target trough concentration (geometric mean of more than 100 μg/mL) was achieved by day 29 and maintained throughout the treatment period following a dosing regimen of bintrafusp alfa, 1200 mg, every 2 weeks, with minimal accumulation (eFigure 7 in Supplement 3). The incidence of treatment-emergent antidrug antibodies was 16.7% (23 of 138; eTable 3 in Supplement 3).

Discussion

In this phase 2 nonrandomized controlled trial, bintrafusp alfa demonstrated clinical activity in patients with recurrent or metastatic cervical cancer who previously experienced treatment failure with platinum-based chemotherapy. The study met its primary end point, with a confirmed ORR of 21.9% (95% CI, 15.5-29.5) per the IRC assessment; ORR was highest in the SCC and HPV-positive subgroups. The median PFS in this study was 1.9 months (95% CI, 1.8-2.2), while PFS rates at 6 and 12 months were 30.6% (95% CI, 23.1-38.5) and 20.1% (95% CI, 13.3-28.0), respectively. The median OS was 13.7 months

Table 1. Demographic and Baseline Characteristics

Characteristic	Patients, No. (%)
Total, No.	146
Age, median (range), y	53 (24-79)
Pooled region	
Asia	88 (60.3)
Europe	41 (28.1)
South America	9 (6.2)
North America	4 (2.7)
Australia	4 (2.7)
Histology	
Squamous cell carcinoma	92 (63.0)
Adenocarcinoma	49 (33.6)
Adenosquamous cell carcinoma	5 (3.4)
Prior radiotherapy	117 (80.1)
Prior anticancer therapies for recurrent or metastatic disease[a]	
0	14 (9.6)
1	81 (55.5)
≥2	51 (34.9)
Type of prior anticancer therapy	
Bevacizumab	73 (50.0)
ECOG performance status	
0	69 (47.3)
1	77 (52.7)
≥2	0
HPV status using a central laboratory[b]	
High-risk HPV positive	102 (69.9)
Low-risk HPV positive	4 (2.7)
HPV negative	22 (15.1)
Unknown[c]	8 (5.5)
Missing[d]	10 (6.8)
PD-L1 expression in tumor tissue measured by 22C3 assay using a central laboratory	
CPS <1	55 (37.7)
CPS ≥1	86 (58.9)
CPS ≥10	45 (30.8)
Not evaluable	4 (2.7)
Missing[d]	1 (0.7)

Abbreviations: CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; PD-L1, programmed cell death 1 ligand 1.

[a] Excludes concurrent chemoradiation therapy.

[b] If HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-66, or HPV-68 was positive.

[c] Test performed, but result was not obtained.

[d] No information gathered on whether a test was performed.

(95% CI, 10.6-17.1) and was shown to be more favorable among patients with SCC histology than in patients with adenocarcinoma (16.8 months [95% CI, 11.8 months to not evaluable] vs 9.1 months [95% CI, 4.6 months to not evaluable], respectively). Despite the small number of patients, a confirmed objective response was observed in 10 of 55 patients (18.2%; 95% CI, 9.1-30.9) with PD-L1-negative (CPS of less than 1 as measured by 22C3 assay at a central laboratory) cervical cancer receiving bintrafusp alfa.

Table 2. Overview of Clinical Activity per the Independent Review Committee

Activity	Patients
Total, No.	146
Best overall response, No. (%)	
Complete response	10 (6.8)
Partial response	22 (15.1)
Stable disease	24 (16.4)
Progressive disease	77 (52.7)
Not evaluable	13 (8.9)
Objective response rate, % (95% CI)[a,b]	21.9 (15.5-29.5)
Disease control rate, % (95% CI)[c]	38.4 (30.4-46.8)
DOR, median (95% CI), mo	NR (7.4-NR)
Durable response rate at ≥6 mo, % (95% CI)	13.0 (8.0-19.6)
Objective response rate based on PD-L1 status, No./total No. (%; 95% CI)	
PD-L1 positive (CPS ≥1)	22/86 (25.6; 16.8-36.1)
PD-L1 negative (CPS <1)	10/55 (18.2; 9.1-30.9)
Objective response rate based on histology, No./total No. (%; 95% CI)	
Squamous cell carcinoma	26/92 (28.3; 19.4-38.6)
Adenocarcinoma	6/49 (12.2; 4.6-24.8)
Adenosquamous cell carcinoma	0/5

Abbreviations: CPS, combined positive score; DOR, duration of response; NR, not reached; PD-L1, programmed cell death 1 ligand 1.

[a] 95% Exact CI using the Clopper-Pearson method.

[b] Best overall response assessment of complete response or partial response.

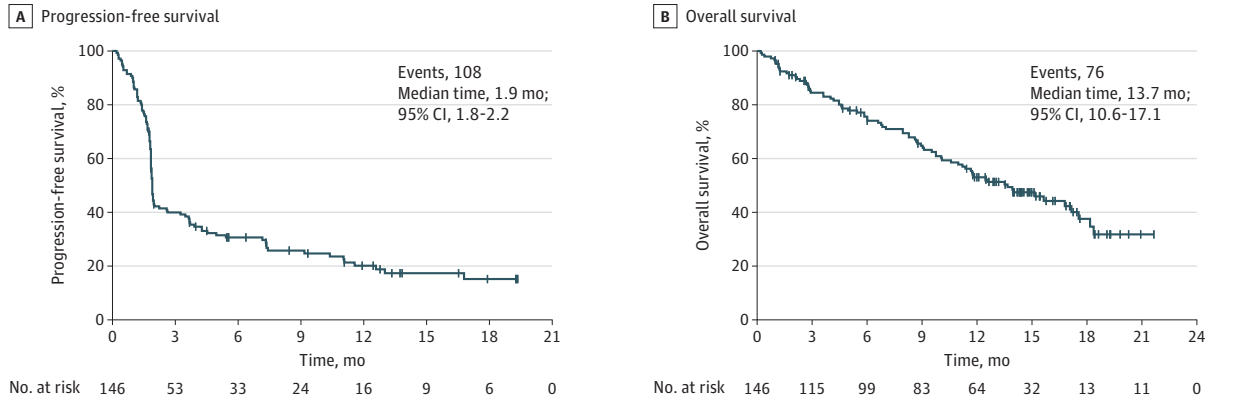
[c] Best overall response assessment of complete response, partial response, or stable disease.

To contextualize these findings, indirect comparisons can be made with relevant studies. In the phase 2 KEYNOTE-158 trial of pembrolizumab, the ORR, median PFS, and median OS were 14.3%, 2.1 months, and 9.4 months, respectively.[6] The median PFS in the phase 3 KEYNOTE-826 for patients with CPS of 1 or greater was 10.4 months.[4] In the phase 3 EMPOWER trial of cemiplimab, the ORR, median PFS, and median OS were 16.4%, 2.8 months, and 12.0 months, respectively; patients with adenocarcinoma/adenosquamous carcinoma and SCC had a median OS of 13.3 and 11.1 months, respectively.[7]

While some response rates appear to be favorable in our study, indirect comparisons must be made with caution, and it is noteworthy that the population in our study may be unique compared with the population in other studies of immunotherapies, which have higher rates of patients with SCC histology and fewer Asian patients. Additionally, the percentages of patients with adenocarcinoma (49 [33.6%]) and PD-L1-negative tumors (55 [37.7%]) were higher than those in other immunotherapy studies, such as those using pembrolizumab and cemiplimab, which have reported 5.1% to 22.2% of patients with adenocarcinoma and 15.3% to 67.4% with PD-L1-negative tumors in their cohorts.[6,7]

In our study, bintrafusp alfa had a manageable safety profile, with no new safety signals identified despite the

Figure 2. Progression-Free Survival and Overall Survival Among Patients Who Received 1 or More Doses of Bintrafusp Alfa



Progression-free survival was measured according to Response Evaluation Criteria in Solid Tumors version 1.1 as adjudicated by the independent review committee.

heavily pretreated population. The higher incidence of bleeding events observed with bintrafusp alfa has been seen in other clinical studies of bintrafusp alfa, in which a higher frequency of low-grade bleeding events has been observed than with immune checkpoint inhibitors or targeted agents.[20-22] Notably, the incidence of bleeding AEs, anemia, and immune-related AEs in this study was higher than previously reported with bintrafusp alfa in other indications, while the incidence of TGF-β inhibition–mediated skin AEs was lower.[22] Exposure safety for bleeding AEs was established in previous studies and indicated that the cervical cancer tumor type was associated with a higher probability of AEs in addition to exposure.[22] 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,[23] dose reduction may be a feasible management approach to reduce the probability of bleeding events while retaining pharmacological activity.[22]

Similar to other studies with bintrafusp alfa, the trough concentration reported in this study indicates that a target occupancy was reached for all 4 targets of bintrafusp alfa (TGF-β1, TGF-β2, TGF-β3, and PD-L1).[24,25] This finding is also consistent with the finding of the previously reported population pharmacokinetic modeling, which concluded that the impact of tumor type on exposure was not considered clinically meaningful.[26] Notably, a relatively high proportion of patients in this study were from Asia (88 patients [60.3%]); however, the previously reported pharmacokinetic analysis also concluded that the impact of patient demographic characteristics (including race) on exposure was not considered clinically meaningful.[26]

A trial of bintrafusp alfa in patients with biliary tract cancer found the incidence of treatment-emergent antidrug antibodies to be 19.0%, similar to the incidence in our study, with no apparent effect on the efficacy or pharmacokinetic profile of bintrafusp alfa.[27] A 2022 review[28] of nivolumab, atezolizumab, avelumab, and pembrolizumab also found antidrug antibodies to have minimal impact on the pharmacokinetics, safety, or efficacy of the drug.

Table 3. Treatment-Related Adverse Events (AEs)

AE	Patients, No. (%)	
	Any grade[a]	Grade ≥3[b]
Treatment-related AEs	106 (72.6)	46 (31.5)
Anemia	25 (17.1)	7 (4.8)
Rash	21 (14.4)	2 (1.4)
Hypothyroidism	15 (10.3)	0
Pruritus	15 (10.3)	2 (1.4)
Hematuria	13 (8.9)	5 (3.4)
Lipase increased	7 (4.8)	2 (1.4)
Colitis	4 (2.7)	4 (2.7)
Hepatic function abnormal	4 (2.7)	2 (1.4)
Adrenal insufficiency	3 (2.1)	2 (1.4)
Keratoacanthoma	3 (2.1)	2 (1.4)
Febrile neutropenia	2 (1.4)	2 (1.4)
Diabetic ketoacidosis	2 (1.4)	2 (1.4)
AEs of special interest[c]		
TGF-β inhibition–mediated skin AEs	7 (4.8)	3 (2.1)
Bleeding	81 (55.5)	25 (17.1)
Anemia	82 (56.2)	45 (30.8)
Immune-related AEs	49 (33.6)	21 (14.4)

Abbreviation: TGF-β, transforming growth factor β.

[a] AEs of any grade reported in 10% or more of patients.

[b] AEs of grade 3 or greater reported in 2 or more patients.

[c] AEs of special interest were defined as serious or nonserious AEs specific to the known mechanism of action of the study intervention of clinical interest, including infusion-related reactions, immune-related AEs, TGF-β inhibition–mediated skin reactions, anemia, and bleeding AEs.

The clinical activity observed here may reflect the underlying role of TGF-β in the pathophysiology of cervical cancer. Most clinical studies of anti-PD-1 therapies have had very large SCC populations, including the EMPOWER study, which showed improved OS in patients with ade-

nocarcinoma/adenosquamous carcinoma (median, 13.3 months) vs SCC (median, 11.1 months).[7] The prolonged OS in SCC vs adenocarcinoma observed here with bintrafusp alfa may reflect the underlying role of TGF-β in the physiology of cervical cancer.[29] The oncogenic effect of TGF-β in cervical cancer may warrant further investigation of therapies targeting TGF-β.

Limitations

This study has limitations. The single-arm, open-label design may restrict the interpretation of the study data. Additionally, the relatively small sample size precludes any meaningful comparisons between patient subgroups.

Conclusions

In conclusion, this phase 2 nonrandomized controlled trial of bintrafusp alfa met its primary end point, which may support the further exploration of bifunctional molecules, particularly those targeting TGF-β and PD-L1, in patients with cervical cancer. While this study focused on patients with recurrent or metastatic cervical cancer with disease progression during or after platinum-containing chemotherapy, the effects of bintrafusp alfa on patients who received checkpoint inhibitors as first-line treatment remains unexplored.

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